eHealth and mHealth Pipelines for Clinical Decision Support to Improve Medication Selection and Safety

by

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Abstract

Although much work has been done over the past decade on developing personalized and evidence-based medicine, such as diagnostic tests based on genetics to better predict patients' responses to therapy, stumbling blocks remain that have prevented knowledge, tests, and other pertinent patient-centric data from becoming routine in clinical practice. The main problem with uptake and implementation centres on an absence of computational infrastructures to deliver an individualized approach at the point of care. This study focused on the creation of re-usable computer and mobile-based components of clinical decision support systems for patient-centric data. The goal was to develop eHealth and mHealth pipelines to not only create interactive delivery systems for medication selection and medication safety, but also to provide templates that can be re-used on provincial, pan-Canadian, and international scales. Through this research, a novel database structure for storing and analyzing data (CASTOR), augmented fast and frugal decision trees (FFTs), and mobile and web-based applications (AntiC), were developed to improve medication selection and medication safety. These projects were initially based on rationalizing, storing, and interpreting large genomic data sets, filtering the ensuing pharmacogenomically relevant data into automated decision trees for medication selection on a country-specific basis, and developing a work-frame template (BOW) to build clinical decision applications (apps) for smartphones and tablets. As a result of this project, ultimately, community and hospital pharmacists in Canada will be better informed about the safe handling and use of oral chemotherapeutics, preventing adverse drug reactions, and Ministries of Health in developing countries will have access to

curated, pharmacogenomics-based decision trees specific to their countries to rationalize medication selection at no extra cost to local healthcare systems. The models we developed (CASTOR, augmented FFTs, and BOW) were deliberately designed and built with re-usable components that can be linked to future projects to generate targeted and focused clinical decision support and mHealth applications wherever needed. This will eventually allow for the implementation of rationalized clinical decision support applications and evidence-based knowledge translation at the point of care.

Preface

Chapters 2-5 of this thesis represent peer-reviewed, accepted manuscripts based on local, national, and international collaborations. Permissions to reproduce the manuscripts in this thesis have been received from the relevant publishers (see Appendix).

CHAPTER 2

Contributions: Chapter 2 of this thesis represents a national collaboration between the Beaulieu-Saucier Centre de Pharmacogénomique (Montréal) and the University of Alberta. I initiated the project, developed and proofed the concept, supervised the development and validation phases, drafted the manuscript and reviewed the final draft. M. Bouffard contributed to the development of the database, contributed to the manuscript and reviewed the final draft. AM. Brown assisted with the test sample set used to validate the database, contributed to the manuscript edits and reviewed the final draft. MS. Phillips and JC. Tardif were directors at the Beaulieu-Saucier Centre de Pharmacogénomique and provided comments. S. Marsh was my supervisor, contributed to the manuscript, and reviewed the final draft. I am the corresponding author on the publication.

Publication: Chapter 2 has been peer-reviewed and published in its entirety through Oxford University Press as *Marc Bouffard, Michael S. Phillips, Andrew M.K. Brown, Sharon Marsh, Jean-Claude Tardif, and Tibor van Rooij. Damming the Genomic Data*

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CHAPTER 3

Contributions: Chapter 3 of this thesis represents part of a global collaboration (PGENI) founded by HL. McLeod and S. Marsh. I initiated the project, developed the augmented FFT methodology and automation, drafted the manuscript and reviewed the final draft. M. Roederer built the original non-FFT format trees that were used for the test-case in the project, contributed to the manuscript edits and reviewed the final draft. T. Wareham verified the validity of the data generated in the project, contributed to the manuscript edits and reviewed the final draft. I. van Rooij contributed to the FFT process, contributed to the manuscript edits and reviewed the final draft. HL. McLeod supervised the original non-FFT tree development, contributed to the manuscript edits and reviewed the final draft. S. Marsh supervised the project, contributed to the manuscript edits and reviewed the final draft. I am the corresponding author on this publication.

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CHAPTER 4

Contributions: Chapter 4 of this thesis represents a local collaboration between a hospital pharmacy and the University of Alberta. I initiated the project, developed the model, the website and the mobile app, drafted the manuscript and reviewed the final draft. S. Rix contributed the test case, contributed to the manuscript edits and reviewed the final draft. JB. Moore contributed to the development of the website and mobile app, contributed to the manuscript edits and reviewed the final draft. S. Marsh supervised the project, contributed to the manuscript edits and reviewed the final draft. I am the corresponding author on this publication.

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CHAPTER 5

Contributions: Chapter 5 of this thesis represents a local collaboration between a hospital pharmacy and the University of Alberta. I developed the computational project (website and mobile app), contributed to the manuscript composition and reviewed the final draft. S. Rix is the corresponding author on this manuscript, developed the pharmacy project (designed the monographs), contributed to the manuscript composition and reviewed the final draft. S. Marsh supervised the project, contributed to the manuscript edits and reviewed the final draft.

Dissemination: The AntiC mobile app has been made freely available through GitHub (https://github.com/vanrooij/AntiC); the license for use is available at: https://github.com/vanrooij/AntiC/blob/master/website-and-api/LICENSE

Publication: Chapter 5 has been peer-reviewed and accepted for publication in its entirety as *Tibor van Rooij, Serena Rix, and Sharon Marsh. AntiC: A Practice Tool for the Safe Use of Oral Chemotherapeutics by Community and Hospital Pharmacists.* Version 2 is reproduced here in full. The final, definitive version of this paper has been published in *Canadian Pharmacists Journal/Revue des Pharmaciens du Canada, 148(3), May/June, 2015, pages 118-124* by SAGE Publications, Inc., All rights reserved. © The Authors 2015 http://online.sagepub.com doi:10.1177/1715163515578454

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List of Abbreviations

A	Adenine
ABCB1	ATP-Binding Cassette, Sub-Family B (MDR/TAP), Member 1
ACT	Artemisinin-based combination therapy
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AI	Artificial Intelligence
AL	Artemether/lumefantrine
ALL	Acute lymphoblastic leukemia
API	Application programming interface
app	Mobile application
AQ	Amodiaquine
ARRA	American Recovery and Reinvestment Act
AS	Artesunate
AWS	Amazon Web Services
AZA	Azathioprine
bid	*bis in die*; twice a day
BMI	Body mass index
BOW	Bridging opportunities work-frame
BRCA1	Breast cancer 1, early onset
BRCA2	Breast cancer 2, early onset
C	Cysteine
CAM	Complementary and alternative medicines
CASTOR	Comprehensive analysis and storage
CBC (diff)	Complete blood count with differential
CCS	Cascading style sheet
CCU	Coronary care unit
CDS	Clinical decision support
CDSS	Clinical decision support systems
CGH	Comparative genomic hybridization
CL_{cr}	Creatinine clearance
CPOE	Computerized provider order entry
CPS	Compendium of pharmaceuticals and specialties
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBMS	Database management system
DIMM	Dual inline memory module
DNA	Deoxyribonucleic acid
DPD	Dihydropyrimidine dehydrogenase
DQ	Design qualification
EA	Enterprise architecture
EAN	European Article Number
EBM	Evidence based medicine
EC2	Elastic Compute Cloud
eHealth	Electronic health
EHR	Electronic health record
EM	Extensive metabolizer
EML	Essential Medicines List

EMR	Electronic Medical Record
ER	Entity relationship
EZPC	Edmonton Zone Palliative Care
FDA	Food and Drug Administration
FFT	Fast and frugal tree
FSB	Front Side Bus
G	Guanine
G-force	Unit of acceleration
GB	Gigabyte
GERD	Gastro-esophageal reflux disease
GH_z	Gigahertz
GIMS	Global information management system
GIS	Geographic Information Systems
GUI	Graphical user interface
GWAS	Genome wide association study
h	Hours
HbA1c	Hemoglobin A1c
HIV	Human immunodeficiency virus
HTML	Hypertext markup language
ICT	Information and Communications Technology
IM	Intermediate metabolizer
INR	International normalized ratio
IQ	Installation qualification
ISAM	Indexed Sequential Access Method
IT	Information Technology
ITU	International Telecommunication Union
LFT	Liver function test
MB	Megabyte
mg	milligram
mHealth	Mobile health
MH_z	Megahertz
min	Minute
mL	Milliliter
MQ	Mefloquine
NAT2	N-acetyltransferase 2
NCI	National Cancer Institute
NGS	Next generation sequencing
NIOSH	National Institute for Occupational Safety and Health
NSAID	Non-steroidal anti-inflammatory drug
OICR	Ontario Institute for Cancer Research
OLAP	Online analytical processing
OQ	Operational qualification
PC	Personal computer
PCEHR	Personally controlled electronic health record
PDA	Personal Digital Assistant
PGENI	Pharmacogenomics for Every Nation Initiative
PHP	Hypertext processor
PM	Poor metabolizer
po	*per os*; by mouth
PoC	Point of Care
PPE	Palmar-plantar erythrodysesthesia

PQ	Performance qualification
prn	*pro re nata*; when necessary
q	*quaque*; once
QA	Quality assurance
QR code	Quick response code
QTc interval	Corrected QT interval
RA	Rheumatoid arthritis
RDBMS	Relational database management system
RFDS	Royal Flying Doctor Service
RHELS	Re-deployable high-energy laser system
RNA	Ribonucleic acid
RPM	Revolutions per minute
SCSI	Small computer system interface
SLCO1B1	Solute carrier organic anion transporter family, member 1B1
SMS	Short messaging service
SNP	Single nucleotide polymorphism
SP	Sulfadoxine/pyrimethamine
SQL	Structured query language
SSZ	Sulfasalazine
T	Thymine
TPMT	Thiopurine methyltransferase
UI	User interface
UK	United Kingdom
UM	Ultrarapid metabolizer
UN	United Nations
US	United States
USD	United States dollars
VKORC1	Vitamin K epoxide reductase complex subunit 1
WGS	Whole genome sequencing
WHO	World Health Organization
wks	Weeks
WWW	World-wide web

1. INTRODUCTION

1.1. Background

Rising healthcare costs associated with patients with chronic disease and disabilities, the growing burden of cancer, and a rapidly aging population have had a major economic impact on healthcare systems worldwide (Coleman et al., 2014, Putrino, 2014, Steele Gray et al., 2014). This has resulted in pressure from national governments on their healthcare systems to reduce the overall costs of medical treatments (Harper, 2014b, Huttin, 2014, Selivanova and Cramm, 2014, Zhu et al., 2014). As both medical knowledge and technology use in healthcare are rapidly advancing, there is an international interest in improving the quality and safety of care by expediting the throughput of medical information with integrated computer-based systems (Black et al., 2011, Knaup et al., 2014). The ultimate aim is to reduce costs through improvements in patient care and outcomes (Sjostrom et al., 2014, Steele Gray et al., 2014). eHealth refers to the pursuit of more efficient ways to deliver healthcare using Information and Communications Technology (ICT) (Harper, 2014b, Huttin, 2014, Selivanova and Cramm, 2014, Zhu et al., 2014). The main objective within this endeavour is the improved selection of appropriate medications and treatments, as well as their safer use.

1.1.1. The History of eHealth

The term eHealth, previously referred to as electronic health or e-health, dates from the changeover of the millennium. However, as shown in the timeline of the history of eHealth in Figure 1.1, eHealth started with Telemedicine, which was later known as Telehealth. Telemedicine uses ICT to provide or support the delivery of healthcare

services when participants are separated by physical distance (Field, 2002). Telehealth, Telemedicine and eHealth are often used interchangeably; however, Telemedicine or Telehealth is a distinct discipline, which predated eHealth, and is now contained as a subset under the all-encompassing term eHealth. Telemedicine is, in many ways, a forerunner of eHealth in the use of technology to increase efficiencies and to bridge the gap between providers and patients; it has established itself in many remote and rural areas (Mars, 2013, Merz, 2014). Telemedicine improved care delivery in rural areas by providing distance access to specialist care, and by reducing the need to travel to, or transport patients from, secluded areas to provide critical medical care (Herrington et al., 2013, Mars, 2013).

The distance based approach of telemedicine dates as far back as 1929 (Figure 1.1), when remote consults were performed via Morse-code in Australia by the Royal Flying Doctor (RFDS) Telehealth consultation services (Margolis and Ypinazar, 2008). Beginning in 1942, a Telepharmacy program, the first of its kind (Figure 1.1), was added by the RFDS which continues today (Margolis and Ypinazar, 2008). In Canada, Telepharmacy services were developed to deal with a chronic shortage of pharmacists in rural and remote settings (Gordon et al., 2012).

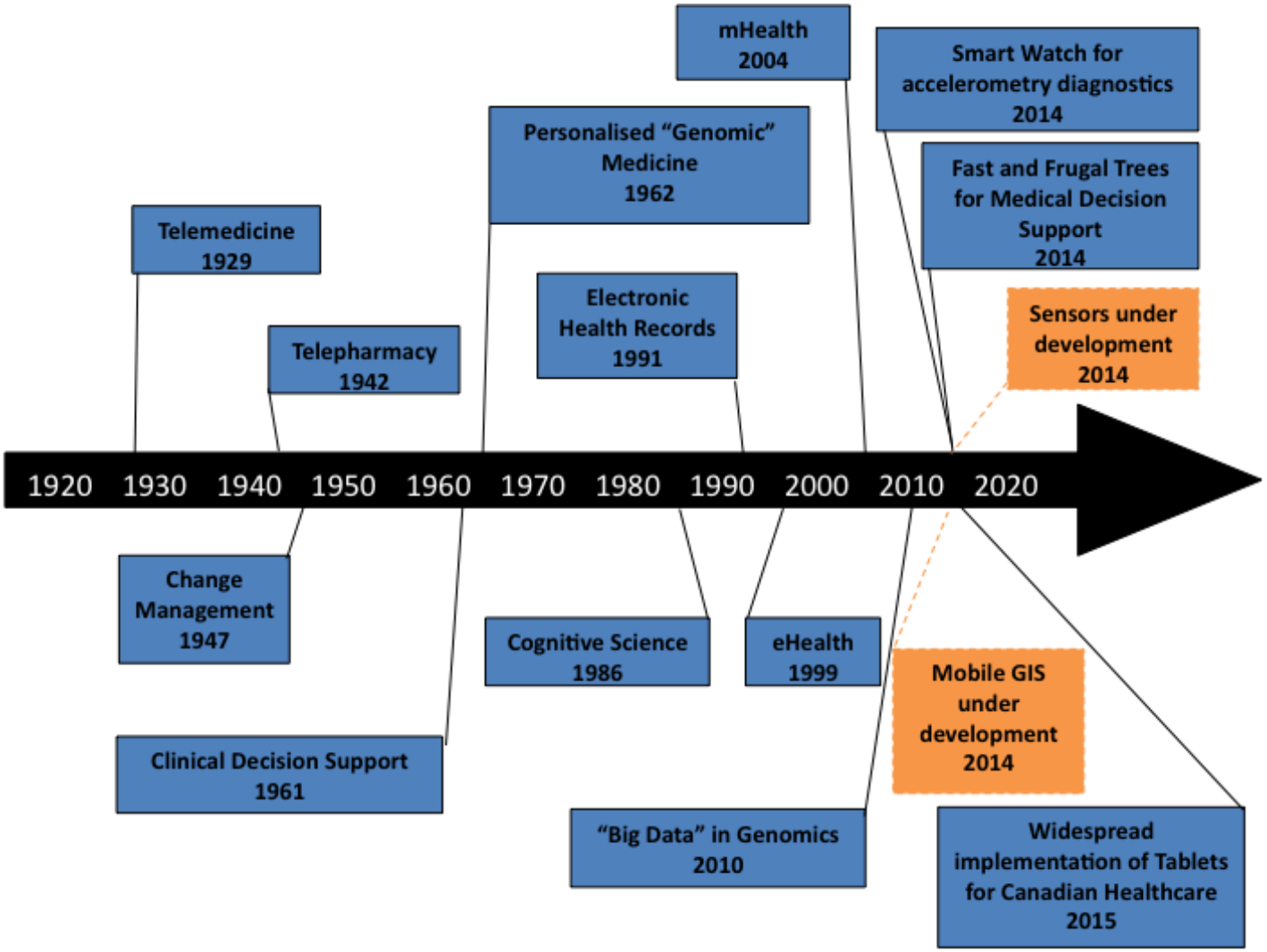

Figure 1.1. The history of eHealth. Many scientific developments have been combined over time to form the field of eHealth. In recent times, unprecedented, inexpensive access to connected computing resources is intensifying research.

1.1.1.1. Electronic Health Records (EHRs)

In 1991 computer science researchers, who tried to describe Electronic Health Records (EHRs), then called Electronic Medical Records (EMRs), concluded that EHRs were electronic files for use in patient care which gave a complete record of what was done and observed clinically in the treatment of patients, and that these records were to be stored permanently in computers (Rector et al., 1991). In 1992, researchers at the State University Hospital Ghent at the Department of Medical Informatics in Belgium identified a need for healthcare personnel to be trained and for the workflow to be adapted when changing from a paper-based system to an EHR (Ceusters et al., 1992). In order to deal with changes brought on by the introduction of technology, healthcare organizations often used Change Management tools (Ben-Assuli, 2014, Harlos et al., 2012). Change Mangement was first introduced in 1947 by Kurt Lewin as a model to guide organizational change (Figure 1.1) (Lewin, 1947, McGarry et al., 2012).

Although eHealth had been around as a concept since 1991 (Figure 1.1), implementation of EHRs saw a surge when broadband (high-speed) internet access was widely introduced about a decade ago; new ways of sharing patient files became technically feasible when the speed and size of data exchange increased (Jennett et al., 2005). Based on increased efforts to change from paper-based systems to automation in healthcare, eHealth became an important term and many definitions were proposed, with different points of emphasis (Oh et al., 2005). However, there was a common understanding that eHealth covered the combination of healthcare and technology (Oh et al., 2005).

1.1.1.2. Personalizing medicine

In 1962, Werner Kalow, a medical doctor in the Department of Pharmacology at the University of Toronto, published the first attempt to systematically pull together the fields of pharmacology and genetics, which later became pharmacogenomics (Figure 1.1) (Kalow, 1962). Pharmacogenomics, the impact of genetics on drug action, aimed to determine patients' individual variability in response to therapies by examining gene variations for drug disposition, response, or toxicity (Evans and McLeod, 2003). Once patients' individual genetic variability was known, it could be used to improve medication selection (Marsh, 2007). Based on this insight, researchers looked for patterns and associations in ever larger amounts of genomic data, identifying relationships of genes and medication interactions, and genes that conferred disease risk (Engen et al., 2006, Hong et al., 2009, Lander et al., 2001, Niu et al., 2009).

In 2010, the generation of data of this genomic research through whole genome sequencing (WGS), and genome-wide association studies (GWAS) had progressed to a point where file sizes were so large that it became known as "Big Data" (Figure1.1). Big Data described not only genomic technologies' enormous amounts of data output, but also referred to the computational problem related to the storage and computer analysis of these extremely large data sets (Merelli et al., 2014). In order to satisfy the storage space and computing power requirements of Big Data, researchers often turned to cloud-computing, where they used broadband to access cost-effective analysis tools and databases on servers outside their research organizations (Bajwa, 2014, Crews et al., 2011). Efforts to apply genomic data in healthcare gave rise to personalized medicine,

and over time pharmacogenomics and eHealth became intertwined (Glauber et al., 2014, Marsh and van Rooij, 2009, van Rooij and Marsh, 2011).

Due to complexity of describing pharmacogenomics' impact on metabolism and action of medications, computers were also needed to automate clinical decision support (CDS) at the point of care (PoC) (Crews et al., 2012). CDS helped to calculate the effect of a patient's genetic background (based on patient's genetic test results and other patient data) on medication selection and dosing for healthcare providers (dos Santos et al., 2014, Drohan et al., 2009, Gage et al., 2008).The idea for CDS was first postulated by Ledley and Lusted in a 1961 paper on the role of computers in medical diagnosis (Figure 1.1); computer use at that time was not widespread as it is today (Ledley and Lusted, 1961). In fact, commercially sold computers like the Ferranti Pegasus took up an entire room (Tweedale, 1992).

Gordon E. Moore, a co-founder of Intel Corporation, postulated in 1965 that the number of transistors in computer circuits was going to double approximately every two years, this prediction held true, and became known as Moore's law (Moore, 2000). As time progressed, complex computing tasks became more accessible for eHealth interventions (Haux, 2006). However, a new obstacle emerged. In many cases, turning medical knowledge into applicable software at PoC was found to not only hinge on the availability of computing resources, it also required algorithms to help in the interpretation of data, and to gain a better understanding of decision-making processes (Tomaszewski, 2012).

In 1986 a cognitive science approach started to try to understand the process of medical decision making (Figure 1.1) (Patel and Groen, 1986). The idea was to identify algorithms that described successful problem-solving strategies of healthcare providers (Moskowitz et al., 1988). A pediatric example of this work was a model that helped predict whether a specific antibiotic was going to be effective in the treatment of children with pneumonia. By answering at most two questions, physicians rapidly assessed whether a specific type of bacteria was the culprit and selected the appropriate antibiotic for treatment (macrolide vs. no macrolide) (Fischer et al., 2002). This was an example of an algorithm that provided a short-cut in answering a complex question. These types of algorithms are collectively known as heuristics (Bodemer et al., 2014, Todd and Gigerenzer, 2000).

1.1.1.3. Wireless medical technologies

The invention of wireless technologies based on either Wi-Fi or mobile access allowed healthcare providers to stay connected to the network while making their communication devices portable (Ventola, 2014, World Health Organization, 2011a). Mobile Health, commonly known as mHealth, was built around the idea that wireless mobile devices (e.g. smartphones, tablets, iPhones and iPads) had a capacity for both communication and computing (Mosa et al., 2012). This encouraged their use for remote care as well as at PoC, where they were applied to reach healthcare objectives (Mickan et al., 2013, Mosa et al., 2012). Researchers demonstrated this potential in 2004 (Figure1.1), when a Personal Digital Assistant (PDA) was outfitted with a miniature camera, a hands free microphone and a Windows operating system (Nazeran et al., 2004). This novel

device was used to show that it was possible to send pictures, audio, and vital signs over a wireless network from a remote site to a hospital, in real-time, to gain access to pre-hospital emergency care (Nazeran et al., 2004).

The ability of mobile devices to support operating systems allowed software developers to create mobile applications (apps) on them, and healthcare related apps became popular on smartphones, tablets, iPhones, and iPads (Mosa et al., 2012, Ventola, 2014). In March of 2015, Saint Elizabeth, one of the largest healthcare providers in Canada distributed 5,000 tablets to healthcare providers in remote areas (Figure1.1). The tablets were connected to a broadband wireless network to allow for sending and receiving of data and were designed to be used by nurses, personal support workers, and rehabilitation therapists to provide home care (Saint-Elizabeth, 2015).

After smartphones and tablets were well established, the onset of wearable technologies, also known as wearables, brought healthcare even closer to the patient (Dobkin and Dorsch, 2011, Shu et al., 2015).These wireless devices detected a range of objective medical measurements, such as heart or pulse rate, blood oxygen saturation, blood pressure, or number of steps taken by a patient through watch-like devices (which were typically integrated with smartphones), or even devices that were worn directly on the body, such as medical sensors (Bellos et al., 2011, Dobkin and Dorsch, 2011, Naslund et al., 2014, Shu et al., 2015, Singleton et al., 2014, Sungmee and Jayaraman, 2014, Wile et al., 2014). In 2014, smartwatches (a type of wearable worn on the patients' wrists) that supported accelerometry (measurements of acceleration in G-force) were tested in a study for the diagnosis of different types of tremors (Wile et al., 2014). The device worked well

and could distinguish between different types of tremors in Parkinson disease (Wile et al., 2014).

In addition to wearables, mHealth opened up the opportunity to integrate geographic information systems (GIS) with mobile technologies (Figure 1.1). The idea was to capture spatial data generated by patients' physical activity, like tracking on a very detailed map. This data could be used, for instance, to measure psychological, social, and environmental influences on activity levels, or to help explain socio-demographic relationships (such as diseases in urban vs. rural areas) (Nhavoto and Gronlund, 2014).

In summary, The delivery of healthcare has undergone changes that are reflective of novel discoveries, access to technologies, demographic changes, and the overall rising costs of providing access to healthcare (Barnett and Jennings, 2009, Black et al., 2011, Finkelstein et al., 2006, Fleischmann et al., 2014, Kajbjer, 2008, Oh et al., 2005, Steele Gray et al., 2014). eHealth was created from, and continues to be created by, the confluence of different fields of science and engineering with opportunities presented by ongoing ICT development. By combining fields of science and technology in novel ways, eHealth has addressed, and continues to address healthcare challenges, such as improving medication selection and medication safety, in the pursuit of better patient outcomes.

1.2. eHealth

Governments in the US and the UK, as well as policy makers in many other countries consider eHealth to be a healthcare priority (Slight et al., 2014). However, barriers to eHealth implementation exist and have included legal, privacy, technological

and adoption issues, as well as the ability to share medical data efficiently (Ben-Assuli, 2014, Goetz Goldberg et al., 2012, Terry et al., 2014). In 2012, Canada trailed countries like the Netherlands and the United Kingdom when it came to eHealth implementation (Terry et al., 2012). In 2013, the absence of information management standards in primary healthcare in Canada led to a lack of system interoperability, which in turn hampered data retrieval and use (The College of Family Physicians of Canada, 2013). In the province of Quebec, in 2014, it was reported that medical data sharing was hindered by a lack of integration across the healthcare system (Fidelman, 2014).

The use of standards and the technological ability to share data efficiently are important because eHealth spans a wide range of healthcare data storage, data access, and data application projects (Al Mallah et al., 2010, Finkelstein et al., 2012, Goetz Goldberg et al., 2012, Shekelle et al., 2006). Research activities in eHealth can be depicted as layers of a pyramid where medical data becomes more integrated and interpreted as it approaches the top (Figure 1.2). Medical data collection includes automatically ordering tests and receiving test results, which EHRs keep track of, alongside individual patient's demographics (age, gender, medical history, previous diagnoses etc.), allergies, and formulary data (Al Mallah et al., 2010, Barnett and Jennings, 2009, Goetz Goldberg et al., 2012, Hsieh et al., 2012, Klein, 2010).

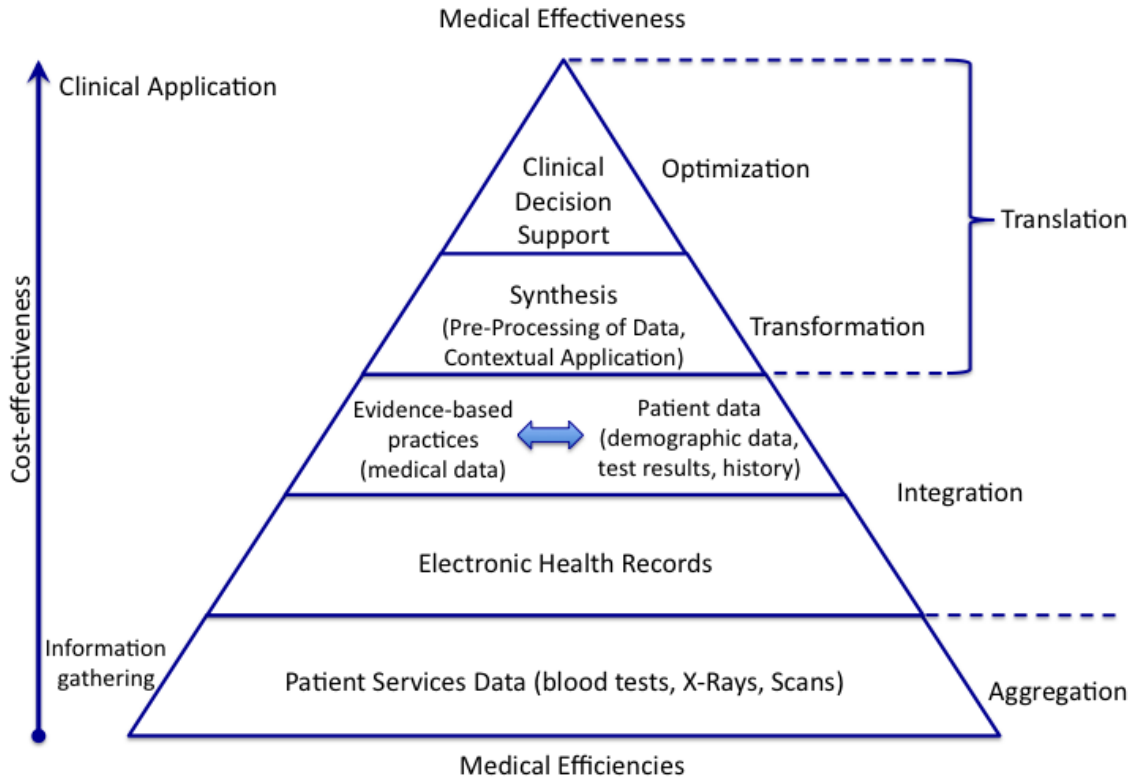

Figure 1.2. The eHealth pyramid. This figure depicts the automated process of collecting patient related information, placing it into a medical context and filtering it for use in effective medical decision-making.

1.2.1. eHealth and multi-disciplinary teams

The successful application of eHealth as a conduit for knowledge translation is a problem that requires a multi-disciplinary approach (Haynes et al., 2010, Sjostrom et al., 2014, van Rooij and Marsh, 2011) (Figure 1.3). Teams need to have the necessary expertise for, and understanding of, the context surrounding a specific eHealth project (Bouamrane and Mair, 2014, Trivedi et al., 2009, van Rooij and Marsh, 2011, van Rooij et al., 2012). The closer an eHealth project is to affecting front-line patient treatment the

more multifaceted the development and implementation team becomes (Bouamrane and Mair, 2014, van Rooij et al., 2012).

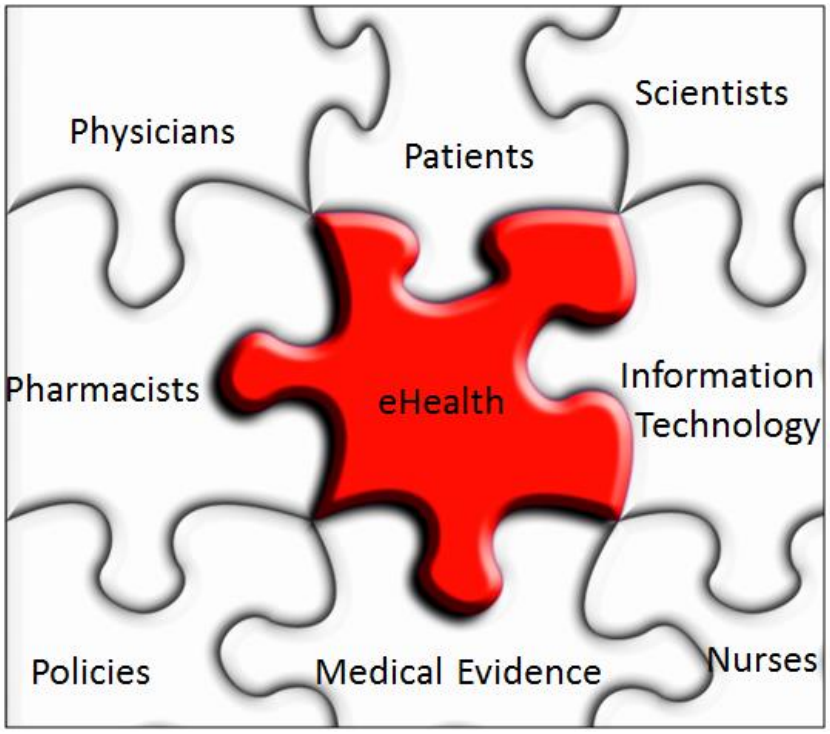

Figure 1.3. eHealth as an essential piece of the knowledge translation puzzle. Because many different fields are involved simultaneously, multidisciplinary teams with complementary backgrounds and expertise are needed to help solve issues regarding meaningful implementation of eHealth.

In a regional implementation through the National Health Services (NHS) in the Greater Glasgow area, an automated system was created to provide comprehensive patient data (access to medical history) via a clinical portal on an intranet between multiple hospitals (Bouamrane and Mair, 2014). This enabled effective surgical pre-assessment based on the availability of relevant medical information, and the ability to

communicate between members of a preoperative team. In order to achieve this, the multi-disciplinary development team included the preoperative team, software developers, management, and deferred to two levels of governance to help with the rationalisation and standardisation of the project (Bouamrane and Mair, 2014).

In 2013 eHealth was described as a cross-disciplinary cooperative effort combining health sciences, engineering, and social sciences, where business modeling related system designs to organizational context to meet functional expectations upon implementation (Van Velsen et al., 2013). eHealth projects were seen as multifaceted and addressed issues such as innovation, sustainability, relevance, and accountability (Sjostrom et al., 2014). At PoC implementation, case studies are needed to measure eHealth intervention outcomes as evidence of clinical utility, and these assessments need to be understandable by, and meaningful to partnerships of healthcare providers and decision makers (Haynes et al., 2010, Phillips et al., 2014, van Rooij et al., 2012). The realization of the potential of eHealth depends on concerted efforts of multi-disciplinary teams as they address medical, ethical, socio-economic and technological challenges (van Rooij et al., 2012).

1.2.2. CLINICAL DECISION SUPPORT (CDS)

CDS uses computers to provide healthcare providers with evidence-based knowledge and patient-specific information (Figure 1.2). This information is presented in a filtered and applicable format, to be integrated at the appropriate time into the healthcare providers' decision-making process. The overall goal of CDS is to enhance

healthcare (Cresswell et al., 2012, Osheroff et al., 2007, Overby et al., 2013, Paterno et al., 2012, Rothman et al., 2012, Welch and Kawamoto, 2013).

In order to support decision making, CDS applies computer systems to healthcare processes in different ways (Cresswell et al., 2012, van Rooij, 2007). For instance, CDS can alert healthcare providers through the use of computer-based alarms to incorporate patient information from the EHR (e.g. a prescription is contraindicated because the patient has an allergy to the medication that was just prescribed based on their EHR record) (Chaffee and Zimmerman, 2010, Cooley et al., 2012). Additionally, CDS can be used to automate evidence-based data, such as clinical guidelines, recommendations, dosing algorithms, and other contextually relevant information to turn it into actionable (curated, applicable and relevant) information at PoC at the exact moment when patient-care is being delivered (Bright et al., 2012, Cresswell et al., 2012, Hoffman et al., 2014). In combining and structuring clinical knowledge and other patient-related information (Figure 1.4), CDS can present alerts, interpretations, and recommendations to healthcare providers in their normal clinical workflow (Bright et al., 2012, dos Santos et al., 2014, Osheroff et al., 2007). In this manner, CDS can assist healthcare providers to make more informed decisions by providing rapid, efficient access to relevant medical data (Garg et al., 2005, Osheroff et al., 2007). Different types of CDS are suited to different healthcare settings. Software applications that provide CDS can either be stand-alone, integrated with EHRs, or integrated with other relevant databases (Barnett and Jennings, 2009, Collins and Elsaid, 2011, Cresswell et al., 2012, Drohan et al., 2009, Hum et al., 2014).

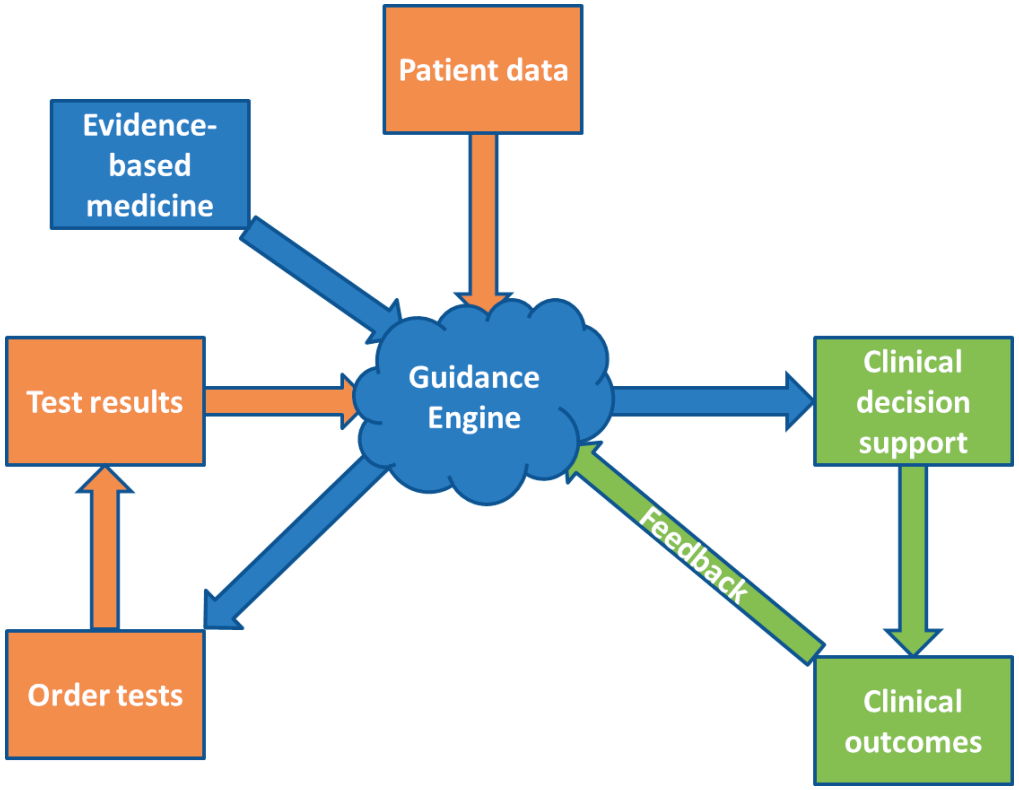

Figure 1.4. CDS can access data from multiple data sources. By combining, filtering and, structuring the data from different data sources, CDS can provide guidance to healthcare providers at PoC.

Automation of healthcare processes through CDS are considered to represent the highest functional level in eHealth (Figure 1.2), and implementation has been predicted to lead to an increase in the quality of provided services and cost savings (Jones et al., 2013, Phansalkar et al., 2011, Rothman et al., 2012, Ullman-Cullere and Mathew, 2011). The idea is that medical effectiveness is increased when evidence-based data is made available, interpreted, and clinically applied to reach an appropriate treatment (e.g. the

process of picking the right medication and establishing its safe use for a specific patient) (Black et al., 2011, Jones et al., 2013, Kroenke et al., 2013, Man et al., 2014, Mickan et al., 2013). In order to achieve this, CDS uses either passive or active decision support to inform healthcare providers of relevant information regarding medications or treatment regimens at particular times during the care process (Rothman et al., 2012).

1.2.2.1. Active CDS

Active CDS is provided by computerized systems that alert and prompt healthcare providers to use recommendations or interpretations, where these alarms and warnings are made possible through integration with an EHR, or other relevant databases that provide clinical knowledge (Chaffee and Zimmerman, 2010, Klein, 2010, Phansalkar et al., 2011, Rothman et al., 2012). Active CDS can have access to complete medical records of individual patients and this is known as an integrated CDS (Hum et al., 2014, Ullman-Cullere and Mathew, 2011). Computerized provider order entry (CPOE) systems are an example of systems that can provide active, integrated CDS. CPOE systems are electronic prescribing and dispensing systems, mostly used in hospital settings (McKibbon et al., 2011). Healthcare providers put their instructions for treatment and care of patients directly into CPOE systems when prescribing or dispensing medications, rather than using paper-based methods (e.g. charts, prescription pads) (Barnett and Jennings, 2009).

Through an assessment of the medications the patient is already taking, CPOE systems can alert healthcare providers about potential drug-drug interactions when they enter a new prescription for a specific patient into the system (Chaffee and Zimmerman,

2010). CPOE systems can also flag doses that seem to be outside of normal therapeutic ranges, or issue an alert when detecting duplication in medication prescriptions (Chaffee and Zimmerman, 2010, Curtain and Peterson, 2014, Kirkendall et al., 2014). CPOE systems are also used by pharmacists when dispensing medications (Chaffee and Zimmerman, 2010, Collins and Elsaid, 2011). The implementation and use of CPOE systems has been proven to reduce errors related to prescribing and dispensing of medications (Bubalo et al., 2014, Collins and Elsaid, 2011).

1.2.2.2. Passive CDS

Passive CDS use requires more effort when compared to active CDS systems (Garg et al., 2005). Healthcare providers need to recognize when a consultation of the computerized system would be useful, and they must make a specific request of the system before receiving advice (Rothman et al., 2012). A passive CDS may not be connected to an EHR or other relevant databases and does not issue alerts or prompts (Chaffee and Zimmerman, 2010). Furthermore, it can require the healthcare provider to enter some data to make a judgment (Gage et al., 2008).Using passive CDS, healthcare providers can access information on demand, such as patient order sets (a group of common clinical tests related to specific symptom presentations in patients) access to knowledge sources, or context-related guidelines and protocols (Chaffee and Zimmerman, 2010, Rothman et al., 2012). Passive CDS can sometimes be the optimum option because an unintended consequence that can limit the usefulness of active CDS is alert fatigue (Ash et al., 2007, Black et al., 2011). Alert fatigue can be experienced by

healthcare providers who are subjected to too many stimuli from the system e.g. an overabundance of alarms or prompts (Curtain and Peterson, 2014).

1.2.2.3. Hybrid CDS (Active CDS + Passive CDS)

The use of active or passive CDS is not mutually exclusive; they can both be used in the same CDS system. A 2010 study on CDS in a CPOE system at the University of Michigan Health System in the US found that the system contained both passive and active CDS (Chaffee and Zimmerman, 2010). In this case, the passive CDS component was used to look up medical names and terms, links to information, relevant results, and order sets. The active CDS component of the system alerted healthcare providers based on patient data, such as suspected errors in medical logic, allergies, deviations from the regular dose, and drug-drug interactions (Chaffee and Zimmerman, 2010).

1.2.2.4. CDS effectiveness

The effectiveness of CDS hinges on both clinical workflow integration and the ability to make context-appropriate information available in real-time (Ash et al., 2007, Cooley et al., 2012, Cresswell et al., 2012, Jones et al., 2013, Rothman et al., 2012, Trivedi et al., 2009). Specific actions based on automated recommendations improved medication selection, reduced medication errors, and avoided adverse drug events (ADRs) (Berner et al., 2006, Collins and Elsaid, 2011, Goldspiel et al., 2014, Osheroff et al., 2007). For instance, CDS use in pharmacy settings improved prescribing practice by increasing communication between pharmacists and physicians (Curtain and Peterson, 2014). Garg et al. found improvement in patient outcomes for both active and passive

CDS use, but noted that outcomes seemed to be inconsistent and deserving of more study (Garg et al., 2005). Osheroff et al. did not indicate if the systems they studied were active or passive, but found that CDS had been effective in improving patient outcomes at healthcare institutions and clinics, by giving healthcare providers timely access to medical knowledge (Osheroff et al., 2007). However, this direct link between CDS and clinical outcomes is not established in all research findings (Bright et al., 2012, Cresswell et al., 2012, Hibbs et al., 2014). Several studies have found that, although evidence on CDS systems showed that they were effective at improving health care processes in different medical settings and contexts, there was mixed evidence based on measurements of clinical outcomes (Bright et al., 2012, Cresswell et al., 2012, Hibbs et al., 2014). Patient benefits in these studies were found to be absent, modest or inconsistent, or simply not measured at all (Bright et al., 2012, Cresswell et al., 2012, Hibbs et al., 2014). Only a few studies exist on CDS effectiveness in community pharmacy practice, they show positive effects on prescribing practices but lack patient outcomes data (Curtain and Peterson, 2014).

1.2.2.5. CDS risks and unintended consequences

Although CDS systems can improve performance when used by healthcare providers, their introduction was accompanied by the risk of unintentionally introducing errors in the data (Ash et al., 2007, Kirkendall et al., 2014). CDS implementations can be costly, and hospitals and pharmacies need to budget for computer infrastructure, and especially training, as failure to do so may endanger patients by inadvertently introducing new safety issues (Slight et al., 2014). In addition to this, CDS implementation has also

led to the unintended elimination of, or shift in roles, and has introduced problems with keeping content up-to-date, lack of flexibility in systems, and alert fatigue (Ash et al., 2007, Black et al., 2011, Curtain and Peterson, 2014). Effective management of CDS applications is tied to careful selection and maintenance of content, combined with an understanding of the context of the technology implementation as well as the healthcare provider's workflow (Ash et al., 2007, Hoffman et al., 2014).

1.2.2.6. CDS based on locally applicable guidance

Locally developed guidelines and CDS for use in specific healthcare niches may hold greater relevance for healthcare providers and therefore facilitate uptake (Areskoug Josefsson et al., 2012, Drohan et al., 2009). A retrospective study showed that by understanding and responding to local types of pneumonia, locally-derived algorithms achieved better accuracy in predicting initial therapy in the treatment of late pneumonia (Becher et al., 2012). Although it has been argued that national guidelines simply need to be improved to better meet the needs of regional clinician decision makers, rather than having subsets of local guidelines (Lourenco et al., 2010).

In 1996, a 7 year descriptive epidemiologic study in a community hospital in Salt Lake City, Utah, assessed almost 64,000 patients that were prescribed antibiotics (Pestotnik et al., 1996). It found that applying locally developed guidelines based on healthcare providers' consensus, through computerized decision support, had a beneficial effect on both clinical and financial outcomes. The 7 year study found that using local guidelines the total costs of antibiotics was cut in half for the hospital pharmacy budget, antibiotic use and outcomes improved, and adverse effects due to antibiotic use in

patients were reduced by 30% (Pestotnik et al., 1996). Improved antibiotic use has a mitigating effect on the rise of antibiotic-resistant pathogens (Becher et al., 2012, Pestotnik et al., 1996, Sintchenko et al., 2005).

In a successful implementation of an active CDS in India, locally developed Indian guidelines and algorithms were made available in both Telugu, a local language, and English on tablets to provide information and decision support on cardiovascular disease (CVD) management. This was made available to public non-physician healthcare workers as well as physicians in rural Indian settings. This study evaluated the implementation and concluded that tablet-based CDS had the potential to help improve CVD outcomes in India within the primary health care system (Praveen et al., 2014).

In Belgium, locally applicable and developed medical guidelines (including treatments for most common diseases and symptoms, advice on diagnosis, and medication selection and dosage) were made available nationwide to physicians, alongside international guidelines, in both official languages (French and Dutch) (Van de Velde et al., 2013). This was done through a centralized database that integrated computer-based decision support with several commercially available EHRs (Van de Velde et al., 2013). A survey of a pilot implementation showed that physicians' attitudes towards this system were positive, and those who had used the system indicated that they would continue to do so (Van de Velde et al., 2013).

1.2.2.7. CDS and evidence-based medicine (EBM)

EBM is defined as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients (Sackett et al., 1996).

EBM faces barriers to uptake at PoC including healthcare providers' lack of awareness of guidelines and lack of time to keep up with new guidelines (Areskoug Josefsson et al., 2012, Trivedi et al., 2009). Furthermore, it may be impossible for healthcare providers to be continuously aware of all clinical guidelines, alongside patients' medical history, in the delivery of healthcare when using a paper-based system (Doebbeling et al., 2006).

A study done in the County of Jönköping in Sweden showed that healthcare providers there were not likely to increase their knowledge of EBM by themselves (Areskoug Josefsson et al., 2012). Out of 1,445 study participants only 11% indicated that they kept current with the latest clinical guidelines (Areskoug Josefsson et al., 2012). In order to improve patient care, healthcare providers will require more effective ways of incorporating evidence-based guidelines into their workflow (Areskoug Josefsson et al., 2012, Jones et al., 2013, Klein, 2010, Paterno et al., 2012). Computerized evidence-based guidelines present an alternative to paper-based guidelines and provide a solution to address barriers to uptake by improving dissemination and access (Devine et al., 2014, Osheroff et al., 2007, Trivedi et al., 2002). CDS can be used to automate and deliver interventions such as recommendations, guidelines, and algorithms to healthcare providers so they can better integrate them when providing care for patients (Figure 1.5) (Bright et al., 2012, dos Santos et al., 2014).

In clinical settings, EBM is more easily integrated when it fits well within the care-delivery process (O'Connor et al., 2013, Van de Velde et al., 2013). Using CDS researchers can insert EBM into the clinical workflow at the exact place and time, where and when decisions are made (Trivedi et al., 2009, Van de Velde et al., 2013).

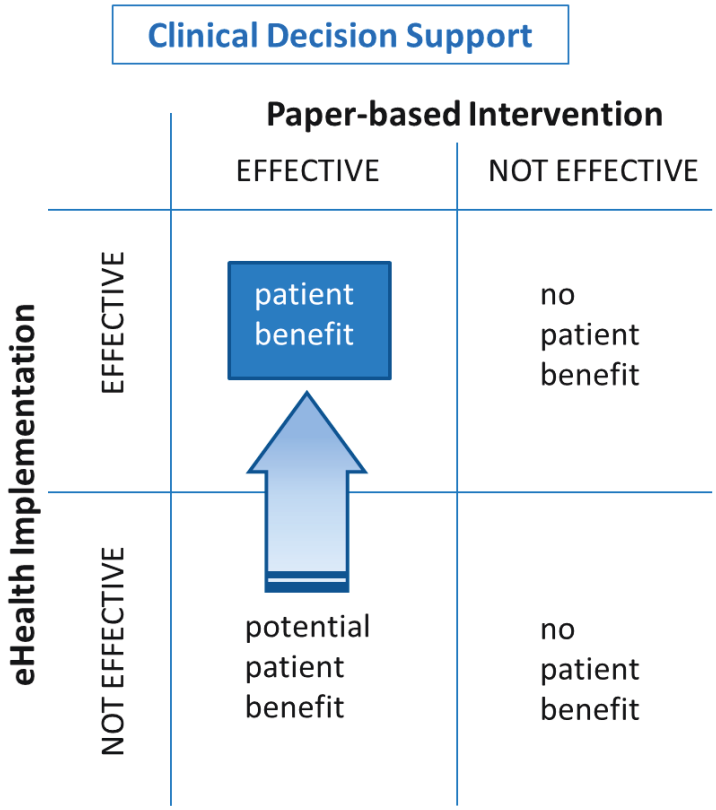

Figure 1.5. eHealth implementation can incorporate paper-based EBM interventions into CDS. Using CDS, EBM guidelines can be more effectively applied to patient-care.

1.2.2.8. Clinical decision support systems (CDSS)

Clinical Decision Support Systems (CDSS) is a term that refers to the computer architecture of specific software applications providing CDS. This architecture has a centralized database, focuses on integration and interoperability with healthcare systems and health related data repositories, and by design can offer connectivity to multiple devices (e.g. laptops, desktops, smartphones, tablets) (Sartipi et al., 2011, Trivedi et al.,

2009). In the literature CDS and CDSS are sometimes used interchangeably. However, the architecture of CDSS is what enables the integrated use of up-to-date EBM guidelines and algorithms across a healthcare organization, and it is this capacity that is seen as an essential part of high-quality medication management (Taba et al., 2012).

A review in 2012 found that CDSS were mentioned in roughly one third of the published eHealth literature (Cresswell et al., 2012). However, it is not clear whether the small number of CDSS proved to improve quality and safety would continue to do so if they were used outside the context in which they were originally developed (Black et al., 2011). A 2014 review of 8 case studies in pharmacy showed that CDSS had affected prescribing practices, improved medication safety, and brought about increased communication between pharmacists and physicians, or between pharmacists and patients for education purposes (Curtain and Peterson, 2014).

1.2.2.8.1. CDSS architecture

CDSS architecture creates a CDS software application capable of supporting multiple methods of access by different mobile or non-mobile devices to a centralized database. In order to meet the functional goal of providing decision support, CDSS architecture combines software and hardware in an interconnected manner. The CDSS architecture consists of three parts (Sartipi et al., 2011, Trivedi et al., 2009).

1. A user interface: User interfaces are the only part of the CDSS that are visible to the healthcare provider. Possible user interfaces are desktops, laptops, tablets, and smartphones.

2. A guidance engine: The guidance engine is a software system that prepares the data for presentation in the user interface by applying logic (e.g. clinical algorithms, clinical guidelines, or heuristics) to transform the data stored in the database.
3. A database: The database is used for both storage and retrieval of medical data relevant to the CDSS.

As shown in Figure 1.6, the user interface (presentation layer), guidance engine (logic layer) and database (data layer) of the CDDS architecture model can be implemented as a three-tier application, where functionalities can exist in different places in the network (e.g. the guidance engine could be located on a different server from the database) (Chu and Cesnik, 2000).

Other approaches to implementation of CDSS have included an agent-based architecture (agents are small self-contained software applications that can interact with other agents in a computer system to form a larger software application) and a service oriented architecture whereby the software application invokes smaller instances of services which have been coded into the system (e.g. check if patient requires dose adjustment, or check for drug-drug interactions) (Koutkias et al., 2014, Wilk et al., 2013). CDSS can transfer EBM to a device (e.g. smartphone, tablet, desktop) that is most closely integrated into the healthcare providers' natural workflow (Wilk et al., 2013).

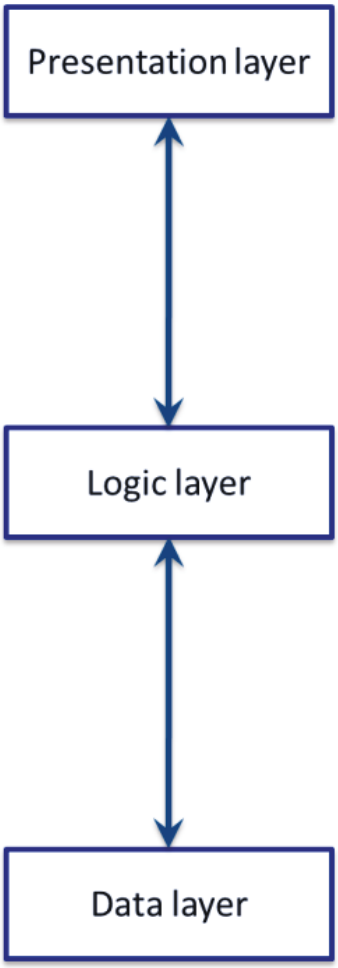

Figure 1.6. CDSS as a three-tier architecture. This multi-layered approach to software development consists of interconnected presentation, logic and data storage layers to optimize speed, consistency and applicability of data transfers.

1.2.2.8.2. CDSS development

There are many obstacles to the development, implementation, adoption, and acceptance of CDSS e.g. data creation, storage, interpretation, ongoing revision, appropriate visualisation and presentation, adequate response times, ease of use, as well

as access to expertise (Charani et al., 2013, Lewis and Wyatt, 2014, Mosa et al., 2012, van Rooij, 2007). CDSS are complex systems that require multi-disciplinary teams for development (De Bus et al., 2014, Fleisher et al., 2014, van Rooij and Marsh, 2011). The clinical task that the CDSS is aiming to optimize needs to be fully understood, as well as the clinical environment where the implementation is attempted (Ash et al., 2007, Wilk et al., 2013). Healthcare providers' involvement can help with both assessing relevance and application of medical data (Cresswell et al., 2012), and relating the time or resource constraints inherent in healthcare settings (Ash et al., 2007, Taba et al., 2012, Trivedi et al., 2009, Wilk et al., 2013).

Alongside the input of a medical expert, the multi-disciplinary team requires software developers with a range of skills including database development, algorithmic design, and multi-tier software application development, to fulfill the requirements posed by the CDSS architecture (Al Mallah et al., 2010, De Bus et al., 2014, van Rooij and Marsh, 2011, van Rooij et al., 2012). Technological barriers to CDSS development include the integration of large heterogeneous datasets (e.g. Big Data, structured and unstructured data, and incomplete or deficient data), disparate data sources (e.g. reference guides, protocols, guidelines, recommendations, published clinical data, and schematics), and complex algorithms (e.g. dosing algorithms, genomic algorithms) (Crews et al., 2012, Welch et al., 2014). Once the data is integrated in a centralized database its delivery and visualization must be focused (too much information is distracting and time consuming), actionable, and intuitive (easy to find and use) (Sartipi et al., 2011, Trivedi et al., 2009).

Processing and filtering of data stored in the CDSS database often requires the use of complex algorithms for delivery and display of actionable knowledge (Crews et al., 2012, Finkelman et al., 2011, Seixas et al., 2014). Furthermore, CDSS are never static and will have to implement administrative access (e.g. a password protected website) to allow healthcare providers to update the evidence-based data, and have flexible source code for software developers to modify or fine-tune algorithms (Jones et al., 2013, Paterno et al., 2012, Rothman et al., 2012).

The entire process of CDSS development can be time-consuming and prone to trial and error approaches as some parts of these systems may require new development (Haux, 2006, Trivedi et al., 2002, Trivedi et al., 2009, van Rooij, 2007). However, considerable overlap exists between individual CDSS projects (Cresswell et al., 2012, McKibbon et al., 2011, Wilk et al., 2013). Additionally, development of CDSS often encounters the same or similar issues (Bright et al., 2012, Cresswell et al., 2012, Drohan et al., 2009, Hum et al., 2014, Kilsdonk et al., 2013, Koutkias et al., 2014, Marsh and van Rooij, 2009, McKibbon et al., 2011, Patapovas et al., 2014, Rezaei-Yazdi and Buckingham, 2014, Trivedi et al., 2002, Trivedi et al., 2009, Ullman-Cullere and Mathew, 2011, van Rooij, 2007). Barriers and facilitators to development are shown in Table 1.1. Furthermore CDSS share common architecture requirements (Sartipi et al., 2011, Trivedi et al., 2009). This suggests that software could be shared among CDSS projects. Unfortunately, CDSS development is often tightly integrated with existing eHealth systems (Chaffee and Zimmerman, 2010), which hampers re-usability of successful implementations (Black et al., 2011). A strategy built on the use of open-

source code (code that can be freely re-used by others) to speed up CDSS development has been suggested (Wilk et al., 2013).

Barriers	Facilitators
Absence of standards	Interoperability
Absence of guidelines	Healthcare provider as a member of the team
Economic (costs, resources)	Multi-disciplinary team
Lack of access to data sources	Access to design, architecture, algorithms, code
Lack of consensus	Fit within the clinical workflow
Lack of customization options	Intuitive, ease of use
Lack of technical ability	Speed, responsiveness
Lack of clinical ability	Ability to regionalize data application

Table 1.1. Barriers and facilitators for CDSS development.

1.3. mHealth

The use of mobile and wireless technology to achieve healthcare objectives has a latent ability to profoundly change the delivery of care in global health systems (World Health Organization, 2011a). A relatively recent and evolving model in the dispersal of healthcare services and information, mHealth, through systems built around wireless communications devices, aims to improve patient health outcomes (Klonoff, 2013). Mobile health or mHealth has been defined as a subset of eHealth that is driven by both the penetration and exceptional growth of mobile technology use (currently there are more than 5 billion mobile phone users globally (Kallander et al., 2013)), and is based on the development of software applications (apps) on a mobile platform to provide health

services and manage patient information (de la Torre-Diez et al., 2015, Kallander et al., 2013, Payne et al., 2012). A somewhat broader view is that mHealth is indeed a sub-segment of eHealth but it is one that provides medical and public healthcare practice through mobile devices, such as PDAs, mobile phones, smartphones, and (wearable) patient monitoring devices. However, mHealth can also use laptops and tablets, and while it can indeed be based on apps, it can also use telephony, short messaging service (SMS, also known as texting), or videoconferencing (Brinkel et al., 2014, Klonoff, 2013).

The application of mHealth has the potential to become a disruptive innovation (it may replace or displace earlier technologies) in healthcare and greatly affect medical workflows (Weinstein et al., 2014). According to UN estimates, half the people living in remote areas now have a mobile phone (World Health Organization, 2011b) and worldwide there are about 2.3 billion mobile devices (e.g. smartphones, tablets) capable of running apps with broadband (high-throughput) access to data (International Telecommunication Union, 2014). Furthermore, smartphones outnumber computers almost 2:1 in low and middle income countries (International Telecommunication Union, 2014).

Building on the rapid expansion of wireless network coverage and mobile device use among varied populations, mHealth has an opportunity to improve the delivery of healthcare services to both individuals and communities (Gurman et al., 2012, Kallander et al., 2013, Lewis et al., 2012). For instance, tablets with broadband access have been used by healthcare providers in Canada to improve home care in remote communities (Saint-Elizabeth, 2015), and in India to access best practices in the treatment of CVD in

rural settings (Praveen et al., 2014). Not all mHealth use is based on large physical distances, research projects have also included home-monitoring of patients for cancer medication side-effects, the use of smartwatches in disease diagnosis, and the development of a smartphone app to give advice on pain management to adolescents with cancer (Jibb et al., 2014, Sobnath et al., 2014, Wile et al., 2014).

Alongside novel projects, mHealth can also be added to existing eHealth projects (Nhavoto and Gronlund, 2014). Overall, opportunities are rife for mobile technologies to be used in the delivery of healthcare (Table 1.2). Connected smartphones, tablets, iPhones, iPads and other mobile devices with operating systems provide a development platform for mHealth apps (Table 1.2). However, development teams need to be aware of obstacles to the successful introduction of mHealth, e.g. ethical issues, establishing clinical utility, and cost-effectiveness when selecting technologies (Klonoff, 2013).

Application / Technologies	Distance-based Care	Education	Monitoring	Medication Adherence	Goal-Tracking (physical therapy)	Patient-centric Use	Decision Support
Laptop	x	x				x	x
Desktop	x	x				x	x
Smartphones	x	x		x	x	x	x
Smartwatch			x	x	x		
Fitbit, step counters					x		
Tablet, iPad	x	x				x	x
Wearable sensors			x		x		
Video-conferencing	x	x				x	
GIS			x		x		
Smartcard			x			x	

Table 1.2. There are now a multitude of technologies readily accessible to both healthcare providers and patients/care-givers to allow tracking and interventions at both point-of-care and at home. Each technology has strengths and weaknesses as a healthcare tool. GIS: Geographic Information Systems.

1.3.1. MOBILE APPLICATION (APP) DEVELOPMENT

Smartphones have provided a platform for downloadable mobile apps. The low-cost of, and ease of access to this platform have resulted in medical app development intended for use by healthcare providers, as well as by the general patient population (Connor et al., 2014a, Marcano Belisario et al., 2013). Mobile app use is pervasive among healthcare providers in general, and use is considered greater among younger healthcare providers (Dempster et al., 2014). However, one study indicated no effect of age on smartphone ownership (Ventola, 2014).

The desire of healthcare providers to use medical apps is great, both for reference and CDS purposes, however the currently available apps are often deemed of poor quality (Franko and Tirrell, 2012). This problem could be remedied by the involvement of medical professionals in content generation, validation, peer review, and regulatory oversight of healthcare-related apps (Connor et al., 2014a, Dempster et al., 2014). The US Food and Drug Administration (FDA) currently reviews around 20 medical mobile apps per annum (Lippman, 2013).

Medical apps have the potential to assist healthcare providers in their day-to-day activities. Smartphones and tablets are increasingly used as part of clinical care delivery (Burdette et al., 2012, Lin et al., 2014, Lippman, 2013, Saint-Elizabeth, 2015). The current number of apps in medical or health related fields range from estimates of 17,000 to at least 40,000; however, less is known about healthcare providers' actual use of these tools, and if there is a measurable impact on quality or efficiency of delivery of care (Lippman, 2013, Man et al., 2014). One problem affecting cross comparisons is the fact

that medical mobile apps fall into different categories of application and encompass a wide range of use cases e.g. medical apps intended for patient use, medical reference apps for healthcare providers, educational material apps for medical student use, calculator apps for medication dosing, as well as CDS apps (Aungst, 2013, Ventola, 2014).

1.3.1.1. Mobile apps for patient use

The World Wide Web (WWW) is commonly used by patient populations to get more information on health related issues. This 'googling' can lead to highly inaccurate results, as in a study that showed that neither Italian women of childbearing age, nor Italian healthcare professionals could find data online in keeping with established international guidelines on the topic of preconception (health issues that are important to women trying to get pregnant) (Agricola et al., 2013). Issues also existed when using the WWW to get more information on Caesarian sections in Brazil, as researchers there found that information was incomplete, especially regarding clinical practice, short-term and long-term maternal risks, and potential benefits of a Caesarean section (Fioretti et al., 2014). Additionally, a British study found that questions concerning mumps, measles and rubella, autism, the human immunodeficiency virus (HIV), and breast feeding were often answered incorrectly when using Google to look for issues affecting children's health (Scullard et al., 2010).

In an effort to get more accurate and curated data on diseases and therapies, patients are accessing specialized patient apps on smartphones and tablets. Unfortunately, the standard of quality of mobile medical apps and the accuracy of the data delivered by

these apps varies wildly (Lippman, 2013). In Spain, a study looked at the quality of information in smartphone apps aimed at HIV-infected patients. A total of 41 Smartphone apps were evaluated by 17 different experts with a standardized questionnaire based on guidelines for mobile medical apps put forward by the FDA, the Agency of Health Quality in Andalusia, and Happtique (an app certification program) (Robustillo Cortes Mde et al., 2014). After evaluation only one app rated as excellent and 27 apps failed to reach minimum standards for quality (Robustillo Cortes Mde et al., 2014). A 2013 study on asthma apps found that using smartphones and tablets for self-management of asthma by patients was not yet advisable, citing a lack of studies that created a convincing evidence base for doing so (Marcano Belisario et al., 2013). This type of finding was echoed by a Norwegian study that tested the use of a daily self-management app for type 2 diabetes, to try and improve elevated glycated hemoglobin A1c (HbA1c) levels in patients (Holmen et al., 2014). After 120 patients used the app for one year there was no significant decrease in HbA1c levels, in either the app intervention or the control group (Holmen et al., 2014). For patients with type 2 diabetes self-monitoring is associated with depression, so this particular intervention may in fact be harmful for some (Mendoza and Rosenberg, 2013).

1.3.1.2. Mobile apps for medical reference material

Mobile app use for medical reference material was the first mHealth field to become well established (Lippman, 2013). Medication references provided information such as medication name, indications, dosages, drug-drug interactions, cautions, and contraindications. The most used reference app in the United States is Epocrates but

many others exist e.g. Medscape, Micromedex (Lin et al., 2014, Lippman, 2013, Mosa et al., 2012, Ventola, 2014). One study in 2012 reported that ninety percent of physicians in the United States used mobile device apps to access information on medications (Mosa et al., 2012). An obvious benefit was the ability to provide downloadable updates, which could be accessed easier and faster than new editions of a printed work (Murfin, 2013, Payne et al., 2012).

Burdette et al found that there were well-referenced apps available for use in infectious disease management, but that no single app covered all use cases (Burdette et al., 2012). Some reference apps included multiple medical calculators (e.g. dose by weight calculator, body mass index (BMI) calculator) (Mosa et al., 2012, Ventola, 2014); however, there was no regulation of the information that was included in these apps, so assessment of the validity of this data was difficult (Murfin, 2013). An evaluation of available smartphone medical apps for neurosurgery identified stumbling blocks in the absence of a mechanism to verify the accuracy of medical information, and a lack of technical validation of apps (Zaki and Drazin, 2014). More oversight was recommended for reference apps being used for diagnoses and treatment decisions (Moodley et al., 2013).

1.3.1.3. Mobile apps for medical education

In Singapore, a study showed that psychiatrists were able to put textbook content alongside videos on a mobile compatible website. This was done using commonly available platforms that did not require prior technological training. Psychiatry students responded positively to the prospect of being able to access mobile course content

through this development (Zhang et al., 2014). In Germany, students expressed that they would like to see more videos and multimedia, alongside other interactive content, when accessing medical textbooks as mobile apps (Sandholzer et al., 2014).

In order to reduce infant mortality, a project geared to involve expecting fathers in prenatal health used tablet devices to help improve birth outcomes through targeted education of men with low health-literacy in the United States (Mackert et al., 2014). Of particular note here is that education of expectant fathers is a proven strategy in the developing world, which shows that lessons learnt in low and middle income countries may find application in first world nations (Mackert et al., 2014). In dentistry, mobile apps are increasingly used by students, patients and dentists to access information for educational purposes (Khatoon et al., 2013). However, the medical information provided for this purpose needs to be evidence-based and rigorously peer-reviewed to be valid (Khatoon et al., 2013).

1.3.1.4. Mobile CDS apps

Providing decision support is considered a high-level activity for medical data translation (Rothman et al., 2012). Indeed, medical professionals indicate that they would like to use more CDS apps, but note that there is currently a deficiency of high-quality decision support apps available (Franko and Tirrell, 2012, Tripathi et al., 2014). In one study in 2014, 85% of 115 urologists that responded to a survey expressed interest in decision-making apps, and 49% already used urological apps (Dempster et al., 2014).

In Sweden, an app called LIFe-reader is a CDSS used by nurses in geriatric homecare (Johansson et al., 2010). With the LIFe-reader app nurses can use a smartphone

to scan the European Article Number (EAN) on the medication package to access information on a specific medication. This system can also automatically flag drug-drug interactions, inappropriate medications, or duplication of medications (Johansson et al., 2010).

In a study on the treatment of depression, 14 physicians and trainees used a smartphone app with a symptom-based approach to select antidepressants (Man et al., 2014). The app provided evidence-based recommendations and medication monographs, and was found to be an effective tool for increasing confidence level in antidepressant drug selection by educating physicians (Man et al., 2014). However a study that evaluated 159 different apps related to neurosurgery found that, despite a large potential pool of apps, there was an absence of quality content for decision support (Tripathi et al., 2014).

1.3.2. WEARABLES

Wearable wireless technologies, such as smartwatches, electronic wristbands, and sensors allow both healthcare providers and patients to monitor vital signs and symptoms (e.g. blood pressure, heart or pulse rate, cardiac output, electrocardiograms, blood oxygen saturation, activity level) for diagnostics or chronic disease management at the patient's home (Bellos et al., 2011, Dobkin and Dorsch, 2011, Naslund et al., 2014, Shu et al., 2015, Singleton et al., 2014, Sungmee and Jayaraman, 2014, Wile et al., 2014). Wearables are extremely portable devices capable of continuously monitoring patients during their normal daily routines (Wile et al., 2014). These devices may decrease the

need for hospital visits and are worn on the patients' body and enable personalized information collection (Dobkin and Dorsch, 2011, Sungmee and Jayaraman, 2014).

Examples of wristband devices for single purpose activity tracking are the watch-like FitBit and FuelBand, which measure fitness related data such as heartbeats and the number of steps taken (Naslund et al., 2014). Other examples of wearables are mobile medical sensors which can measure heart or pulse rate and blood oxygen saturation, or bands which can measure blood pressure (Shu et al., 2015). Smartwatches have a wider range of applicability because they are programmable, and support the use of apps. (Naslund et al., 2014, Wile et al., 2014).

Wearables are perceived as medically useful (Bellos et al., 2011, Brito et al., 2010, Castellaro et al., 2011). In one study, a group of obese patients with schizophrenia spectrum disorders, bipolar disorder, or major depressive disorder used either a Fitbit or Fuelband coupled with iPhones (the use of iPhones was necessary to access an app that connected with the wrist-worn devices) as an aid for activity tracking to promote weight loss (Naslund et al., 2014). The study showed the feasibility of this approach as well as acceptance by patients, who were very satisfied with using mobile technology to increase their physical activity level, noting ease-of-use, goal-setting, self-monitoring, and social connectivity of devices (Naslund et al., 2014). A medical need for wearable devices that could identify and track behaviors in autistic children was identified, as wireless physiological monitoring has the potential to provide predictors of unwanted behaviors during their development (Singleton et al., 2014).

Wearables put out continuous data streams (and many wearables on the same patients will have many data streams) that can be transmitted from the home directly, via Wi-Fi or a smartphone, to a remote data analysis server, to be combined and interpreted by real-time active CDS into understandable information for healthcare providers to act upon (Dobkin and Dorsch, 2011). An example of this is a prospective study that created a prototype wearable focused on real-time epileptic seizure prediction. The wearable device sent out a stream of data for monitoring purposes, which was picked up by different seizure prediction algorithms run on a portable PC, the goal of this study was to create a device as part of a larger project to determine which of one the algorithms most accurately predicts patient seizures (Castellaro et al., 2011).

1.4. Medication Selection

In 2012 in England, prescribing was the most common healthcare intervention across all healthcare sectors (Prescribing and Primary Care Services Health and Social Care Information Centre, 2013). In 2013, Canadians spent an estimated $34.5 billion on medications, of which an estimated $29.3 billion was spent on prescribed medications (Canadian Institute for Health Information, 2014). Despite the wide use of medications, many issues exist whereby prescriptions for medications for specific patients may be suboptimal, inappropriate, and even lead to serious ADRs and hospitalisation (Chin et al., 1999, Gallagher et al., 2007, Marengoni, 2013, Routledge et al., 2004).

Prescribers are faced with the need to make a correct decision when writing a prescription for a specific patient (Moskowitz et al., 1988). In order to inform this

decision, prescribers consider both the patient and the different medications that are available (Fischer et al., 2002). After a diagnosis has been established (e.g. based on patient provided information, physical exam results, laboratory results, suspected side-effects of medications the patient is already taking etc.), prescribers evaluate possible medications (Cornell and Dorsey, 2012). In the process of medication selection, prescribers take in account, among other factors, patient demographic data, disease symptoms, family history, environmental factors, renal and hepatic function, comorbidities, allergies and concurrent medications. The characteristics of medications themselves are simultaneously under consideration, concerning, for instance, diminished efficacy with long term use, or the assessment of rapid onset versus longer-acting agents (Gurwitz, 2004). In this process, the prescriber needs to be aware of the needs of special populations such as pediatric populations, pregnant women, and the elderly as dose adjustments may be necessary (Gurwitz, 2004, Routledge et al., 2004). Studies show that elderly patients are at particular risk for medication selection errors, because in this group the toxicity of medications taken together may be greater than the cumulative individual toxicity of each medication; adding another medication to this list presents therefore a larger than expected chance of toxicity which needs to be weighed in the medication selection decision (Gurwitz, 2004, Marengoni, 2013, Routledge et al., 2004).

While trying to decide on the most appropriate medication for a patient, prescribers try to be informed of all of the co-factors that influence this decision, and access to medical records provided by EHRs has proved to be helpful (Barnett and Jennings, 2009, Bouamrane and Mair, 2014, Drohan et al., 2009, Goetz Goldberg et al.,

2012, Klein, 2010). In addition, the complexity of medication selection has led to the use of CDS to more directly aid in the process of establishing the right medication for a specific patient (Baysari et al., 2011, Berner et al., 2006, Garg et al., 2005, Koutkias et al., 2014, McKibbon et al., 2011, Routledge et al., 2004). In one study, medication selection was improved by a CDS that was provided on a handheld PDA (Berner et al., 2006). This CDS included a prediction rule to assess nonsteroidal anti-inflammatory drug (NSAID) related gastrointestinal risk and subsequently issued recommendations. The system was shown to improve prescribing practices in a randomized control trial (Berner et al., 2006).

CPOE systems with CDS have also been used to improve medication selection (Lainer et al., 2013, McKibbon et al., 2011). A CDS integrated with CPOE flagged nine potentially inappropriate medications for elderly patients (the average age of patients in the study was 74 years) and recommended alternative medications. This approach was successful, physicians that used the system reduced prescriptions of potentially inappropriate medications to seniors (Terrell et al., 2009). In a randomized trial in an emergency department a CDS that was integrated in a CPOE was found to be effective in helping to decrease excessive dosing of medications in older patients with renal insufficiency (Terrell et al., 2010).

1.4.1. PHARMACOGENOMICS

Many medications are prescribed on a one size fits all model (Marengoni, 2013). However, it is impossible to predict what effect a given medication will have in a particular patient. Patients may benefit from a medication, respond partially or not at all,

or experience toxicity and ADRs (Evans and McLeod, 2003). Pharmacogenomics helps to explain this large individual variability in response to any given medication by incorporating the genetic background of individuals into medication selection (Evans and McLeod, 2003).

Individuals have genetic variation that affects pharmacokinetics, the absorption distribution, metabolism, and excretion (ADME) of medications, as well as pharmacodynamics, and the total amount of drug target available (Engen et al., 2006). Genomic research can find single nucleotide polymorphisms (SNPs), which are one base DNA variations in genomic sequence (the most common variation in populations), as well as deletions and insertions of nucleotides, that can affect protein expression, structure, and function, with specific relevance to a patient's medication response (Carr et al., 2014, Gage et al., 2008, Olund et al., 2009). These variations at the DNA level can help to predict the efficacy of certain medications, or the efficacy of the medication at certain doses (Gage et al., 2008, Marsh, 2007). It can also determine that a particular medication is not going to have a therapeutic effect in a specific patient, or the likelihood of toxicities, based on their genetic profile (Evans and McLeod, 2003, Marsh, 2007). Of course, other patient characteristics (e.g., comorbidities, drug interactions, compliance and environmental effects) also play a large role in establishing the efficacy of medications. However, pharmacogenomics allows healthcare providers to more narrowly define the selection of medications and dosing to an individual or targeted population group (Crews et al., 2012, Evans and McLeod, 2003, Marsh and van Rooij, 2009, McMahon and Insel, 2012).

The incorporation of pharmacogenomic data and tests has been proven to be medically effective (Bombard et al., 2013, Carr et al., 2014, Drohan et al., 2009, Gage et al., 2008). Genomic data that can guide medication selection for patient care has been tested and validated, and pharmacogenomic tests have been approved for public use by regulatory agencies such as the US FDA (Marsh, 2007, van Rooij et al., 2012). Nevertheless, routine use of these tests in clinical settings has not been widely established (Bombard et al., 2013, Crews et al., 2012, van Rooij et al., 2012). There is often a lack of knowledge on how to interpret pharmacogenomics data to inform medication and dosing choices in clinical practice (Bombard et al., 2013, Crews et al., 2012, Mitropoulos et al., 2012). Thus, major stumbling blocks are the ability to process genomic data, and to provide clinically interpretable guidance on medication selection to healthcare providers in a realistic time frame (Crews et al., 2012, Tutton, 2014, van Rooij and Marsh, 2011).

The absence of storage, analysis and interpretation systems accessible at PoC have hampered the wide-scale uptake of pharmacogenomics (Brito et al., 2010, Marsh and van Rooij, 2009, Musen et al., 2014, van Rooij and Marsh, 2011). Improved storage and processing are required to translate genomic sequence information into personalized medicine (Crews et al., 2012, Welch et al., 2014). Additionally, information on pharmacogenomics, such as drug recommendations and adverse effects, will need to be linked to a list of prescribed drugs for each individual (Alvan et al., 2013). The problem can therefore be divided into two parts: one is the storage and analysis of large amounts of genomic data, the other is integration and the interpretation of this data at PoC (Crews

et al., 2012, Glauber et al., 2014, Marsh and van Rooij, 2009, van Rooij and Marsh, 2011).

1.4.1.1. Pharmacogenomics in the developing world

Pharmacogenomic factors that can influence medication selection in patients can be measured by regulatory approved tests (Marsh and van Rooij, 2009, van Rooij et al., 2012). In developing countries this need for testing presents a hurdle to access, as genomic tests are costly (Mitropoulos et al., 2011). However, a current workaround may be offered by treating on a population rather than an individual level, and prioritizing medications contained exclusively within national drug formularies to get some, if not all, of the pharmacogenomic benefits (Mitropoulos et al., 2012, Roederer and McLeod, 2010). As such, this is a disruptive approach, using self-reported ethnicity as a significant predictor of metabolism, transport, and drug target genetic variability for individual drugs and dosages (Engen et al., 2006).

In every country, local (sub) populations exist with identifiable genetic variability due to a different prevalence of pharmacogenomics markers known to affect medication's success rate (Marsh, 2008). By applying knowledge of the genetic background of (sub) populations to prioritize medication selection from the World Health Organization's (WHO) essential medicines list (EML), better patient outcomes could be achieved on a population level (Roederer et al., 2011b). The EML is a list of medications that each country, regardless of their economic status, must carry (Roederer et al., 2011b). The use of medications on the EML could be rationalized if selection could be based on the overall risk represented by frequency of polymorphisms in the key genes in each country

(Mitropoulos et al., 2011, Roederer et al., 2011b). Based on this approach, to help developing countries use genetic information to improve National Drug Formulary decisions, guidelines on common diseases (e.g. malaria, helicobacter pylori, gout, and rheumatoid arthritis) have been created to translate genomic sequence into meaningful clinical guidance (Roederer et al., 2011a). However these paper-based guidelines are not standardized, and are difficult to update and disseminate, CDS is therefore also needed to pre-process and translate the global data on pharmacogenomics into locally applicable and interpretable guidance (van Rooij et al., 2015c).

1.4.1.2. Big Data

In 2004, BIOMED, a study funded by the European Commission (EC) to look at different issues and challenges of both medical informatics and bioinformatics, found that with the onset of large-scale genomic research there was going to be considerable overlap between the two disciplines. They both struggled with the concept of translating genomic knowledge to point-of-care (Martin-Sanchez et al., 2004). By 2007, advances in genomics had led expectations to rise about their integration into real-world health care and disease prevention. Evidence-based guidelines on the application of pharmacogenomic data were rare at that point, and attempts to move them into healthcare practice encountered barriers, including a paucity of research needed to support translation of genomics into human health (Khoury et al., 2007).

In healthcare, Big Data refers to the extremely large data sets generated by genomic research and the complexities of storage and the analysis of this data to reveal associations relating to medication use and human health (Merelli et al., 2014). Genomic

data collection has intensified through the use of Next Generation Sequencing (NGS) technologies (Abul-Husn et al., 2014, Carr et al., 2014). In comparison to traditional Sanger sequencing, NGS is high-throughput, and allows for whole genome sequencing (WGS; determining the DNA sequence of the entire genome of an individual), through faster, cheaper, and more effective sequencing of DNA and RNA (Carr et al., 2014, Welch et al., 2014). As costs keep falling and technology develops, WGS may become cost-effective enough to perform at PoC (Carr et al., 2014). A preliminary approach to this is pre-emptive genotyping (prospective genotyping) where one blood test is used to genotype patients for multiple polymorphisms (genetic variation e.g. SNPs) within genes associated with ADME (O'Donnell et al., 2014, Pulley et al., 2012). The idea is that one large prospective test pre-empts multiple smaller genetic tests and could have repeated utility (O'Donnell et al., 2014, Pulley et al., 2012). Results from the prospective test could be archived and accessed later if the medication context for that specific patient would require it (e.g. a new prescription, a multi-medication review), providing that interpretative guidance for the relevant polymorphisms would be available at that time (O'Donnell et al., 2014, Pulley et al., 2012). This could indeed lead to re-use of the same prospective test; however, with the important caveat that in order to apply pharmacogenomic knowledge regarding the stored SNP data, guidelines must exist (Al Mallah et al., 2010). In order to allow for the re-use of prospective genomic tests, pre-emptive genotyping requires significant automation of processes (e.g. storage, CDS) (Crews et al., 2012, Hoffman et al., 2014, O'Donnell et al., 2014, Pulley et al., 2012).

Researchers at St. Jude Children's Research Hospital proved the feasibility of pre-emptive genotyping and this approach is currently under study at the University of Chicago in the US (Hoffman et al., 2014, O'Donnell et al., 2014, Pulley et al., 2012). Depending on the number of SNPs tested for, and the technology used (e.g. NGS), the data set generated by this approach will be very large i.e. too big to store in an EHR (Welch et al., 2014). Due to the size of genomic data generated there is a need for a system whereby data can be stored separately from the EHR, but close to it, in its own database (Potamias et al., 2014, Welch et al., 2014).

1.4.1.3. Pharmacogenomics and CDS

Databases that store genetic variation directly related to pharmacokinetics and pharmacodynamics, and therefore medication efficacy and toxicity, are essential for the clinical application of pharmacogenomics (Potamias et al., 2014). However, according to a systematic review in 2013, CDS interventions for personalized medicine based on pharmacogenomics were not well established (Welch and Kawamoto, 2013). There were very few pharmacogenomics CDSs compared to the overall field of CDS, with little integration of systems, and most still required healthcare providers to manually enter the patient's clinical and genomic data to generate a recommendation (Welch and Kawamoto, 2013). Genomic CDS applications were custom made for single use cases (Welch and Kawamoto, 2013). They were focused on few genes e.g. BRCA1 or BRCA2 mutations for the assessment of hereditary risk of breast and ovarian cancer in women, and VKORC1 polymorphisms and CYP2C9 alleles in the dosage of warfarin, a commonly used anti-coagulant (Drohan et al., 2009, Gage et al., 2008).

In 2014, in an early prototype usability test in the US, CDS alerts were embedded in a CPOE system (Devine et al., 2014). Seven cardiologists and three oncologists confirmed that the application of pharmacogenomics knowledge informed prescription decisions, and noted that user-interfaces should not be teeming with information but rather provide trimmed down, context-specific, curated information, along with interpretation (Devine et al., 2014). In another study, CDS algorithms for three medications, abacavir, carbamazepine, and allopurinol, were implemented in an EHR, and prescribers have ordered tests as a direct result from using the CDS (Goldspiel et al., 2014).

In the US, research is ongoing at the University of Chicago to display genomic information, related to pre-emptive genotyping of patients, to physicians in outpatient settings (O'Donnell et al., 2014). Researchers at St. Jude Children's Research Hospital proved the feasibility of CDS based on pre-emptive genotyping. In their study 1,016 patients were genotyped for 230 genes, and results of polymorphisms in four gene from the tests (TPMT, CYP2D6, SLCO1B1, and CYP2C19) were implemented into an EHR alongside interpretive guidance on their interactions with 12 medications (amitriptyline, azathioprine, clopidogrel, codeine, fluoxetine, mercaptopurine, ondansetron, oxycodone, paroxetine, simvastatin, thioguanine, and tramadol) (Hoffman et al., 2014). Results on the other 226 genes were stored pending suitable guidelines for their use (Hoffman et al., 2014), which underlines the need for pharmacogenomic guidelines in to help with interpretation in the process of clinical application. Pharmacists trained in pharmacogenomics manually reviewed each test and upon approval transferred the results

to the EHR (Hoffman et al., 2014). Informatics processes included automation of test results, and the development of an active CDS containing 55 different alerts (Hoffman et al., 2014). Based on the same approach, prototype development is ongoing at Vanderbilt University in the US to provide pharmacogenomic decision support by combining a patient's preemptive genomic test results with the patient medication list, and to give the physician visual alerts when genotype results correlate with risk of using specific medications (O'Donnell et al., 2014).

1.4.1.3.1. Cognitive science and medical decision-making

Both meeting patient throughput requirements (e.g., in emergency departments) and meeting the complexity of establishing the right diagnosis (e.g., via genomic testing) can put tremendous pressure on healthcare professionals, potentially producing unnecessary errors in diagnosis and subsequent treatment (Marewski and Gigerenzer, 2012). Using cognitive science, the steps in successful human decision-making can be codified and mapped in a mathematical fashion (Todd and Gigerenzer, 2000), which ultimately allows for integration and implementation in computer systems.

One focus of cognitive science is problem-solving, the creation of models that try to capture and represent the reasoning process whereby healthcare providers make successful decisions (Busemeyer, 2014, Moskowitz et al., 1988). Cognitive science research in this area is directly related to the symbolic approach branch of artificial intelligence (AI), which tries to capture and describe human intelligence (Wang and Ruhe, 2007). Cognitive science was successfully used in medical settings to create tools for decision-making (Marewski and Gigerenzer, 2012, Wegwarth et al., 2009). Cognitive

science models of medical reasoning were used to describe the process of medication selection (e.g. the selection of an antibiotic for pneumonia in pediatrics) and establishing a diagnosis (e.g. detecting depression in patients) (Fischer et al., 2002, Jenny et al., 2013).

Cognitive science models, hierarchical tree structures (Figure 1.7), and inferential statistical analyses (sampling to make generalizations about populations) are all examples of inference procedures. Inference procedures try to draw conclusions about given data. CDSS can combine medical databases with inference procedures (using the logic layer described in Section 1.2.2.8.1) to offer decision-making support to healthcare providers (e.g. establishing the most suitable treatment for a specific patient) (Tomaszewski, 2012). For example, a cognitive model was developed to detect patients at risk of attempting suicide. This model was implemented in a CDSS using a hierarchical tree structure for inference (Rezaei-Yazdi and Buckingham, 2014). Mental health clinicians, as the assessment progressed, were automatically redirected in real-time to questions that were most relevant, based on the data they had just entered into the system (Rezaei-Yazdi and Buckingham, 2014). The approach was successful and provided a model for improving CDSS in similar situations where healthcare providers' information needs change dynamically while interacting with patients (Rezaei-Yazdi and Buckingham, 2014).

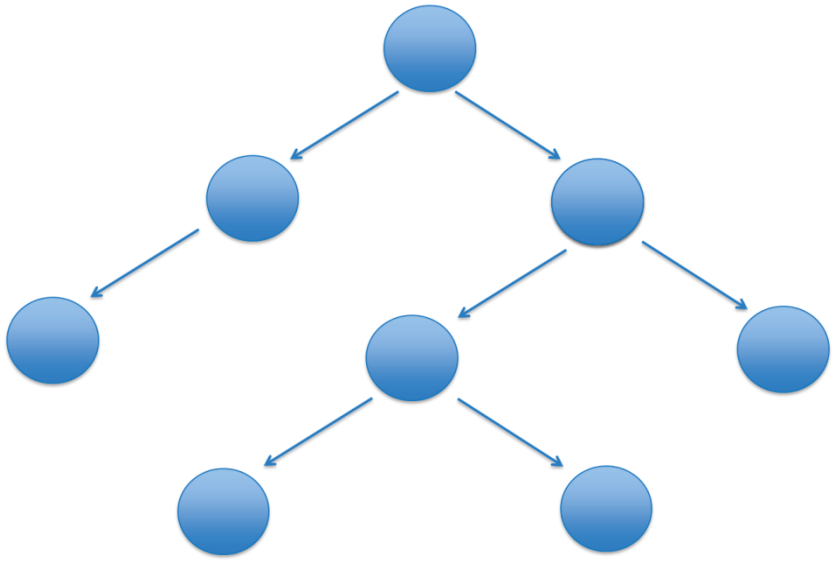

Figure 1.7. A hierarchal tree structure is graphical way of representing structural dependencies in a system (e.g. an organizational chart).

1.4.1.3.2. Heuristics

Healthcare providers regularly make successful decisions despite having access to limited or incomplete information (Katsikopoulos et al., 2008, Marewski and Gigerenzer, 2012, Wegwarth et al., 2009). Cognitive science has postulated that healthcare providers' decision-making in some situations is not based on an assessment of all medical information related to a given indication, but instead relies on heuristics (Katsikopoulos et al., 2008, Marewski and Gigerenzer, 2012, Wegwarth et al., 2009). Marewski and Gigerenzer define a heuristic as a decision strategy that ignores part of the available information and focuses on only a few relevant predictors (Marewski and Gigerenzer, 2012). These predictors act like keys on the available data and allow healthcare providers

to make efficient decisions quickly. For example, for the pediatric prescription of macrolides, a heuristic was developed that used only two predictors: age and duration of fever, to assess the likelihood of mycoplasma pneumonia in children with community acquired pneumonia (Fischer et al., 2002, Marewski and Gigerenzer, 2012). Table 1.3 describes the differences between an exact algorithm and a heuristic algorithm.

Brute Force Algorithm	Heuristic Algorithm
Considers all the data	Considers only part of the data
Uses an exhaustive search	Uses relevant predictors
Calculates all possible probabilities	Uses predictors to narrow down the search
Analyzes all probabilities to make a decision	Uses only a few 'highly relevant' predictors to make a decision

Table 1.3. The differences between a brute force and a heuristic algorithm in treatment of available medical data for the creation of decision aids.

Heuristic algorithms do not use all available medical data to decide on a diagnosis or treatment, and may appear to be of a lower standard than an exhaustive search as a decision making strategy (Table 1.3) (Wegwarth et al., 2009). However, statistical methods are not necessarily superior to heuristics, as heuristics can capture clinical expertise and experience, whereas statistics cannot (Luchins, 2012). In many cases heuristics can lead to decisions that are more accurate in comparison to a longer and more involved assessment of the available data (Bodemer et al., 2014). In specific situations in healthcare, for example where clinical decisions are made under time constraints, or with incomplete data, heuristics can provide an easier and faster approach to come to the right conclusion (Durand et al., 2012, Wegwarth et al., 2009).

1.4.1.3.3. Fast and Frugal Trees (FFTs)

Fast and frugal trees, known as FFTs (a specific type of hierarchical tree) are an example of how heuristics can be implemented to make medical decisions (Bodemer et al., 2014, Jenny et al., 2013, Marewski and Gigerenzer, 2012, van Rooij et al., 2015c). FFTs can help simplify CDS and cut through complexity using a heuristic approach. FFTs use binary decisions ("yes" or "no" type of questions) in an efficient manner, and only uses very few of them to arrive at a decision (Katsikopoulos et al., 2008, Luan et al., 2011). FFTs are easy to use and transparent (easy to communicate and teach), and can be accurate (Luan et al., 2011, Marewski and Gigerenzer, 2012, Todd and Gigerenzer, 2000).

A hospital in Michigan in the US had a problem that 90% of patients with severe chest pain were sent to the coronary care unit (CCU), whereas many of these patients should have been assigned to a regular hospital bed instead. Two approaches to remedy this problem were attempted. The first approach created a chart with 50 probabilities to consider prior to referral. Using this chart, physicians had to use a calculator to perform a logistic regression to find out if the patient should be referred. In the second approach an FFT was developed that physicians used to ask a few 'yes or no' type questions. With at most three questions the patients were either referred to the CCU, or not. The FFT approach had larger sensitivity (correct referrals to the CCU), a lower false-positive rate (incorrect referrals to the CCU), and was found to be easier to understand and use than the logistic regression approach (Green and Mehr, 1997, Marewski and Gigerenzer, 2012).

1.4.2. MEDICATION SELECTION PIPELINE

The overall question is how to accelerate the process of integrating pharmacogenomic knowledge and discoveries (including Big Data) into medication selection and dosage recommendations (Crews et al., 2012, Denny, 2014, Khoury et al., 2007, Potamias et al., 2014). Research has outlined that moving genomic research into clinical practice requires a component-based approach consisting of genomic data storage that is close to PoC, consistent interpretation of pharmacogenomic data and test results, availability of clinical guidelines for medication selection, and CDSS to provide interpretation and visualisation (Alvan et al., 2013, Crews et al., 2012, Drohan et al., 2009, Marsh and van Rooij, 2009, Welch et al., 2014). There are concerns that previously published CDSS are not applicable outside of the implementation context they were originally developed in (Black et al., 2011). Additionally, there is a distinct absence of studies that describe computer architecture components for genomic CDSS in sufficient detail necessary for implementation at a new clinical site, or how these components would fit together once implemented (Welch and Kawamoto, 2013).

Genomic data should preferably be stored in a specialized database separately from the EHR (Welch et al., 2014). And, as described in Section 1.4.1.3.3, the FFT methodology could be used for CDS implementation, and has, as an inference heuristic, the potential to be implemented in CDSS (Tomaszewski, 2012). Genomic CDSS can therefore be split into two components, data storage and analysis, and data interpretation and visualisation.

It is important to note that guidelines must exist before they can be optimized (Crews et al., 2012, Devine et al., 2014). Once guidelines are transformed into a heuristic, a healthcare provider needs to check both the applicability and accuracy of the chosen predictors (Marewski and Gigerenzer, 2012). These predictors need to be fine-tuned as new data becomes available so the system can be kept current (Ash et al., 2007, Cresswell et al., 2012). Healthcare providers' involvement is required in both the creation of guidelines and medical algorithms (e.g. heuristics) (Becher et al., 2012, Black et al., 2011, Cresswell et al., 2012, Drohan et al., 2009). In the translation of pharmacogenomics to personalized medicine there is a need for a multi-disciplinary team, and the development and use of computer architecture components that provide a re-usable blueprint for real-world implementation (Crews et al., 2012, Welch and Kawamoto, 2013, Wilk et al., 2013).

1.5. Medication Safety

Between 2001 and 2013, medications were among the fastest-growing categories of health system spending in Canada (Canadian Institute for Health Information, 2014). Measured over the period from 2007 to 2010, 13.9% of the US population aged 18 and over were found to have taken five or more prescription drugs in the preceding 30 days (National Center for Health Statistics, 2014). Due to an aging population and a rise in complex diseases, polypharmacy (patients typically above 65 years of age taking more than four medications simultaneously) had risen, and with that rise the chance of harmful medication interactions had increased (Grando et al., 2012, Gurwitz, 2004, Marengoni,

2013, Routledge et al., 2004). Errors, toxicities and ADRs are also commonly seen in medications with complex regimens and narrow therapeutic indices (Weingart et al., 2010). Oral anticancer therapies and polypharmacy have put additional pressure on healthcare providers, as they are faced with a wider range of medications and patient use contexts to be familiar with (Banna et al., 2010, Marengoni, 2013). Technology use may help to secure against medication errors, as many of these errors are associated with poor or incomplete access to, and application of, pertinent information (Bubalo et al., 2014, Grando et al., 2012).

Relevant data for safe medication use can be found in disparate data sources e.g. the National Cancer Institute's common toxicity criteria, or sources related to agents causing a prolonged QT interval (e.g. as a risk factor for sudden death) and P-glycoprotein medication interactions (e.g. for tissue distribution of medications) (Connor et al., 2014b, P-glycoprotein drug interactions, QTc Interval Prolonging agents). However, multiple, or all, of these disparate sources may be needed to determine the safe use of a single medication for a specific patient. Pharmacists could have trouble locating all the correct data, or have incomplete access to relevant data (e.g. do not have the latest editions of medication guides, may not be aware that guidelines exist for certain uses). In these cases CDS is an obvious choice to improve medication safety in pharmacy practice (Ventola, 2014).

Safe medication practice is hindered by medication errors that can occur at any point in the process of medication delivery to the patient (Bubalo et al., 2014, Tarrant et al., 2015). This process can involve multiple disciplines and healthcare providers (e.g.

physicians, nurses, and pharmacists) in multiple settings (e.g. clinic, hospital, pharmacy). The handovers in this process can introduce issues with communication between healthcare providers whereby patients could experience issues with continuity of care (Tarrant et al., 2015). In this process, pharmacists fulfil an important role in assuring medication safety as they are most familiar with the complete list of medications a specific patient is taking, including prescription, over-the-counter medications, and any complementary and alternative medicines (CAM). In providing pharmaceutical care, pharmacists can incorporate many factors that affect medication safety (e.g. comorbidities, concurrent medications) to mitigate errors (e.g. incorrect doses, drug interactions, and inappropriate use of medications) (Hepler and Strand, 1990). However, pharmacists may not be familiar with some medications if they were not trained in specialized fields (e.g. oncology), and when information on these medications and their interactions is not readily available or incomplete, they cannot be taken into account fully when assessing safety (Charpentier et al., 2012).

1.5.1. MEDICATION SAFETY AND CDS

A 2011 review found that CDSS were relatively common in studies in hospital settings, on prescribing and monitoring, such as CPOE and e-Prescribing (computer use for generation, sending and dispensing of medical prescriptions) systems; however, CDSS in community pharmacy use were less commonly studied (Curtain and Peterson, 2014, McKibbon et al., 2011). Concerns exist that commercially available CDS for CPOE systems may not fit well with intended use in local settings (Phansalkar et al., 2011). Some organizations mentioned that costs, needed to customize the clinical contents of

commercially available CDS prior to regional or local clinical use, were a barrier to implementation (Phansalkar et al., 2011).

Mobile devices with CDS could provide pharmacists with integrated access to information on medication use and help combine medication knowledge sources (Ventola, 2014). However, there are very few studies on apps intended for use by pharmacists (Aungst, 2013). A 2013 study on pharmacy-based apps evaluated 27 available smartphone tools and found multiple reference works, medical calculators, educational, and productivity related apps (Aungst, 2013). However, none of these qualified as CDS as they all lacked one or more criteria. Comprehensive and curated data, filtered and applicable content, local application of data, fit within the workflow, presentation in a consistent and concise format, and the ability to be kept up-to-date (as described in section 1.2.2) are requirements for a CDS (Ash et al., 2007, Berner et al., 2006, Chaffee and Zimmerman, 2010, Drohan et al., 2009, Jones et al., 2013, McKibbon et al., 2011, Osheroff et al., 2007, Rothman et al., 2012, Trivedi et al., 2002, Trivedi et al., 2009). Healthcare providers' input into CDS apps could help address their shortcomings, and research has indicated the need to more fully involve healthcare providers into the development process of CDS (Cresswell et al., 2012, Drohan et al., 2009). However, models on how to achieve this in real-world contexts to build CDS apps are currently not available.

1.5.1.1. Medication adherence and CDS

A famous quote outlining the issue of medication adherence is from Dr. C. Everett Koop, a former surgeon general of the United States, who once said: "Drugs don't

work in patients who don't take them." (Slabodkin, 2014). Unfortunately, the provision of a correct and safe medication to a patient does not guarantee that the patient will take the medication as prescribed, nor that they will be safe. Patients' ability to adhere to the medication regimen can greatly affect their outcomes (Foulon et al., 2011). Pharmacists and other healthcare providers do attempt to educate patients and instill the need to adhere strictly to medications (Curtain and Peterson, 2014, Foulon et al., 2011, Given et al., 2011, Siden et al., 2014). However, patients can under, and over comply to medications, causing therapeutic outcomes to suffer, or toxicities to be induced (Allen and Williamson, 2014, Foulon et al., 2011). Additionally, patients may also struggle with complex medication regimens (Slabodkin, 2014).

Alert-based active apps can provide reminders to patients to try to improve adherence (DiDonato et al., 2015). Patient's attitudes towards mHealth intervention-based apps were studied in a group of patients owning a smart device that were 50 years and older and on statin therapy (DiDonato et al., 2015). The patients in this group saw potential benefits in adherence apps but had technology and interface concerns, and required the app to work on an accessible technology in a way that fit within their lifestyle (DiDonato et al., 2015). In Taiwan, in an interdisciplinary study (medicine, sociology), a three-tier cloud-based mHealth application based on QR codes (a type of two dimensional barcode) has been proposed to assist elderly patients with multiple chronic conditions in the complex task of medication management (Tseng and Wu, 2014). In the proposed system patients could scan QR codes of medications provided by different clinics using their smartphones into a medication management app and be

notified of any drug-drug interactions. Eighteen patients between the ages of 55 and 75 were asked in a survey if they would use this system if it became available and 95% of them answered that they would (Tseng and Wu, 2014).

1.5.1.2. Oral Chemotherapy

A recent surge in the approval and use of oral chemotherapeutics has made it possible for cancer patients to be treated at home (Allen and Williamson, 2014, Collins and Elsaid, 2011, Foulon et al., 2011, Geynisman and Wickersham, 2013, Given et al., 2011, Hammond et al., 2012). This has obvious advantages for the patient, who can avoid disruptive and time-consuming hospital visits to receive chemotherapy. Travel times to and from hospitals for treatment are also of particular concern to those living in rural areas.

While oral chemotherapy does have advantages over the traditional regimens, there are also disadvantages associated with its use (Banna et al., 2010). Oral chemotherapeutic medications often have a narrow therapeutic index (Banna et al., 2010, Segal et al., 2014). Additionally the metabolism of oral chemotherapeutic agents is easily affected by medication or dietary interactions, which can significantly reduce their effectiveness or result in toxicities for the patient (Banna et al., 2010, Segal et al., 2014).

Although most oral chemotherapy medications are dispensed by oncology-trained pharmacists, this practice is changing. For example, in a survey conducted in Spain, 48.1% of oral chemotherapeutics were dispensed by ambulatory care pharmacists (Conde-Estevez et al., 2013). Non-oncology trained pharmacists are now required to assess medication safety (e.g. drug-drug interactions, toxicity and diet) and to educate

patients on the safe handling and use of these generally toxic medications (Felton et al., 2014).

There are also prescribing issues that need to be addressed and pharmacists' interventions and assessments can help to identify and solve problems before they cause harm to the patient (Charpentier et al., 2012, Felton et al., 2014). Therapies can be ordered incorrectly that may interfere with the patient's chemotherapy, or in combination with other medications (e.g. pain or nausea relief) can lead to severe toxic side-effects. In France, a study monitoring oral chemotherapy use by oncologists found wide variations in prescription practices and monitoring of toxicity despite existing guidelines (Bourmaud et al., 2014). A lack of formal oral chemotherapy prescribing has also been observed across cancer centres in Ontario, Canada (Ahmad et al., 2014). Prescribing errors may not be recognized by pharmacists unless they have access to all the relevant information on prescribing practices of oral chemotherapeutic medications.

The adherence to guidelines for oral chemotherapy use is deemed essential because of the toxicities of these medications, as well as their potential side-effects (Bourmaud et al., 2014). However, in the US, a survey of oncology pharmacists found that most institutions did not yet have special requirements for oral chemotherapy prescriptions (Weingart et al., 2007). Additionally, an Irish study performed in 2012 found that 64% of community pharmacists did not feel they had the relevant information to safely dispense oral chemotherapeutics, and 74% felt their patients were at risk from oral chemotherapy prescribing and dispensing within the current system (Hammond et al., 2012). Without ready access to all the pertinent information for the safe use of oral

chemotherapy, issues such as drug-drug interactions from treatments for co-morbidities and side-effects become serious safety concerns (Chan and Ismail, 2014).

1.5.1.2.1. Oral chemotherapy and CDS

The need for CDS with this class of medication was clear from the outset, when there were very few oral chemotherapeutic agents available. In 2005, a web-based CDS was tested on 36 physicians with 8 fictitious cases on appropriate oral chemotherapy dosage adjustments in the treatment of childhood acute lymphoblastic leukemia (ALL) (Bury et al., 2005). This study found that CDS had the potential to increase protocol compliance while decreasing prescribing errors (Bury et al., 2005).

Pharmacists are well positioned to have a beneficial impact on oral chemotherapy use by providing an additional level of assessment through pharmaceutical care (Felton et al., 2014). CDS can be used to provide comprehensive data in a concise and curated format (e.g. medication monographs) as well as to integrate guidelines (e.g. protocols and dose adjustments) for oral chemotherapy use in community and hospital pharmacy settings. In aging populations, it is anticipated that more patients will be prescribed oral chemotherapy, increasing the need for automated tools to aid in patient safety (Felton et al., 2014).

In order to increase safety and provide a fail-safe at the prescribing level, a CPOE system was developed for use with oral chemotherapeutics and was shown to reduce prescribing errors in a hospital setting (Collins and Elsaid, 2011). The addition of CDS with EBM would further allow an assessment of concurrent medications, including complementary and alternative medications, as well as patient diets to catch

inconsistencies and to mitigate toxicities (Weingart et al., 2010). However, a comprehensive CDS for use by community pharmacist to improve safety in oral chemotherapeutic use is lacking (Charpentier et al., 2012). This situation may be due to a lack of multi-disciplinary partnerships in the development and implementation of CDSS, as well as the absence of a described methodology or framework on how to build CDSS for medication safety uses (Haynes et al., 2010, Koutkias et al., 2014).

1.5.2. CHANGE MANAGEMENT

eHealth is not simply a matter of applying technological solutions; it is also a challenge on an organizational level for healthcare institutions (Knaup et al., 2014, Trivedi et al., 2009). Alongside technological system changes, there are also underlying organizational changes related to the adoption of eHealth infrastructure (Wells et al., 2014). Stakeholder buy-in (the support of levels of management and healthcare providers that are adapting to eHealth use) is an important part of eHealth implementation as healthcare organizations in the majority of cases require some level of Change Management to prompt the adoption of a new system (Pearce et al., 2014, Shaw et al., 2013).

Change Management is defined as the action or process taken to transition an individual or group from a current state to a future desired state of being (Varkey and Antonio, 2010), and can become part of the overall implementation of an eHealth project. Models may become so intertwined that there is a specific overall Change Management and eHealth strategy combination that is applied (Saunders and Scott, 2014). When it comes to CDS implementation, change often fails to materialize in healthcare delivery or

guideline application because of a lack of Change Manangement (Harlos et al., 2012). A more concerted effort to combine management principles and eHealth is predicted to more consistently deliver evidence to PoC (Harlos et al., 2012).

1.5.3. MEDICATION SAFETY PIPELINE

The use of mHealth approaches for CDS may fit well within current workflows of pharmacists. Using handheld computers for patient record keeping, pharmacists reported improvements to patient documentation, and recorded more interventions, with fewer empty fields and increased accuracy (Mickan et al., 2013). In a 2014 study in the United Kingdom, 211 pharmacists were surveyed on the usefulness of mobile device use in pharmacy practice, 55% of them indicated that apps were useful in the context of patient consultations, and this number rose to 80% for apps related to patient education; however, concerns remained on the lack of regulation for apps and workplace policies (Davies et al., 2014).

According to a review by Aungst, decision support for pharmacists can be improved by the use of smartphones, tablets, iPhones and iPads with real-time access to medication information across many different reference sources (Aungst, 2013). Pharmacists have an important role in the development process of CDSS for medication safety, as they are experts in assessing relevance and context-appropriate use of medical data and can assess clinical workflow integration (Cresswell et al., 2012). A 2013 study showed that pharmacist-guided development of CDS had decreased the prescription of potentially inappropriate medication and other unsafe medications to pregnant women (Lainer et al., 2013). Pharmacist involvement is also required to locate and assess

relevant evidence-based data and to sustain this relevance through updates after implementation (Ash et al., 2007).

The effectiveness of CDS depends on both the fit with clinical workflow and the ability to provide support in real-time (Cresswell et al., 2012). In the development of CDSS, available devices for user interface purposes would require assessment in light of the intended use. The selection of computing devices needs to be based on a fit for purpose, a fit within the intended workflow, the ability to share data effectively, as well as device responsiveness (real-time data interactions) (Table 1.2) (Aungst, 2013, Berner et al., 2006, Brath et al., 2013, Burdette et al., 2012).

CDS apps could provide community pharmacists with improved access to EBM for use in the assessment of patient safety (Ventola, 2014). However, models on how to achieve this in practice do not currently exist and little is known about CDS app development in pharmacy (Aungst, 2013, Curtain and Peterson, 2014, DiDonato et al., 2015, Ventola, 2014).

1.6. Rationale

eHealth has a focus on improving medication selection and safety through the use of computerized systems (Baysari et al., 2011, Crews et al., 2012, Hoffman et al., 2014, Kajbjer, 2008, Koutkias et al., 2014, Tora et al., 2014). In order to meet the demand for effective medication use, EBM has to be translated through CDS. EBM dissemination and use by healthcare providers is hampered by lack of access, and lack of translation into clinical utility (Cornell and Dorsey, 2012). CDS can be integrated across

heterogeneous medical data sources through the use of CDSS. Subsequently smartphones, tablets, laptops, and desktops can be used to improve access by providing updatable CDS. Through CDSS, healthcare providers can access CDS in a timely, consistent manner, and use it for patient-specific decision-making on medication selection or safety. Development of CDSS is complex as problems exist in multiple areas. Data storage and analysis issues include large sets of heterogeneous data, disparate data sources, security, and analysis times. Additionally, there is the complexity of the data to be integrated, e.g. unformatted, unrelated, complex medication selection algorithms, which require updates when new data emerges. For ease of use CDSS needs to provide near-instantaneous data access. Furthermore, the interpretation and presentation of data requires visualization of actionable data, which also has to reflect updates with new data in real-time. In addition these systems need to be re-usable across different healthcare sites, and content within these systems should be able to change to reflect a new local context (Haux, 2006). All of these problems need to be addressed prior to CDS implementation. In the translation of EBM there is a need for the development of re-usable components that provide a formalized blueprint for real-world implementation of CDSS. The benefits of these components would be re-usability, reduced complexity, flexibility, and a reduction of effort required for future CDSS development. Not all CDS implementation can be addressed by one CDSS. For example, active and passive CDS require different CDSS strategies. Active CDS needs to support a dynamic, constant stream of updates (e.g. new prescriptions, new genotypes), whereas updates to passive CDS are more intermittent (e.g. new medications, new reference sources). Unless CDSS

is *a priori* designed in the form of re-usable components, pipeline development to link different eHealth systems will continue to be hampered by data storage, analysis, interoperability, interpretation, and visualisation issues.

1.7. Hypothesis

Novel combinations and applications of software can be used to create formalized and re-usable CDSS pipeline components for active and passive CDS.

1.8. Study objectives

1. Construct a secure, low-cost database on a commonly used platform that will hold large pharmacogenomic (Big Data) datasets in a local environment, and will have the capacity to run commonly used statistical tests quickly and efficiently.
2. Include pharmacists in the development stages of CDSS, as experts in assessing relevance and application of medical data, and to incorporate pharmacists' real-world workflow knowledge into systems design and technology selection.
3. Standardize pharmacogenomic decision trees based on pharmacist-derived flow charts using heuristics, and implement them in automated interactive software to rationalize medication selection.
4. Construct a standardized, re-usable CDSS model, which healthcare providers can re-use in the future to create mobile CDS apps.

5. Provide a feasible mHealth platform accessible through handhelds such as smartphones and tablets, for community pharmacists to, within their current workflow, assess comprehensive and localized knowledge on oral chemotherapeutic medications to improve medication safety.

1.9. Study Flow

Database design, heuristics, change management, and three-tier data architecture techniques were used, along with readily available software, hardware and cloud-computing resources to build re-usable, automated CDSS pipeline components for both active and passive CDS (Figure 1.8). Big Data can be locally stored and analysed in a cost effective, secure format (Chapter 2) for future use e.g. inclusion into medication selection algorithms (Chapter 3). EBM data from disparate sources was collated by pharmacists Mary Roederer from the University of North Carolina, Chapel Hill, USA for globally applicable pharmacogenomically enhanced medication selection (Chapter 3; Figure 1.8a); and Serena Rix from the Grey Nuns Hospital, Edmonton, Alberta for safe use and dispensing of oral chemotherapeutics in Canada (Chapters 5; Figure 1.8b). These curated medication selection flow charts, and medication safety monographs were used as test cases to develop the automated interpretation and visualization of data in standardized, formalized formats (Chapters 3-5). Pipeline components built here are automated and updatable in real time. Active CDS required CDSS consisting of both data analysis and storage (Chapter 2) and novel heuristics in the form of the augmented fast and frugal tree (Chapter 3) components; passive CDS required the development of a re-

usable model for mHealth app development (Chapter 4), and implementation on Android and iOS handheld devices, and secured website access to keep data current (Chapter 5).

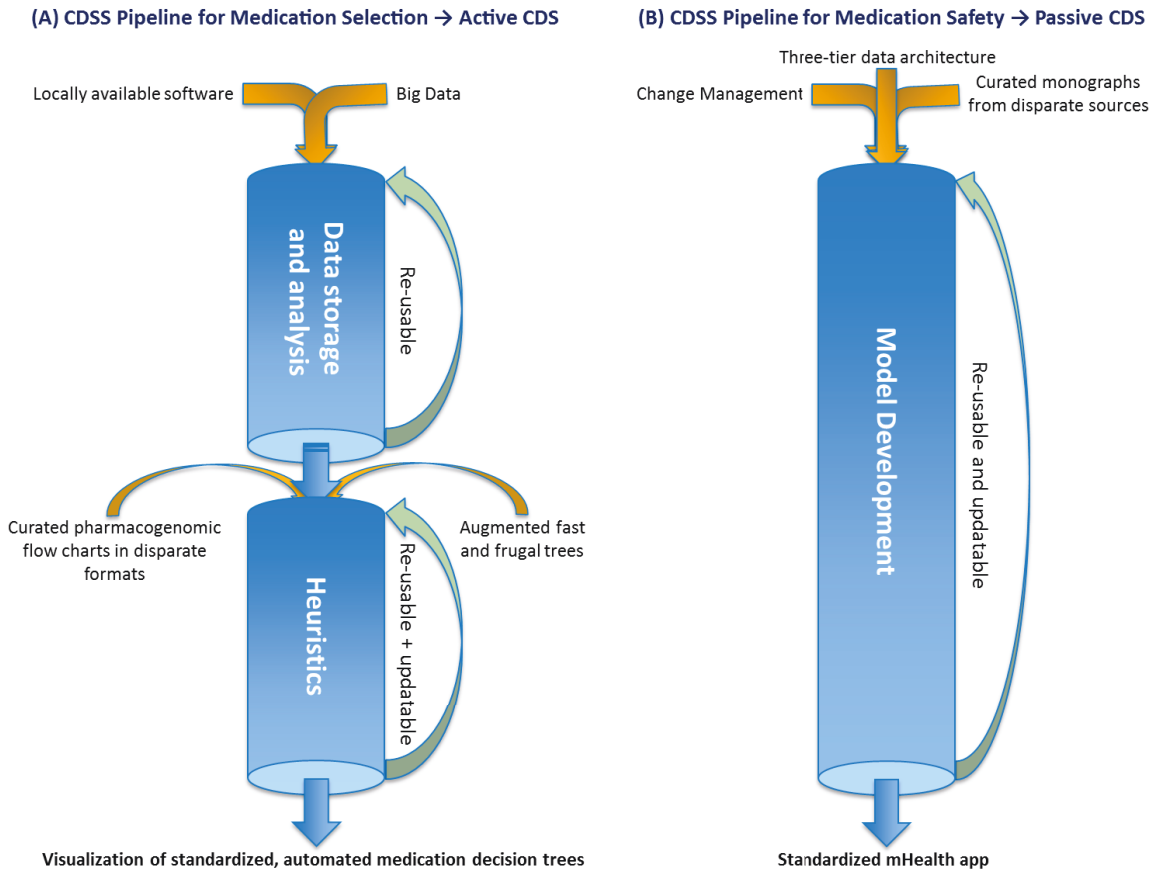

Figure 1.8. Study Flow.

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2. DAMMING THE GENOMIC DATA FLOOD USING A COMPREHENSIVE ANALYSIS AND STORAGE (CASTOR) DATA STRUCTURE

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2.1. Abstract

Data generation, driven by rapid advances in genomic technologies, is fast outpacing our analysis capabilities. Faced with this flood of data, more hardware and software resources are added to accommodate datasets whose structure has not specifically been designed for analysis. This leads to unnecessarily lengthy processing times and excessive data handling and storage costs. Current efforts to address this have centered on developing new indexing schemas and analysis algorithms, whereas the root of the problem lies in the format of the data itself. We have developed a new data structure for storing and analyzing genotype and phenotype data. By leveraging data normalization techniques, database management system capabilities and the use of a novel multi-table, multidimensional database structure we have eliminated the following: 1) unnecessarily large dataset size due to high levels of redundancy, 2) sequential access to these datasets and, 3) common bottlenecks in analysis times. The resulting novel data structure horizontally divides the data to circumvent traditional problems associated with the use of databases for very large genomic datasets. The resulting dataset required 86% less disk space and performed analytical calculations 6,248 times faster compared to a standard approach without any loss of information.

2.1.1. DATABASE URL

http://castor.pharmacogenomics.ca

2.2. Introduction

Since the release of a working draft of the human genome project, there has been a proliferation of technologies to perform large-scale genotyping. The research possibilities provided by genome-wide analysis have created a data deluge reminiscent of Moore's Law (Moore, 2000). In a single year, one massively parallel sequencing machine can produce nearly nine times the amount of data currently housed in the U.S. Library of Congress (Antofie et al., 2007, Fayyad et al., 1996, Férey et al., 2005).

Currently, lengthy analysis times required for the vast quantities of genotype data generated make interactive analysis impractical (Fayyad et al., 1996). Sequential access, such as retrieving data from flat files, e.g. PLINK input files (Purcell et al., 2007), has the limitation that all prior data must be processed in order to access datum at the end of the file, and this process must be repeated for each variation of the original analysis. Furthermore, they are memory-bound. Alternately, the use of databases has been hampered due to challenges in data loading time and performance. The development of new techniques and tools is therefore necessary, as historical solutions have been rendered impractical due to the extreme volume of data generated (Antofie et al., 2007, Fayyad et al., 1996, Férey et al., 2005).

Efforts at reworking this analysis process have focused on three main areas: data structures, data indexing and data analysis. Initially, the improvement of data structures began with a logical model of genomic and phenotypic data using object-oriented structures (Antofie et al., 2007, Barbasiewicz et al., 2002), relational databases (Antofie

et al., 2007), or mark-up languages (Cohn, 2000), which add a lot of model description metadata. These structures are more suited to providing data context and long-term storage than high-speed analysis (Sen and Sinha, 2005), although some allow basic analytical querying (De Francesco et al., 2009). Recent data indexing efforts seek to improve pattern or sequence search performance. While these have shown a significant performance increase for specific targeted tasks, they have the drawback of increasing the dataset size by up to ten times (Barsky et al., 2008, Cooper et al., 2004, Phoophakdee and Zaki, 2008). Hardware-based solutions such as cloud computing, peer-to-peer networks, and other distributed computational concepts are now used to prolong the useful lifespan of software by increasing processing power. Other solutions circumvent the problem of large datasets altogether at the cost of losing content (Hong et al., 2009). Current data warehousing and data sharing methodologies are making progress but fall short of providing a solution for rapid analysis (Olund et al., 2009).

There are three obvious areas for improvement: 1) reduce dataset sizes without any loss of information (also reducing long-term data storage costs) 2) eliminate the need for sequential access and 3) organize data to allow for rapid analysis. Our solution attempts to address all these areas of concern. Using established computer science principles we have developed the Comprehensive Analysis and STORage (CASTOR) methodology, a normalized, multi-table and multidimensional database structure for storing and analyzing genotype and phenotype data.

2.3. Methods

2.3.1. Data Normalization

Data normalization restructuring techniques reduce redundancy and increase the flexibility of a poorly structured dataset without loss of information (Ramakrishnan and Gehrke, 2003). These techniques are frequently used to make a data structure suitable for implementation in a relational database management system (RDBMS).

Common genomic datasets such as Illumina's Genomestudio output files, certain PLINK input files and the Gencode GTF format are all examples of data structures that, despite being produced by, or for, automated analysis contain a significant amount of redundant data and therefore violate the principles of normalization.

In a typical Illumina Genomestudio results file 63% of the output file is composed of unnecessarily redundant data. Only a single instance of each datum is required to communicate the necessary information; however fields such as sample identifier, the name of the Single Nucleotide Polymorphism (SNP) in question, and SNP position are repeated for each row contained in the sequential file (Table 2.1). Since both SNP name and SNP position are associated with the SNP in question and not the sample, their inclusion on each row violates the second normal form. Because of this, data which should take up a total of 17 million characters (9 character SNP name + 8 character SNP location = 17 characters x 1,000,000 SNPs), or 0.009% of the final dataset, instead takes up 119 billion characters (17 characters x 1,000,000 SNPs x 7000 samples), or 63% of the final dataset.

This dataset is a result of a combination of two different data structures: SNP information (SNP and SNP Positions) and sample information (Sample Identifier) in order to accommodate one piece of datum that depends on both (SNP value).

In order to address this redundancy, we have separated the dataset into two individual but related tables. A SNP reference table, containing a list of all SNPs used in the study and their associated position, and a genotype results table containing sample information and all genotypic results.

The SNP reference table uses SNP name as the primary key and related fields as non-prime attributes. This results in one row of information for each SNP present in the study. The genotype results table contains a single row for each sample in the study, with each column representing the results of an individual SNP. This format is similar to the PLINK PED file format (Purcell et al., 2007), which also has one sample per row, using columns to represent the SNPs. This approach leads to a large number of columns. A study involving 1,000,000 SNPs would result in a dataset with 1,000,001 columns (1 column for sample id, and 1 column for each SNP). This is impractical as a sequential file, and impossible to implement as a database structure, as a table with these dimensions is not supported by any current database management system (DBMS).

2.3.2. MULTI-TABLE

While a DBMS cannot accommodate an unlimited number of columns per table, most can accommodate a nearly unlimited number of tables per database. The number of tables is limited by the capacity of the underlying file system or, in the case of Microsoft's SQL Server, by the number of database objects permitted (over 2 billion). It

is this property that we exploit to accommodate our 1 million SNP wide structure, horizontally dividing the single, large, genotype results table of 1 million SNPS into 2000 tables, each with 501 columns (500 SNPs and a sample identifier as primary key). This new structure is currently supported by all major DBMSs.

Each column in the genotype results table is denoted generically (snp1, snp2 etc.) and is included in the SNP reference table allowing rapid identification of the specific SNP. In doing so, uploading a new dataset would require no structure changes (such as renaming each column).

2.3.3. MULTIDIMENSIONAL ENCODING

Multidimensional databases are optimized for rapid and adhoc computer-aided analysis or online analytical processing (OLAP) (Colliat, 1996) by encoding all alphanumeric data as numeric data, and isolating descriptive data from the data required for the analysis. Using this methodology we have divided the information into dimension tables and fact tables. Dimension tables contain descriptive data including all the original alphanumeric descriptors and the code that replaces them in the fact tables. The fact tables contain only numeric data and are used to conduct the bulk of the analysis. Each possible combination of two alleles is encoded numerically into 10 values (Table 2.2).

This encoding results in a smaller, faster, and more flexible dataset, which is more suitable for analysis. While the structure and content change, none of the information contained in the initial dataset is lost.

Phenotypes are similarly encoded. Phenotype data already in numeric format remains unchanged; however an entry is made in the phenotype_dim table (Table 2.3) to

ensure that the context of the phenotype is not lost. Each alphanumeric phenotype is assigned an integer code in the phenotypes_discrete_dim table and a parent entry is added to the phenotypes_dim table (Tables 2.3 and 2.4). Numeric codes from phenotypes_discrete_dim are used to populate the phenotype fact tables. Using this methodology, almost all alphanumeric values are converted to numeric values, making these tables suitable for automated analysis. Note that free-form text entries however, cannot be encoded in this way and therefore should be avoided whenever possible if automated analysis is the goal.

2.3.4. TEST PLATFORMS

The test platforms for all tests were Dell 2 x Quad Core Xeon E54102x6MB cache, 2.33GHz, 1333MHz FSB, PE2900, with 16GB 667MHz Dual Ranked DIMMS and 8 x 300GB 15K RPM SCSI 3Gbps mounted in RAID 1+0 for 1.2 mirrored terabytes of disk space. The operating system was RedHat Enterprise Linux 5, and the MySQL Community Server 5.0.67 compiled for RHEL5 (MyISAM) or Oracle 11G were used as the DBMS.

Tests were conducted using both DBMSs, but only Oracle 11G was able to manage the 7 billion rows contained in the original dataset, and therefore was used for all load, statistical and data return comparisons on the original dataset.

Two computer hosts were used. The first host handles only the dimension tables and the software client responsible for issuing the database queries and the collection of results. The second host, configured to maximize the performance of the DBMS responsible for manipulating the fact tables, performs the analysis.

2.3.5. EVALUATION

In the absence of a sufficiently large publicly available dataset, a very large dataset composed of 7,000 subjects, each with 7,000 phenotypes (both quantitative and dichotomous) and 1,000,000 bi-allelic genotypes for a total of 7,049,000,000 data points was randomly generated and used to evaluate the performance of our novel database structure. A test suite was written in Perl (Wall, 2000), which created the database structure, disabled indices before the dataset was loaded, loaded the dataset and then re-enabled the indices. Load time was defined as the sum of the time required to perform these operations.

Our test suite then measured the impact of the new schema using the same computer hardware and operating system, for a direct comparison. To avoid comparing the speed of a DBMS versus a sequential file, which would require the evaluation of a great number of hardware and operating system variables, the original dataset was also loaded into the DBMS for evaluation (see supplementary data, Section 2.11, for more detail).

The database management system and multidimensional nature of the data were kept constant for both the original and CASTOR datasets to measure only the efficiencies of the novel database structure. A variety of statistical and common GWAS analyses were performed on the datasets (mean, square root, minimum, standard deviation, variance, allele count with a phenotypic filter) (Table 2.5). In addition, we tested how rapidly data could be located and retrieved from the databases.

2.4. Results

Our CASTOR approach converts the sequential file into a normalized and indexed, direct-access database (Figure 2.1). Combining all normalization techniques the dataset was reduced from 98.4 gigabytes to 13.8 gigabytes, a decrease in disk space usage of 86%, without loss of information (Table 2.6). Removing redundant SNP information alone reclaimed over 50 gigabytes of space.

Once loaded, the data can be re-used and re-analyzed without the need to repeat either the conversion or the data load. The significant decrease in load time (90.3 minutes versus 8.23 hours for the original dataset) is primarily a result of dataset size reduction due to normalization, and the corresponding reduction in index size due to the horizontal segmentation of this dataset. The smaller indices are easily loaded into available memory when needed, removing the need to use slower hard disk based virtual memory space often required by larger indices.

As each column in the CASTOR data structure represents a SNP, the database metadata itself is responsible for SNP indexing thus obviating the need to separately index the SNPs for rapid data access, as has been the focus of earlier efforts (Barsky et al., 2008, Cooper et al., 2004, Phoophakdee and Zaki, 2008).

The genotype table from the non-optimized original database (single table) structure had a row count of 7 billion (1 million genotypes for 7,000 samples) and the phenotype table had 49 million rows (7,000 phenotypes for 7,000 samples). With an alphanumeric index (such as the combination of SNP name and sample id), the index alone would take up 111 gigabytes of memory (9 character SNP name + 8 character

sample id = 17 characters * 7 billion records). Our CASTOR database has significantly fewer rows (7,000 per table, one row per sample), but has 2,000 genotype tables and 14 phenotype tables, dividing the dataset into smaller, fragmented indices. Using a single row per sample, the index on each CASTOR table is 55 kilobytes (7,000 samples * 8 character sample id) allowing for very rapid load times. The total size of the CASTOR indices (across all 2000 genotype tables) is 107 megabytes, but since the indices are fragmented across many tables, only those indices needed to fulfill a specific query are loaded at any given time. Table 2.6 illustrates the benefits of the CASTOR approach.

Since DBMSs are optimized for column-oriented calculations, using each column as a list of all genotypes for a particular SNP (SNPs across samples), optimizes the dataset for GWAS-type analyses while still supporting row based calculations across SNPs when necessary.

The final result is a CASTOR dataset (containing all of the original information) that is very wide, comprising over 2000 tables and 1 million columns for genotypes alone, but quite short, with only a single row per sample in each table (Figure 2.1). The resulting multi-table data schema's time required to conduct the performance analysis was reduced by 99.9% by moving from a single table to a multi-table data structure (15.62 hours compared to 9.1 seconds) (Table 2.6).

2.5. Discussion

Applying both well-known and novel data transformation and data architecture techniques we have arrived at a simple and elegant solution that achieves a significant

dataset size reduction and a dramatic increase in processing speed. As data is loaded into the database the data is normalized to remove duplications, then encoded into numerical data and subsequently divided into the novel multidimensional multi-table structure specifically designed for large genetic dataset analysis. Converting the original dataset into a multidimensional dataset has many advantages, such as enabling the use of Online Analytical Processing tools (OLAP) (Colliat, 1996) and increasing the speed of the dataset by eliminating slower alphanumeric data from the analysis task. An additional benefit is the further reduction of the size of the dataset while preserving all of the information contained in the original.

A multi-dimensional encoding scheme can furthermore be used to encode more than just the initial data. For example, the genotypes dimension table (Table 2.2) not only encodes the 10 possibilities of genotype pairs, it also easily separates homozygous pairs (code ≤4) from heterozygous pairs (code ≥5). Counting alleles, a basic calculation in a GWAS, can be accommodated with the following Structured Query Language (SQL) query:

select sum(genotypes_dim.allele_a) from genotypes_dim, gtypes1 where gtypes1.snp2 = genotypes_dim.code and genotypes_dim.allele_a > 0

Where genotypes_dim is the database table that holds the information for each genotype; allele_a is a count of A alleles in a particular genotype; gtypes1 is the table containing the genotypes for the first 500 SNPs; snp2 is the field containing the genotype code for snp2.

If adopted, this approach would offload basic statistical manipulations to the database, provide a platform for automated initial quality control and analysis, and result in savings in disk storage, data archiving and transfer time. Our CASTOR approach, if adopted for biological datasets, would provide a much more reasonable starting point that could enable analytical solutions on laptop computers or other non-specialized hardware, while still benefitting from the performance improvements available to cloud computing and other hardware-based solutions. The CASTOR approach will help meet the demand for high-speed analysis by providing a solid foundation to handle ever-increasing amounts of genetic data. Our dataset can scale to several million samples and nearly an unlimited amount of SNPs with nothing more than a linear impact on performance.

Aside from the stated performance benefits, CASTOR also has a potential impact on storage costs associated with this data. With an average long-term storage cost of $25/month/gigabyte (Butts, 2009), including all overheads, the original dataset composed of 7,000 samples with 1 million SNPs and 7,000 phenotypes would cost $29,520 per year in total storage costs. Based on these estimates the same information in CASTOR format would cost $4,140 per year; which represents a savings of $25,380 per year.

The next step is to incorporate the CASTOR approach into commonly used software packages such as PLINK. The CASTOR approach, as it is DBMS-based, readily accommodates multi-processing and multi-core processor architecture, and should significantly reduce the time required to perform GWAS or similar analyses, as well as extend the lifespan of current software tools by eliminating hardware bottlenecks.

2.6. Funding

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2.7. Acknowledgements

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2.9. Tables

Sample Identifier	SNP	SNP value	SNP position
Sample 1	rs3094315	CC	742429
Sample 1	rs41480945	CC	21227772
Sample 1	rs4040617	CG	95952929
Sample 2	rs3094315	TT	742429
Sample 2	rs41480945	AT	21227772
Sample 2	rs4040617	CC	95952929

Table 2.1. Genomic data structure with a large amount of duplicate data.

Code	Genotype	Allele_a	Allele_c	Allele_g	Allele_t
1	AA	2	0	0	0
2	CC	0	2	0	0
3	GG	0	0	2	0
4	TT	0	0	0	2
5	AC	1	1	0	0
6	AG	1	0	1	0
7	AT	1	0	0	1
8	CG	0	1	1	0
9	CT	0	1	0	1
10	GT	0	0	1	1

Table 2.2. Genotype dimension table (see genotypes_dim in Figure 2.1).

Id	Name	Discrete	Description	Column
1	Medication Dosing (units)	0	Medication dose per day in units	ptype1
2	Pain Severity	0	Severity of patient pain	ptype2
3	Smoking status	1	Never, former, current	ptype3

Table 2.3. Phenotype dimension table (see phenotypes_dim, Figure 2.1).

Code	Phenotypes_dim_id	Label
1	3	Never smoked
2	3	Former smoker
3	3	Current smoker

Table 2.4. Discrete phenotype dimension table (see phenotypes_discrete_dim, Figure 2.1).

Query	CASTOR (seconds)	Original (seconds)
query (gtypes) avg(int):	0.347017	871.454132
query (gtypes) sqrt(int):	0.096701	0.050104
query (gtypes) min(int):	0.319485	716.520514
query (ptypes) stddev(int):	0.014837	1341.081771
query (ptypes) avg(float):	0.010675	1417.641397
query (ptypes) sqrt(float):	0.003062	12.227921
query (ptypes) min(float):	0.009296	0.014992
query (ptypes) stddev(float):	0.013895	3.202807
query (ptypes) var_pop(float):	0.010164	16.41966
query (gtypes) count(int) where int is 1:	0.325984	16.669058
query (gtypes) count(int) where int is 3:	0.358017	641.80022
query (gtypes) count(int) where int is 4 and patient_id = 1234:	0.027244	668.470442

Table 2.5. Query return times based on a single table query (genotype or phenotype). All queries performed on the Oracle 11G DBMS.

	Original	CASTOR
Size of Genotype Data	97 gigabytes	6.8MB x 2000 tables = 13.3GB
Size of Phenotype Data	1.4 gigabytes	34MB x 14 tables = 476 MB
Total Dataset Size	98.4 gigabytes	13.776 gigabytes
Oracle 11G: Load Time (mins)	493.5 (8.23 hours)	90.3 (1.51 hours)
Oracle 11G: Total time to Run All Performance Tests (mins)	937.2 (15.62 hours)	0.15 (9.1 seconds)
Oracle 11G: Total Time to Perform Evaluation (mins)	1430.7 (23.85 hours)	90.18 (1.50 hours)

Table 2.6. Performance comparison results.

2.10. Figure

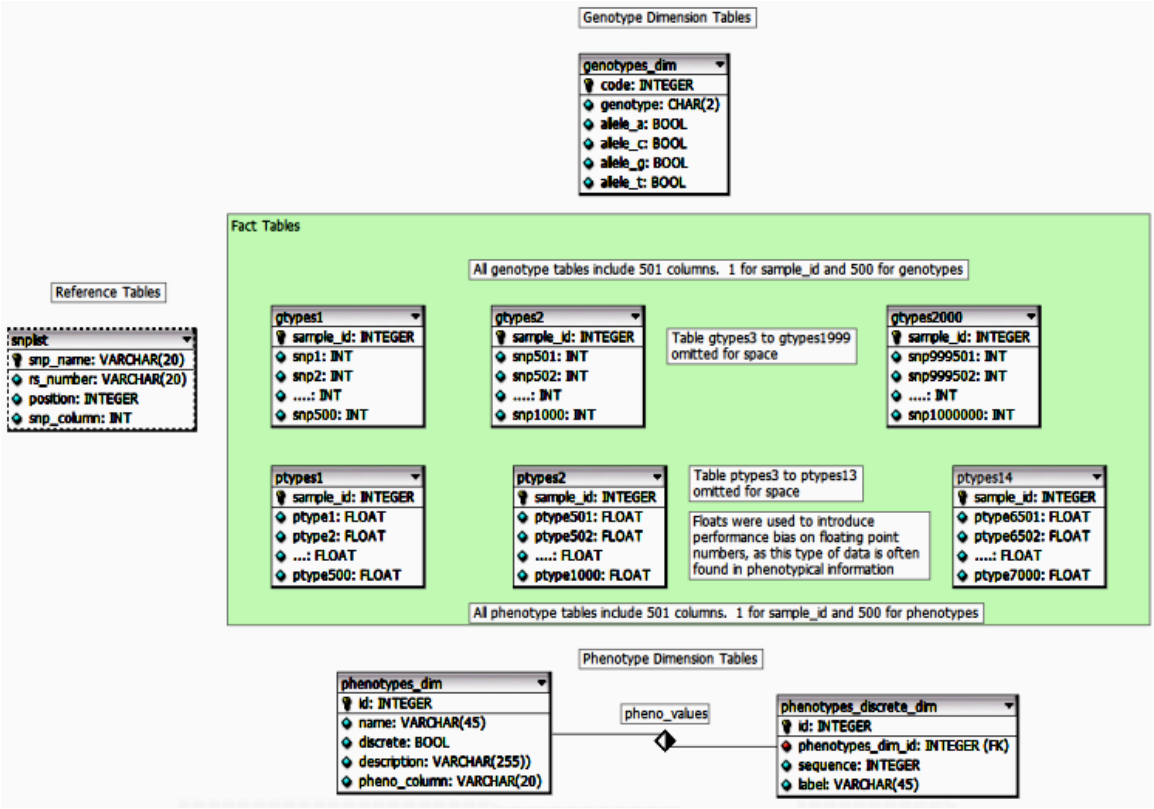

Figure 2.1. CASTOR data diagram.

2.11. Supplementary Data

2.11.1. EVOLUTION OF A CASTOR DATASET FROM A SEQUENTIAL FILE

Published online only as supplemental data at http://database.oxfordjournals.org/content/2010/baq029/suppl/DC1 and castor.pharmacogenomics.ca

2.11.1.1. Step 1

Sequential file (see Table 2.1).

2.11.1.2. Step 2

Normalized into 2 separate tables: 1 very wide genotype information table and one SNP information table

Sample Identifier	snp1	snp2	snp3	…	Snp1000000
Sample 1	CC	CC	CG	…	GG
Sample 2	TT	AT	CC	…	AA

Table 2.7. Very wide genotype information table (1,000,001 columns).

SNP	rs number	SNP position	SNP column
SNP_A-1909444	rs3094315	742429	1
SNP_A-2237149	rs41480945	767376	2
SNP_A-4303947	rs4040617	769185	3
…	…	…	…
SNP_A-2191727	rs12032643	247135059	1,000,000

Table 2.8. SNP Information table.

2.11.1.3. Step 3

The very wide genotype information table is horizontally divided into 2000 genotype result tables (tables 2-1,999 omitted for space).

Sample Identifier	snp1	snp2	snp3	…	snp500
Sample 1	CC	CC	CG	…	GG
Sample 2	TT	AT	CC	…	AA

Table 2.9. Castor genotype table 1.

Sample Identifier	snp999501	snp999502	snp999503	…	snp1000000
Sample 1	CC	CC	TT	…	GG
Sample 2	TT	CC	CC	…	AA

Table 2.10. Castor genotype table 2,000.

2.11.1.4. Step 4

Database is transformed into a multidimensional structure including descriptive "dimension" tables and optimized "fact" tables.

Code	Genotype	allele_a	allele _c	allele _g	allele _t
1	AA	2	0	0	0
2	CC	0	2	0	0
3	GG	0	0	2	0
4	TT	0	0	0	2
5	AC	1	1	0	0
6	AG	1	0	1	0
7	AT	1	0	0	1
8	CG	0	1	1	0
9	CT	0	1	0	1
10	GT	0	0	1	1

Table 2.11. Genotype dimension table.

Sample Identifier	snp1	snp2	snp3	…	snp500
Sample 1	2	2	8	…	3
Sample 2	4	7	2	…	1

Table 2.12. Castor multidimensional genotype table 1.

2.11.2. CASTOR EVOLUTION SCHEMA

Published online only as supplemental data at castor.pharmacogenomics.ca

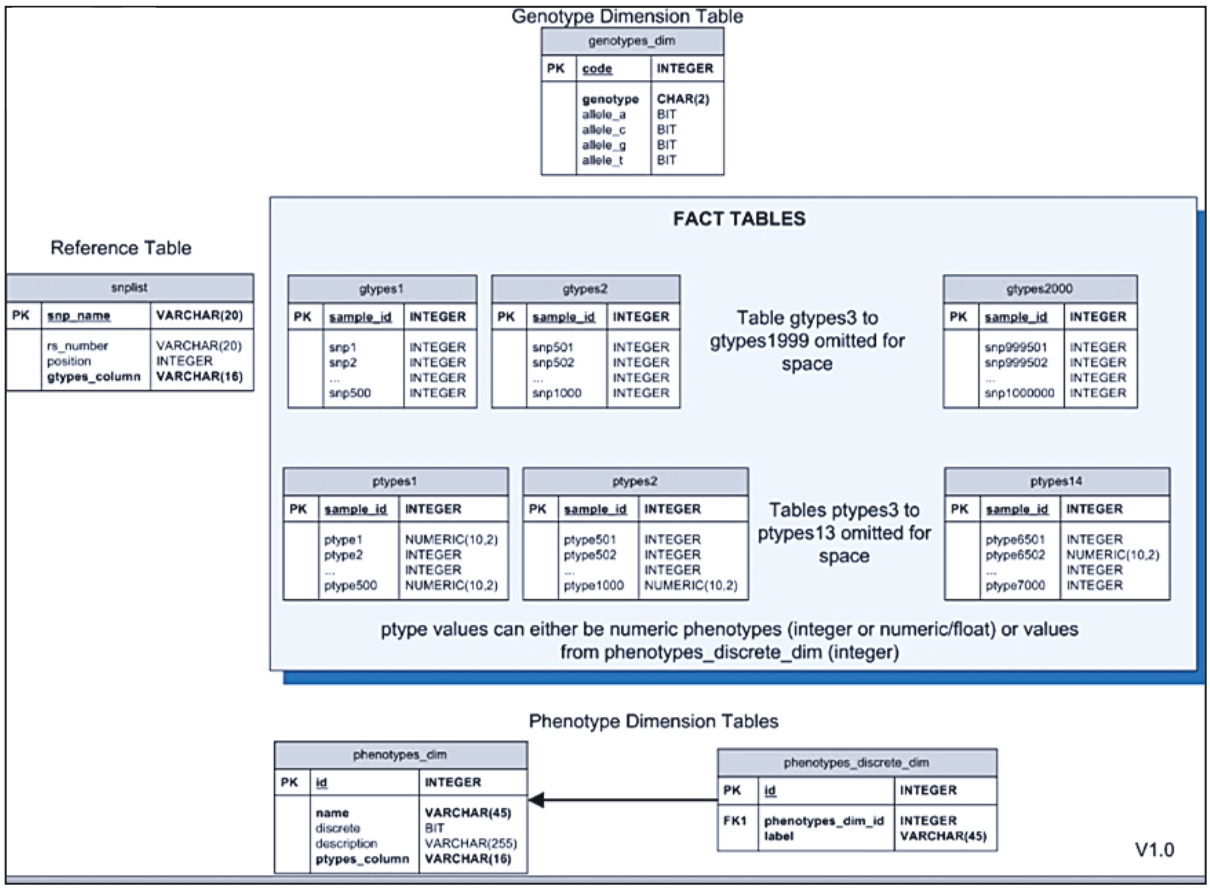

Figure 2.2. CASTOR data schema.

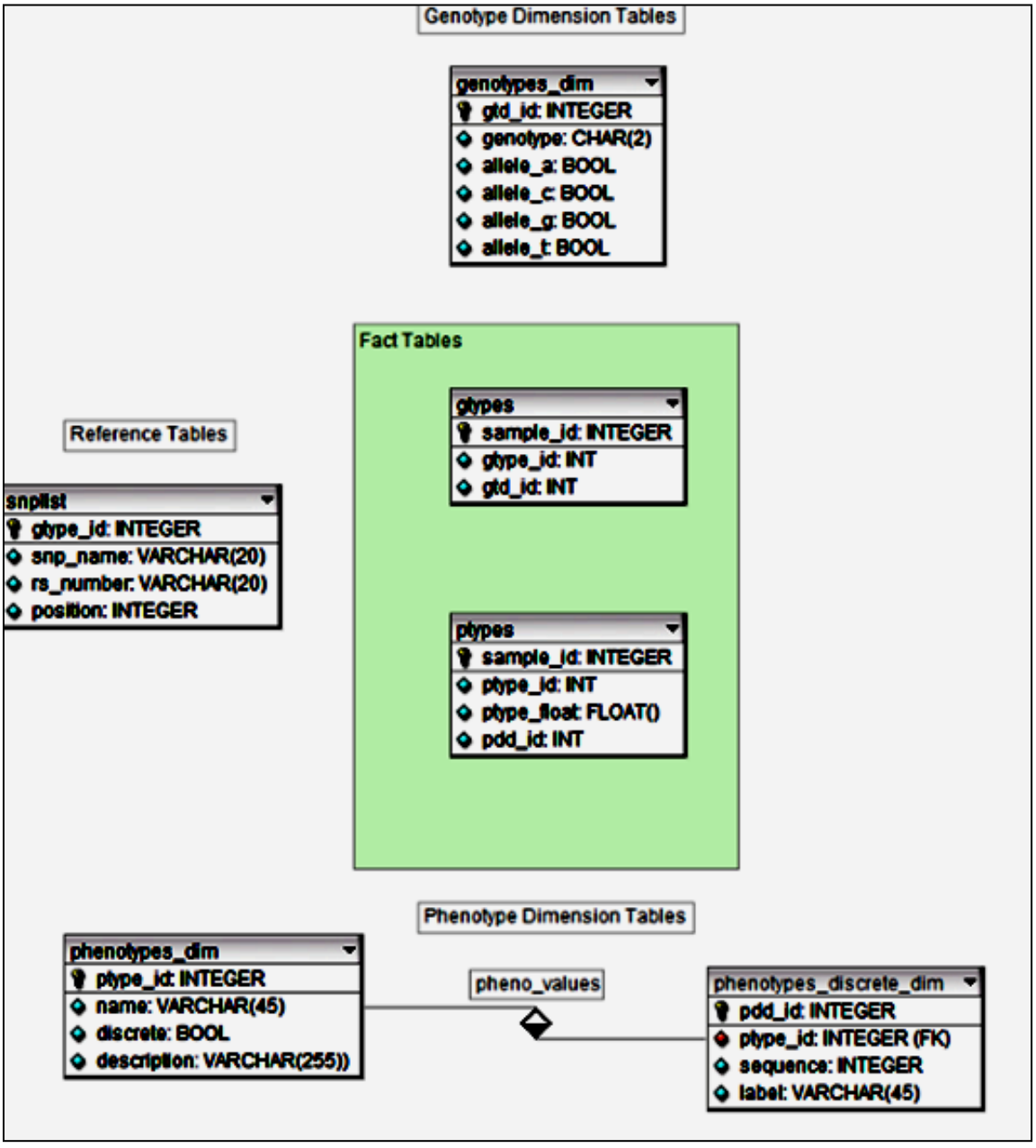

Figure 2.3. Original dataset data diagram.

3. FAST AND FRUGAL TREES: TRANSLATING POPULATION-BASED PHARMACOGENOMICS TO MEDICATION PRIORITIZATION

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3.1. Abstract

3.1.1. AIMS

Fast and frugal decision trees (FFTs) can simplify clinical decision making by providing a heuristic approach to contextual guidance. We wanted to use FFTs for pharmacogenomics knowledge translation at point-of-care.

3.1.2. MATERIALS AND METHODS

The Pharmacogenomics for Every nation Initiative (PGENI), an international non-profit organization, collects data on regional polymorphisms as a predictor of metabolism for individual drugs and dosages. We advanced FFTs to work with PGENI pharmacogenomics data to produce medication recommendations that are accurate, transparent and straightforward to automate.

3.1.3. RESULTS

By streamlining medication selection processes in the PGENI workflow, IT applications can now be deployed.

3.1.4. CONCLUSIONS

We developed a decision tree approach that can translate pharmacogenomics data to provide up-to-date recommended care for populations based on their medication-specific markers.

3.1.5. KEYWORDS

Fast and frugal decision trees, software agent, point-of-care, knowledge translation, information technology, personalized medicine, pharmacogenomics, clinical decision support, e-health, medication prioritization.

3.2. Introduction

Human populations have genetic variability, and this variability can lead to differences in response to certain medications (Badani et al., 2014, Evans and McLeod, 2003, Gage et al., 2008, Marsh, 2007). One of the problems is how to capture, continuously update, and represent this data in a usable format for medical decision making (Al Mallah et al., 2010, Bombard et al., 2013, Bombard et al., 2014, Bouffard et al., 2010, Finkelman et al., 2011, Gage et al., 2008, Marsh and van Rooij, 2009, Phillips et al., 2008, Ullman-Cullere and Mathew, 2011, van Rooij, 2007, van Rooij and Marsh, 2011, Watanabe et al., 2013), especially when that data is sub-optimally formatted (Al Mallah et al., 2010, Bombard et al., 2013, Bouffard et al., 2010, Finkelman et al., 2011, Marsh and van Rooij, 2009, van Rooij and Marsh, 2011). Often there are a mix of tables, protocols and flow-chart formats, drawn up by local specialists with a wide range of computer access and skills (Roederer et al., 2011a). Both meeting patient throughput requirements and meeting the complexity of establishing the right diagnosis and treatment regimen can put tremendous pressure on healthcare professionals which, in turn, can increase the chance of unnecessary errors (Kallberg et al., 2013, Pelaccia et al., 2014). Clinical Decision Support (CDS) can aid in the decision making process and can be an effective tool to assist clinicians in a timely fashion, delivering guidance as part of the clinician's routine workflow (Al Mallah et al., 2010, Bouffard et al., 2010, Marsh and van Rooij, 2009, Musen et al., 2014, van Rooij and Marsh, 2011, van Rooij et al., 2012). The aim of CDS is to achieve higher quality health care (Musen et al., 2014) and to lower overall costs by applying evidence-based medicine (Phillips et al., 2008, van Rooij et al.,

2012), such as the application of genomic risk factors (Al Mallah et al., 2010, Marsh and van Rooij, 2009, Phillips et al., 2008). CDS combines and structures clinical knowledge and other patient-related information to present alerts, interpretations, and recommendations at the appropriate time to the clinician (Al Mallah et al., 2010, Marsh and van Rooij, 2009, Musen et al., 2014, Phillips et al., 2008, van Rooij, 2007, van Rooij and Marsh, 2011, van Rooij et al., 2012). Indeed, CDS has wide applicability (Musen et al., 2014) and can be used from activities as diverse as cancer screening (Carney et al., 2014) and, in the future, potentially could provide diagnosis for Alzheimer's disease (Seixas et al., 2014).

Using Information Technology (IT) to establish active CDS systems (Musen et al., 2014, Sayyad Shirabad et al., 2012) can help automate the drug and dosing selection process based on pharmacogenomics data (Al Mallah et al., 2010, van Rooij and Marsh, 2011) , but a necessary first step is that data and the algorithms that underlie treatment regimens are consistently conceptualized and strictly formalized (Al Mallah et al., 2010, Bouffard et al., 2010, van Rooij, 2007). Once this has been achieved, the knowledge translation of this complex data will additionally require a pre-processing step that aids in the actual application at point-of-care. In other words, there is a missing link between the data and the automated application thereof, necessitating the use of a software agent (Dorin and Geard, 2014, Li and Mackaness, 2014, Sayyad Shirabad et al., 2012, Wang and Paranjape, 2013). Currently, translation is hampered by the absence of a mechanism that can interpret complex data and put it in a relevant and concise format for rapid and applicable decision making (Al Mallah et al., 2010, Carney et al., 2014, Dorin and Geard,

2014, van Rooij et al., 2012). Software agents can assist users in meaningful reasoning by predigesting, to varying degrees, some of the difficulties and intricacies inherent in complex data (Dorin and Geard, 2014, Li and Mackaness, 2014, Sayyad Shirabad et al., 2012, Wang and Paranjape, 2013). Software agents exhibit reasoning and/or learning capacities (Alonso et al., 2003) and are part of a larger group of methodologies in Artificial Intelligence (AI) (Serenko and Detlor, 2004). Thus software agents can aid in speeding up the translation process, and minimize the effort to present applicable data in a usable format (Dorin and Geard, 2014, Mohammadzadeh et al., 2013). However, in order for a software agent to work it needs to operate on a data structure that will support this reasoning capability (Dorin and Geard, 2014).

Data structures, alongside algorithms, form the backbone of any software development process (Venkatachalam et al., 2014). We based our approach on a decision tree model (Venkatachalam et al., 2014) to provide a data structure to support the decision making of the software agent. We hypothesized that decision trees can help us to create an abstract view of the data to aid in the comprehension of pharmacogenomics algorithms, while at the same time allowing us to get rid of needless complexities in both the internal (database) and external (visual) representations of these algorithms. Specifically, we applied the fast and frugal heuristic methodology on decision making (Luan et al., 2011, Martignon et al., 2008), as this tree format has proven to be of use in medical decision support in pediatrics and psychiatry (Fischer et al., 2002, Jenny et al., 2013), and has also been used in emergency medicine (Green and Mehr, 1997), which is by its nature a time-constrained environment. Fast and frugal trees (FFTs) support an

economical form of decision making through simplification of data (Luan et al., 2011, Martignon et al., 2008). We aimed to test the applicability of this fast and frugal tree (FFT) approach to another medical process, namely a medication selection process where the constraints are genomic risk factors. Additionally, we want to see if the FFT model could be easily implemented in IT applications and, in future, provide a data structure for software agents to automatically process genomic algorithms.

Our test case was provided by The Pharmacogenomics for Every nation Initiative (PGENI), an international non-profit organization, based in the USA, which aims to personalize medicine in the developing world. PGENI uses knowledge of regional polymorphisms, as ethnicity itself can be a significant predictor of metabolism, for individual drugs and dosage recommendations. Since regions have genetic variability the frequency of pharmacogenomics markers will affect response to medications in specific (sub) populations. The aim of PGENI is to collect and use these frequency rates in each country/region to inform optimal dosing strategies, even in the absence of patient-specific genotyping (Engen et al., 2006, Marsh et al., 2006, Marsh, 2008, Mitropoulos et al., 2011, Mitropoulos et al., 2012, Pharmacogenomics for Every Nation Initiative, Roederer and McLeod, 2010, Roederer et al., 2011b).

Our input data consisted of PGENI decision data, when available, on diseases with the greatest impact in the developing world (Roederer et al., 2011b). Through PGENI, when data has been collected and curated, the selection of the treatment regimen is based on the overall risk represented by frequency of polymorphisms in the key genes in each country (Roederer et al., 2011b). For example, in the treatment of Rheumatoid

Arthritis (RA) the worldwide population distribution and prevalence of certain genetic variants can play a role i.e. the second line therapy for methotrexate refractory RA, is based on the geographical dispersal of TPMT and NAT2*4 polymorphisms (Engen et al., 2006, Pharmacogenomics for Every Nation Initiative).

Through PGENI, a disruptive population-based approach had culminated in varying decision protocols, flow charts and schematic models to help interpret pharmacogenomics data and inform medication and dosing choices in clinical practice. This had led to representations that, though densely packed with knowledge, were not in the optimal format to provide effective translation for decision making, as both the complexity and wildly differing ways of representing this data created unwanted ambiguity in the decision guidance as exemplified by the PGENI treatment advisories for uncomplicated malaria (Figure 3.1) and pain (Figure 3.2). This made it both time consuming to produce and update the recommendations, and additionally it is difficult for clinicians to interpret the data accurately (Luan et al., 2011, Martignon et al., 2008). Furthermore, it is impossible for databases to store this data efficiently when it is in disparate formats (Bouffard et al., 2010).

Our fast and frugal approach creates decision trees that are accurate while eliminating cognitive bias. In other words, it prunes the decision tree while not losing any decision making power (Luan et al., 2011, Martignon et al., 2008). By eliminating branches and visual clutter the method produces a tight series of yes and no answers (Luan et al., 2011, Martignon et al., 2008). Additionally one of the answers on the tree always directly leads to a decision, allowing an overall increase in decision speed (Luan

et al., 2011, Martignon et al., 2008). These properties save effort in trying to store and interpret data and make it desirable for IT integration (Al Mallah et al., 2010, Bouffard et al., 2010, Marsh and van Rooij, 2009, Phillips et al., 2008, van Rooij, 2007, van Rooij and Marsh, 2011) and human interaction (Luan et al., 2011, Martignon et al., 2008, Safavian and Landgrebe, 1991). Our study developed a methodology based on the fast and frugal approach to formalize the decision-making process for diseases and conditions with known population-based pharmacogenomics interactions and known available drug regimens.

3.3. Methodology

The Fast and Frugal Tree heuristic operates on an ordered sequence of binary cues, where for each node at level n in the tree, one child at level n-1 is labeled by a decision and another child at level n-1 leads to the consideration of the next cue in the ordering. It is often ordered to split the data on a series of most statistically relevant decisions first, leading to a quick partition of the problem space whereby the most common answers can be rank ordered (Luan et al., 2011, Martignon et al., 2008). We chose a format that results in a left leaning tree where a "yes" answer is followed by another question and a "no" answer results in a direct outcome, which in our case would be a medication recommendation.

Our *augmented* FFT modified the previously published FFT (Luan et al., 2011, Martignon et al., 2008) in the following four ways:

1. It added both the ability to test for more than one condition simultaneously: A and/or B as well as their negations, and allowed for additional outcomes in contrast to the dichotomous decision nature of previous FFTs, while maintaining the original FFT skeleton (Luan et al., 2011, Martignon et al., 2008).
2. As the input data for the tree is not machine derived, the tree rank ordering is not directly computable, consequently it has not been explicitly partitioned to have the most statistically relevant question first, followed by the second most relevant, etc.
3. A best fit to the FFT model was determined manually by finding natural splits in the data and removing noisy data, subsequently a domain expert ensured the validity of the chosen cues and equivalency of data content.
4. If during the process of modification, the best fit did occur as a decision tree that was not adhering to the FFT skeleton format it was re-configured by using transformation according to De Morgan's Laws (Goodstein, 2012). The process of applying De Morgan Law 1 and De Morgan Law 2 (Goodstein, 2012) on non-adhering trees is shown in Figure 3.3.

Steps 3 and 4 were used iteratively until the input data was successfully modified to adhere to the augmented FFT format.

Once the trees were in this format we tested the applicability of the format for IT use; the resulting augmented FFTs were implemented into a series of flashcards with a

number of yes/no answers. We used HungryMedia software from GitHub for the purpose of automation (Harrison, 2014).

3.4. Results

In working with the constraints posed by this specific data we had to adapt the FFT methodology (Martignon et al., 2003). Subsequently our implementation approach differs from previously published FFTs (Fischer et al., 2002, Green and Mehr, 1997, Jenny et al., 2013, Luan et al., 2011, Martignon et al., 2008), in that it can test for more than one condition and allow for more than two possible decision outcomes per tree, and that the most common answer is not always necessarily rank ordered from high to low on the right node of the split. However, we retained the terminating right nodes (Green and Mehr, 1997) and therefore eliminated any loops in previous schemas. We strictly enforced a left leaning tree structure with a "yes" answer to the next cue containing the next question, and a "no" answer leading to a recommendation. Additionally, extra steps were added where necessary to resolve conflicts. Figure 3.3 illustrates the process of trading-off an addition to overall tree size to achieve greater simplicity in the augmented FFT. Nonetheless, this resulted in a minimal number of conditional switches to rationalize the earlier schematics into augmented FFTs, reducing each decision outcome, i.e. the PGENI recommendation, to the least possible number of questions without losing accuracy. Furthermore, some schematics required multiple iterations of rationalization before reaching the desired format. Overall, all PGENI input data (13/13 schema) was successfully transformed into augmented FFT format. After this process these trees

maintained all the information contained in the original input. The noticeable reduction in complexity and overall improvement obtained through the augmented FFT approach is illustrated by the following examples: The treatment advisory for uncomplicated malaria in the original diagram is shown as Figure 3.1; by applying the augmented fast and frugal methodology, the flowchart for uncomplicated malaria treatment can now be reduced to Figure 3.4. Likewise in the treatment of pain, the original drawing of the treatment option shown in Figure 3.2 is significantly reduced in the augmented fast and frugal format shown in Figure 3.5. However, as demonstrated by contrasting both cases, no information was lost in either case as a result of the transformation.

A complete cross comparison of the properties of the data in the original format compared to the same data in augmented FFT format is shown in Table 1. FFTs provide a data structure that is ideally suited for IT use. The ability to readily implement our derived data structure, the augmented FFT using IT, is demonstrated in the example workflow outlined in Figure 3.6. The original PGENI schematic is transformed into the augmented FFT. One possible trajectory or path through the decision tree for methotrexate refractory rheumatoid arthritis is shown in Figure 3.6. This approach is generalizable as any format of the original schema for any given medication as developed by PGENI healthcare professionals can be standardized into an augmented FFT format and subsequently be automated.

The end users, e.g. clinicians in each country will now be able to access this information via flashcards (Figure 3.6), which will ask a series of questions specific to the medication in question and incorporate country-specific genotype information for use

on one specific patient at point of care. This ultimately reports the least risk medication option for the disease in question in a particular country/ethnicity.

3.5. Discussion

Currently, driven by both new medical discoveries and information technology, healthcare data is increasingly computerized across all levels and disciplines (Snowdon et al., 2014). Additionally, information that must be managed in a public health context is always changing and often quite complex (Finkelstein et al., 2012, Goetz Goldberg et al., 2012). eHealth is not a straightforward Information Technology (IT) activity that by itself can deliver the sought after improvements in healthcare services' quality and capacity (Marsh and van Rooij, 2009, van Rooij and Marsh, 2011, van Rooij et al., 2012). Although much work has been done over the past decade on novel tests and developing evidence-based medicine, in many cases, complexity in data interpretation and delivery have prevented routine uptake (Marsh and van Rooij, 2009, Musen et al., 2014, van Rooij and Marsh, 2011, van Rooij et al., 2012).

Barriers to successful clinical implementation of pharmacogenomic knowledge are plentiful and well documented. In many cases, policy makers still require more evidence that changing drug selection and/or dosing based on genotype improves patient outcomes in real-world settings. For example, although research has identified a strong correlation between warfarin dosing and an individual's genetic make-up this insight has not yet resulted in widespread clinical uptake. Implementation case studies can help bridge this divide (van Rooij et al., 2012). Arguably, there is a direct connection between

applied pharmacogenomics and IT use in the clinic, as easy access to relevant pharmacogenomics data promises to provide the necessary decision support for clinicians and thus will be a part of the workflow of any evaluation or case study (Marsh and van Rooij, 2009, van Rooij and Marsh, 2011, van Rooij et al., 2012).

The successful application of eHealth requires an automated support approach with the necessary expertise for, and understanding of, the context surrounding specific medical decisions (Marsh and van Rooij, 2009, Musen et al., 2014, van Rooij et al., 2012). Increasing the efficient use of available data, FFTs represent a straightforward but powerful model to work efficiently and effectively when integrated into the clinical workflow (Fischer et al., 2002, Green and Mehr, 1997, Jenny et al., 2013, Katsikopoulos et al., 2008). Recently, an FFT has been developed to help ascertain depression in patients (Jenny et al., 2013). In addition, as demonstrated in this project, FFTs can efficiently guide information search, model available knowledge, and guide pharmacogenomic-based decision making in clinical practice. Once implemented into systems as CDS, FFTs can behave like software agents as they support reasoning and learning capabilities (Alonso et al., 2003, Harper, 2014a, Serenko and Detlor, 2004); this can be achieved by proactively answering questions contained in the tree directly from available data sources, as well as providing an approach whereby clinical outcomes can become an additional input to the system.

With the emerging use of information technology (IT) in the application of medical knowledge in the clinic, efforts to automate CDS are on the rise (Al Mallah et al., 2010, Badani et al., 2014, Bombard et al., 2013, Bombard et al., 2014, Ullman-

Cullere and Mathew, 2011) (Carney et al., 2014, Dorin and Geard, 2014, Li and Mackaness, 2014, Mohammadzadeh et al., 2013, Sayyad Shirabad et al., 2012, Seixas et al., 2014, Wang and Paranjape, 2013, Watanabe et al., 2013). PGENI's research and data collection efforts had culminated in decision flow charts and models (Engen et al., 2006, Marsh et al., 2006, Marsh, 2008, Roederer and McLeod, 2010, Roederer et al., 2011b), but their knowledge-based translation was impeded by the absence of a standardized data structure (Alonso et al., 2003, Carney et al., 2014, Dorin and Geard, 2014, Li and Mackaness, 2014, Luan et al., 2011, Martignon et al., 2008, Mohammadzadeh et al., 2013, Sayyad Shirabad et al., 2012, Seixas et al., 2014, Serenko and Detlor, 2004, Wang and Paranjape, 2013). By applying and modifying the FFT heuristic methodology (Martignon et al., 2003) a model was developed to translate pharmacogenomic data to aid in medication selection. The left-leaning tree used in this project is conceptually simplest but other tree-shapes are possible, and may, in certain situations where additional information is available about the costs of certain cues and classification errors, be preferable (Martignon et al., 2003). Part of a wider trend, for effective translation at point-of-care, the design of software agents coupled to CDS is becoming a requirement to address specific medical front-line needs in the application of evidence-based research (Dorin and Geard, 2014, Li and Mackaness, 2014, Mohammadzadeh et al., 2013, Sayyad Shirabad et al., 2012, Wang and Paranjape, 2013). FFTs solve two problems that are commonplace in the translation of evidence-based medical data: Firstly, reducing the cognitive cost of accurately interpreting differing protocols and flow charts providing guidance (Green and Mehr, 1997, Mitropoulos et al., 2011), and secondly, addressing the

lack of overall standardisation which prevents the scalable IT integration of decision data (Al Mallah et al., 2010, Bouffard et al., 2010, Dorin and Geard, 2014, Li and Mackaness, 2014, Marsh and van Rooij, 2009, Mohammadzadeh et al., 2013, Phillips et al., 2008, Sayyad Shirabad et al., 2012, van Rooij and Marsh, 2011, van Rooij et al., 2012, Wang and Paranjape, 2013). FFTs create a formalized view to aid in the comprehension of evidence-based decision data (Fischer et al., 2002, Jenny et al., 2013, Luan et al., 2011, Martignon et al., 2008), e.g. pharmacogenomic algorithms, while at the same time allowing us to get rid of needless complexities in the visual representation of medical guidance based on the data (Green and Mehr, 1997, Martignon et al., 2003). FFTs were found to be easy to convey to physicians (Dhami and Harries, 2001), and the knowledge contained in an FFT was readily adopted in a study on decision making whether or not to admit patients to the coronary care unit (Green and Mehr, 1997).

Implemented FFTs open the prospect of automatically generating recommendations based on the trees, where data will be processed, as far as possible, without the clinician having to manually answer every question. Put another way, the tree can be truncated by localization and the available data, prior to be presented to the healthcare provider in question. Outcomes data based on recommendations, can create a feedback loop, and become a direct input to subsequent guidance, allowing the implemented FFT to become a learning tree (Harper, 2014a).

Using FFTS as an interpretive and computational framework to deliver support at point-of-care, clinicians can be empowered to make fast and accurate decisions on complex data (Katsikopoulos et al., 2008, Martignon et al., 2003) and thus improve their

use and selection of treatments. Proactively processing and delivering decision guidance on demand, FFTs, as a data structure implemented in software using a transactional database, support the easy storage and retrieval of both context-specific and up-to-date medical data.

3.6. Conclusions

The implementation of FFTs speed up the process of knowledge application by reducing the time needed to accurately interpret the data (Katsikopoulos et al., 2008, Martignon et al., 2003) in differing handmade models and schematics depicting the relationship between genomic markers and medication prioritization. FFTs eliminate any pictorially based cultural (Rashidi-Ranjbar et al., 2014) biases as their interpretation is formalized (Martignon et al., 2003). In effect we augmented the "answer size" and "tested for" values in our decision trees to come up with an *augmented* fast and frugal tree as the to fit within the constraints posed by the data in the project. FFTs provide rationalisation and standardisation of data for medical decision making (Katsikopoulos et al., 2008, Martignon et al., 2003). Because of these characteristics, and the if-then-else approach resulting from its particular tree structure in our augmented FFT, it is also ideally suited for IT use. Left leaning FFT decision trees, as they are rudimentary binary trees, are straightforward to implement in both database management systems and software applications (Bulajic et al., 2012). Automating and visualizing the data effectively for end-users, we converted our augmented FFTs into a series of flash cards

(Harrison, 2014) thereby showing the ability to simplify and streamline medication prioritization and selection processes (Figure 3.6).

When implemented through IT, FFTs can provide active CDS systems (Musen et al., 2014), with a software agent (Dorin and Geard, 2014, Li and Mackaness, 2014, Mohammadzadeh et al., 2013, Sayyad Shirabad et al., 2012, Wang and Paranjape, 2013) that can cut through complexity by providing a heuristic approach to contextual guidance (Katsikopoulos et al., 2008, Martignon et al., 2003). When provided with clinical outcomes data, FFTs have the potentiality to become a learning tree. Tree structures are easy to understand for humans (Fitch, 2014) and machines alike (Bulajic et al., 2012). This project emphasizes that FFTs provide a structure for active CDS deployment to support knowledge-based translation. Whereas here FFTs address the lack of standardization hampering the scalable IT integration of pharmacogenomics guidance data, we believe this tenet will hold true for other evidence-based guidance data as well. More research is therefore urgently needed to look at broader clinical implementation of FFTs as a data structure to support the development of software agents in CDS.

3.7. Future Perspectives

In the immediate future, we anticipate that the PGENI genotype database will continue to be updated, thus allowing data to be used with region or country specificity (Mitropoulos et al., 2011, Mitropoulos et al., 2012). Region-specific genotype data could therefore be incorporated into the pre-selection of FFT trees. For example, in regions with low TPMT genotype frequencies, the recommendations would automatically be

filtered to pre-answer this question. By storing FFT trees alongside these updates, FFT selection and reconstitution can become a dynamic process dependent on clinician derived input such as region or (sub) population, disease type, or disease state.

Ultimately, medical informatics support for personalized medicine will centre around data organization and interpretation, most pressingly the ability to make rapid decisions on highly complex data or data sets. In a Big Data environment (Denny, 2014), CDS will require cognitive toolsets; both to make sense of data and in order to present it in the appropriate context for accurate decision making. Cognitive science techniques will help inform and shape pharmacogenomics applications, which can benefit greatly from applying tree based data structures, such as fast and frugal decision trees (FFTs), to create a divide and conquer approach on the data. It will become increasingly important not only to identify the shortest path to a particular pharmacogenetically-enhanced treatment advisory, but also to learn to ask the right questions.

3.8. Key Issues

3.8.1. Introduction

- Pharmacogenomics helps to explain the large individual variability in response to any given medication.
- Information Technology (IT) through eHealth can help in personalising medication selection.

- Genetic variability can inform medication selection criteria on a population basis to reduce toxicities, improve treatment responses for patient (sub) populations, and improve overall clinical outcomes.

3.8.2. METHODOLOGY

- Standardisation of data through the use of decision trees provides a model to incorporate sensitivity to both country and regional population's needs in the translation of personalized medicine to point-of-care.
- Fast and Frugal Trees (FFTs) can be modified to work with pharmacogenomic data

3.8.3. RESULTS

- Fast and Frugal Decision Trees (FFTs) allow for rapid decision making on complex pharmacogenomic data.
- FFTs provide an ideal data structure for IT implementation. Using FFTs as a data structure in software helps to prepare complex data for use at point-of-care.

3.8.4. DISCUSSION

- Encapsulated in CDS, FFTs have the potentiality to support software agent behaviours like reasoning and learning.

3.8.5. CONCLUSION

- Clinical decision support systems will require software agents to translate complex data to point-of-care.

3.8.6. FUTURE PERSPECTIVES

- In a Big Data environment, cognitive science toolsets will be used to shape and inform pharmacogenomic applications to provide decision support to clinicians.

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3.11. Table

Before	After
Differing representations	Common representation
Differing navigation schemes	Explicit navigation scheme
Partially implicit or semi-explicit navigation scheme	Single (internally constant, universal) navigation scheme
Varying cognitive issues across representation and within execution of navigation schemes	Consistent cognitive load with respect to representation and execution
Need to read/process/consider all data	Need to consider data only when needed
Assessment termination point is not clearly indicated	Obvious termination
Not reconstructable from database	Reconstructable from database and updatable
Software implementation problematic	Direct software implementation possible

Table 3.1. A cross comparison of the properties of earlier schematics labelled before, and the inherent benefits after turning this data into augmented FFT format.

3.12. Figures

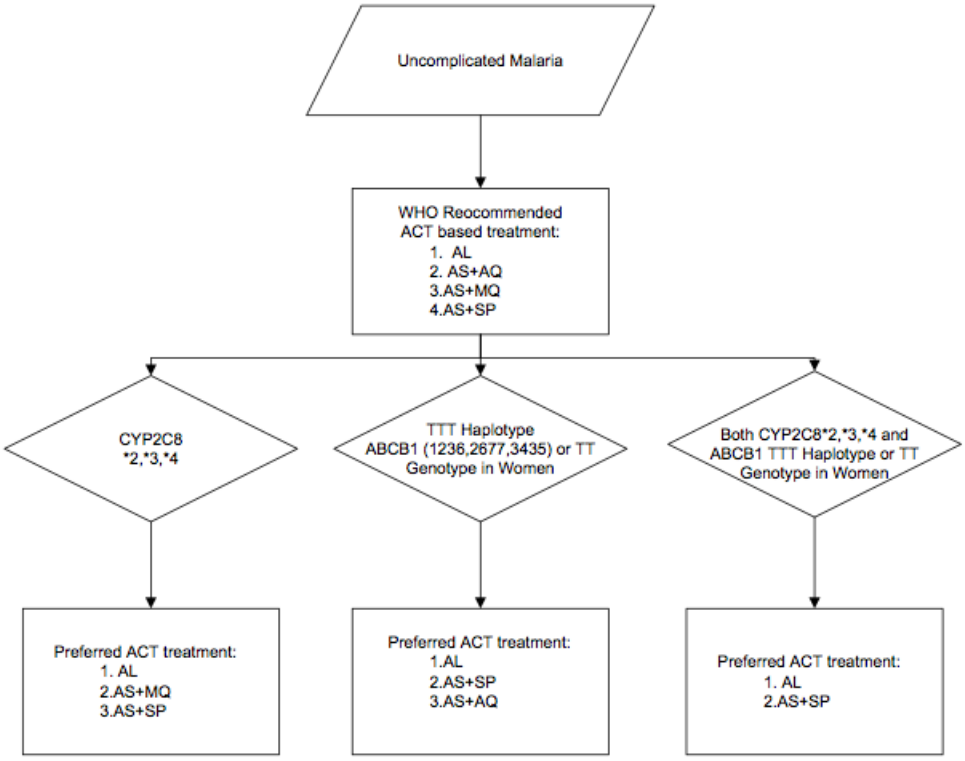

Figure 3.1. The PGENI pharmacogenomically-enhanced treatment advisory for uncomplicated malaria not in FFT format. ACT: Artemisinin-based combination therapy; AL: Artemether/lumefantrine; AQ: Amodiaquine; AS: Artensuate; MQ: Mefloquine; SP: Sulfadoxine/pyrimethamine; WHO: World Health Organization).

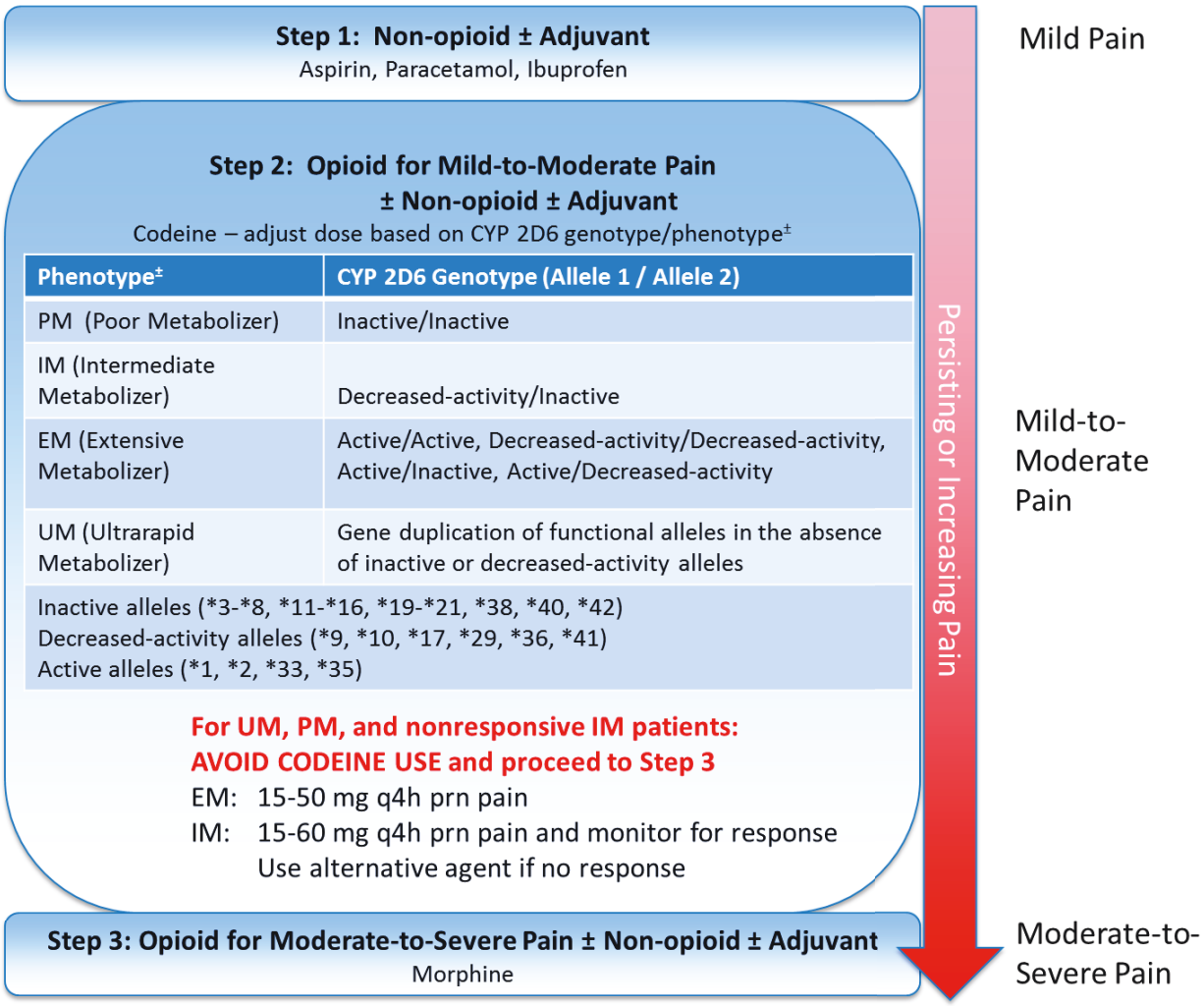

Figure 3.2. The PGENI pharmacogenomically-enhanced treatment advisory for pain not in FFT format.

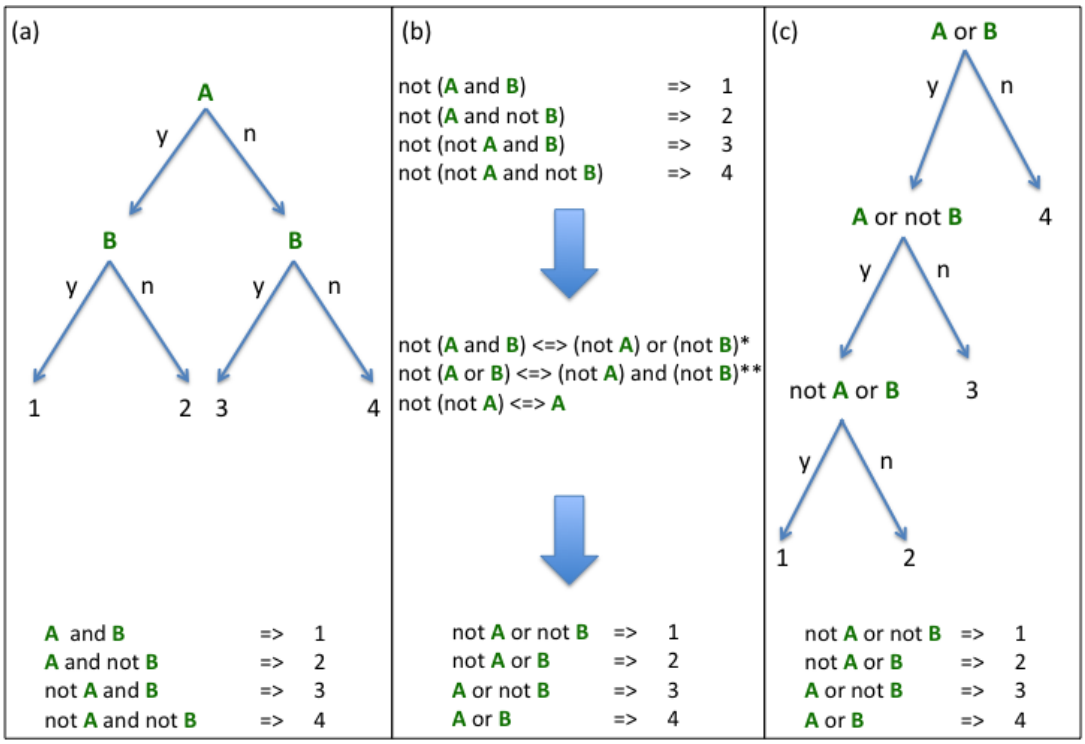

Figure 3.3. Trade-off of simplicity and depth when converting a PGENI tree to augmented FFT format. (a) The PGENI tree, with cue-conditions leading to each outcome; (b) Transformation of cue-condition formulae to allow each outcome to be accessible via ``no'', as required in augmented FFT format. This is done by applying De Morgan's (*De Morgan #1; **De Morgan #2) and standard logic laws; (c) Corresponding augmented FFT.

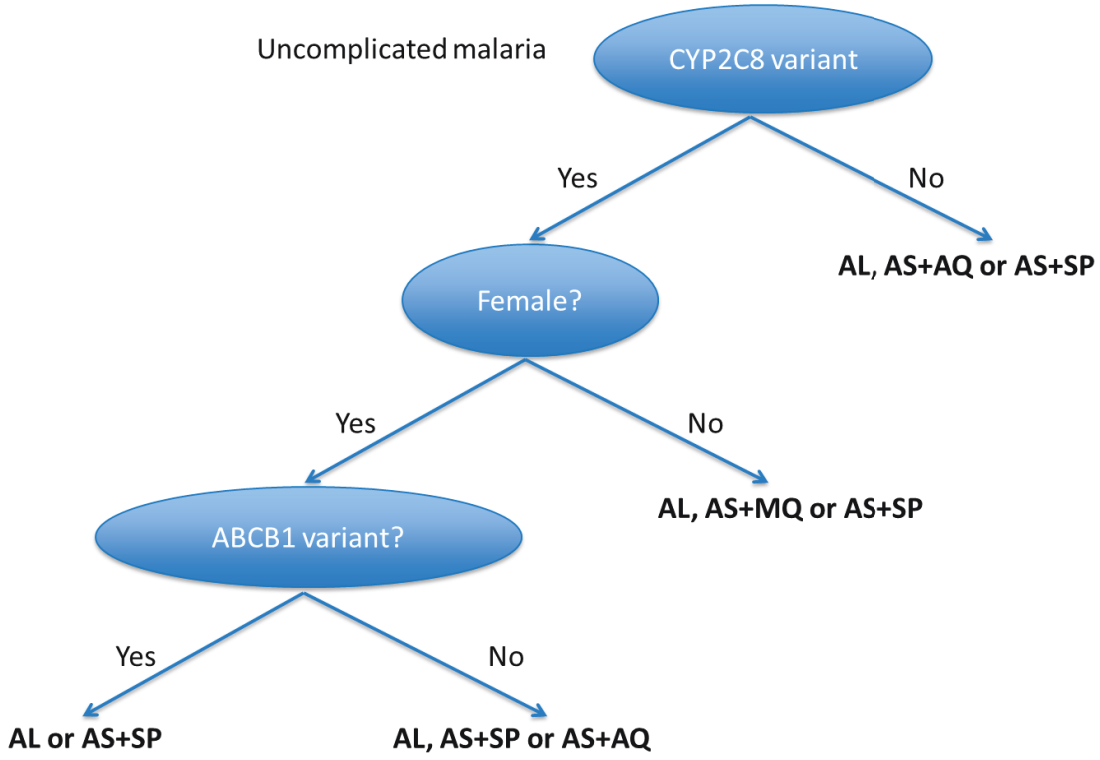

Figure 3.4. The PGENI treatment advisory for uncomplicated malaria in FFT format. Bold text represents drugs listed on the WHO Essential Medicines List. AL: Artemether/lumefantrine; AQ: Amodiaquine; AS: Artensuate; MQ: Mefloquine; SP: Sulfadoxine/pyrimethamine.

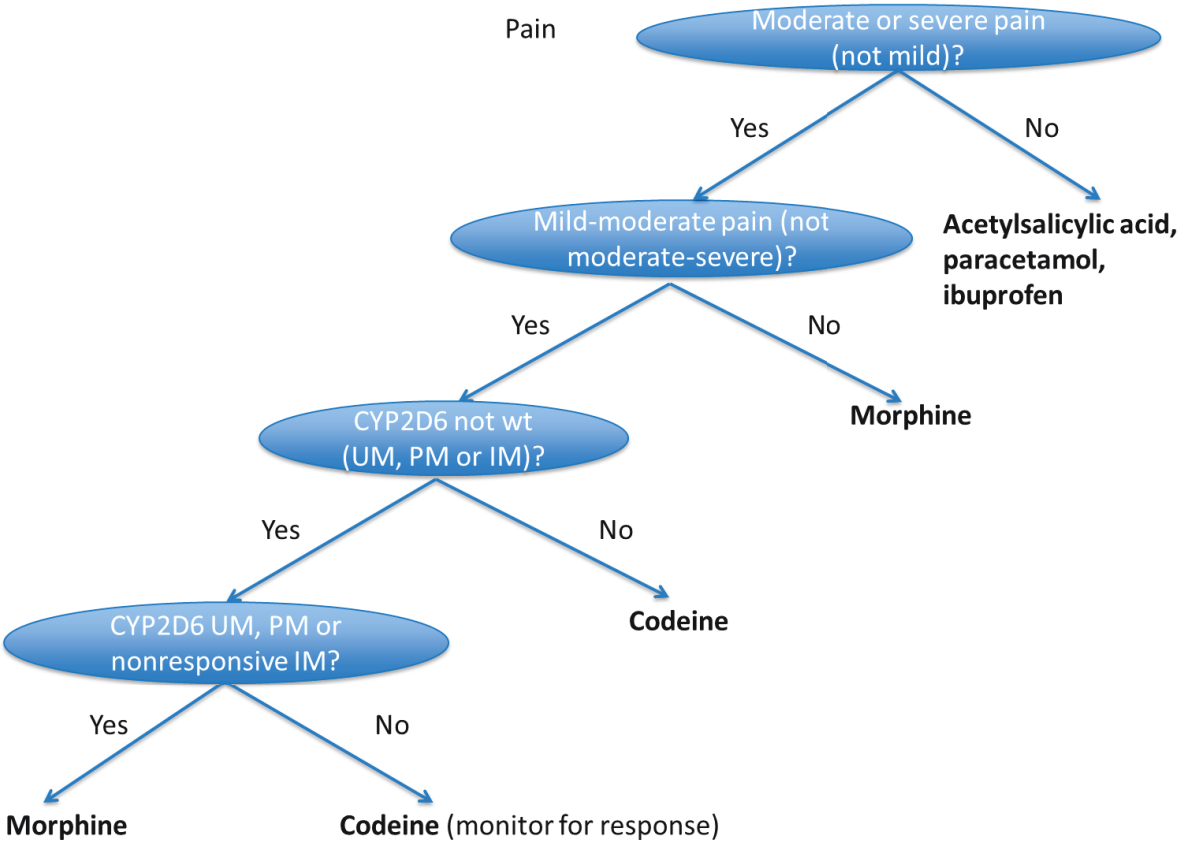

Figure 3.5. The PGENI treatment advisory for pain in FFT format. Bold text represents drugs listed on the WHO Essential Medicines List. Paracetamol is also known as acetaminophen in North America. IM: Intermediate metabolizer; PM: Poor metabolizer; UM: Ultrarapid metabolizer.

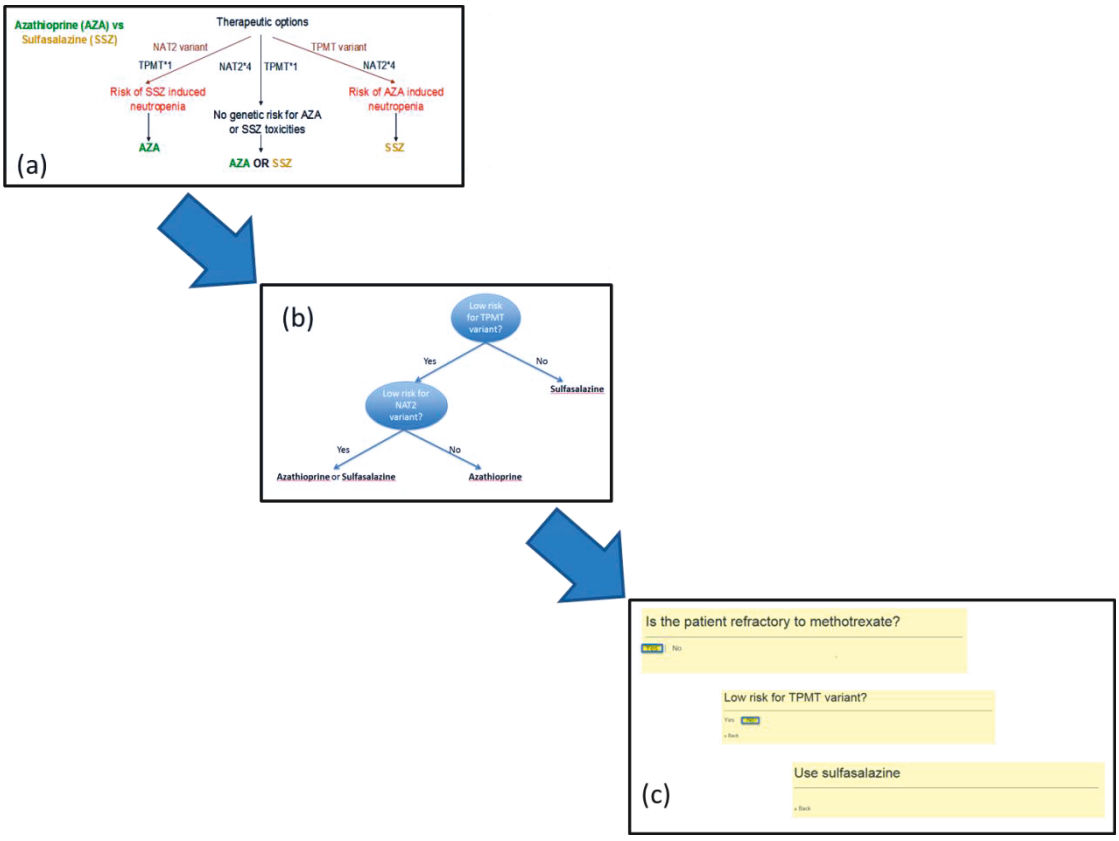

Figure 3.6. Flow of data through the PGENI project. (a) Schema including known pharmacogenomic information for each disease, in this case methotrexate refractory rheumatoid arthritis, were developed by PGENI healthcare professionals. No template or standardization techniques were used and each schematic has a different appearance. (b) We apply our augmented FFT methodology to develop standardized medical decision trees for each disease, these follow the same format regardless of the original schematic appearance. (c) We converted the augmented fast and frugal trees from (b) into a series of flash cards with yes/no answers for easy access and use at point-of-care.

4. A BRIDGING OPPORTUNITIES WORK-FRAME TO DEVELOP MOBILE APPLICATIONS FOR CLINICAL DECISION-MAKING

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4.1. Abstract

4.1.1. BACKGROUND

Mobile applications (apps) providing clinical decision support (CDS) may show the greatest promise when created by and for frontline clinicians. Our aim was to create a generic model enabling healthcare providers to direct the development of CDS apps.

4.1.2. METHODS

We combined Change Management with a three-tier Information Technology (IT) architecture to stimulate CDS app development.

4.1.3. RESULTS

A Bridging Opportunities Work-frame (BOW) model was developed. A test case was used to successfully develop a mobile application.

4.1.4. CONCLUSIONS

Healthcare providers can re-use this globally applicable model to actively create and manage regional decision support applications to translate evidence-based medicine in the use of emerging medication or novel treatment regimens.

4.1.5. KEYWORDS

Clinical Decision Support, Clinical Guidance, eHealth, mHealth, Mobile Application Model Development, Point-of-Care

4.2. Lay Abstract

Medical information needs to be structured in a way that it can be used in a time-constrained environment. This project looked at the process of creating mobile applications (apps), to help medical professionals rapidly apply new knowledge to better treat patients. We developed a novel system that allowed medical professionals to have a leading role in development. With the input from a pharmacist we created a mobile application to deal with pharmacy and patient-related decisions surrounding newly available anti-cancer pills. Other medical professionals could also use this approach to make apps to provide information with relevance to their medical decisions.

4.3. Background

The efficient translation of evidence-based science to point-of-care is a well-known problem (Charani et al., 2013, Mosa et al., 2012, van Rooij et al., 2012). Uptake can be hampered by a lack of delivery systems or by the absence of required policy changes (Al Mallah et al., 2010, van Rooij and Marsh, 2011, van Rooij et al., 2012). According to a recent scoping review (a review category that outlines existing research), the use of handheld computers is on the rise in clinical settings where they are used by healthcare professionals for patient documentation, patient data access, and general information lookup (Mickan et al., 2013). However, there are few examples of their use in clinical decision support (CDS) with the aim to translate evidence-based data to point-of-care (Mickan et al., 2013, Prgomet et al., 2009). Handhelds may be most effective when used in time-constrained settings, but effectiveness and outcomes research is generally lacking (Mickan et al., 2013, Prgomet et al., 2009). Most documented decision support is not specific to a particular workflow and simply concerns the use of digital versions of generally available drug information (Berner et al., 2006, Prgomet et al., 2009). However, when based on locally developed guidelines, decision support is accessed frequently and has a measurable impact (Berner et al., 2006, Sintchenko et al., 2005). For example, based on this premise, handhelds have been used in an outpatient setting to improve treatment decisions for the prescription of nonsteroidal anti-inflammatory drugs (NSAIDs) (Berner et al., 2006). And, in a critical care setting, tailored decision support led to reduction in the number of antibiotic prescriptions, as well as the overall length of a patient's hospital stay (Sintchenko et al., 2005). A mobile

application (app) on a smartphone providing evidence-based recommendations and medication monographs was found to be effective for guiding antidepressant drug selection (Man et al., 2014). Improving access to relevant context-specific data for use by healthcare providers is predicted to have a direct effect (Justo et al., 2014, Wong et al., 2014).

At present, the most popular handheld platforms, based on overall market penetration as well as current use in clinical settings, are Android and iOS devices (Franko and Tirrell, 2012). Driven by the ubiquity of these mobile technologies and an increasingly health-aware population, there has been a recent surge of mobile health application software development, also known as mHealth (Bajwa, 2014, Lewis and Wyatt, 2014, Mosa et al., 2012). Decision support presents an innovative possibility in the use of mHealth (Kallander et al., 2013). Mobile applications, or apps, are in principle well positioned to provide CDS to healthcare providers, as they could help to address real-time deficiencies in medical knowledge, or to translate new evidence-based knowledge within the context of a patient's visit (Charani et al., 2013, Mosa et al., 2012). Indeed, medical professionals indicate that they would like to use more CDS Apps, but note that there is currently a deficiency of high-quality decision support apps available (Franko and Tirrell, 2012).

Many hurdles exist when trying to implement mobile health applications with an aim to provide on-the-spot decision support. CDS systems are complex (Al Mallah et al., 2010, De Bus et al., 2014, van Rooij and Marsh, 2011). The creation of medical CDS systems, including CDS Apps, can be hindered by a lack of expert input, or a lack of

technology implementation know-how, or both (Al Mallah et al., 2010, De Bus et al., 2014, van Rooij and Marsh, 2011, van Rooij et al., 2012). Additional obstacles lie in project organization, expertise, data interpretation, content creation, content revision, and appropriate visualisation or presentation (Charani et al., 2013, Lewis and Wyatt, 2014, Mosa et al., 2012). The design and implementation of decision support tools in an mHealth context is sufficiently wide ranging that none of the participants can fully understand all intricacies of the project as a whole, necessitating multi-disciplinary teams (Fleisher et al., 2014). Stakeholders' core competencies and capabilities should align with specific concerns around knowledge management (Hussain et al., 2004); a clear definition of roles and responsibilities of different domain experts in the development process therefore becomes a prerequisite. Furthermore, upon completion, all CDS apps require ongoing involvement of a medical expert (Jibb et al., 2014).

In dealing with complexity in large-scale eHealth projects, Enterprise Architecture (EA) approaches have been successfully applied (Virkanen and Mykkanen, 2014). In eHealth, EA looks at both IT architecture and business processes to create the change required to achieve a particular strategy (Mykkanen et al., 2013). In other words, EA combines an IT architecture framework with an organizational chart to help implement new systems. User acceptance of new systems can be increased by involving end users in the development process (Damodaran, 1996), and user empowerment in quality assurance (QA) has been brought forward as a critical tool for end-user sign-off (Chong and Choi, 2005). Furthermore, empowerment fosters commitment and increases awareness of the usability and usefulness of a software solution (Chong and Choi, 2005,

Damodaran, 1996, Hussain et al., 2004). Additionally, as an IT architecture framework, three-tier client/server architectures have known advantages for maintenance, re-use and flexibility in clinical information systems settings (Chu and Cesnik, 2000).

Based on this, and in order to address the obstacles to CDS development, we hypothesized that CDS app development would benefit from a small-scale EA model to address project complexity, stakeholder roles and responsibilities, end-user acceptance, and ongoing involvement of an expert healthcare provider. Our aim was to create and test a generic, re-usable model that would make it possible for healthcare providers, who are domain experts, to guide the development of CDS apps, as they create a system to upload and edit evidence-based data to be integrated into decision making processes. To this end we aimed to create a Bridging Opportunities Work-frame (BOW) model.

The test case for the application of our BOW model was provided through a project to improve and promote the community pharmacist's role in oral chemotherapy medication management. Taking chemotherapy in tablet form has obvious advantages for the patient, who can avoid disruptive and time-consuming hospital visits to receive chemotherapy. Furthermore, there appears to be an overall cost saving due to the lack of hospitalisation to receive the therapy (Banna et al., 2010). However, this leads to higher information access requirements for pharmacists (Chan and Ismail, 2014), and non-oncology trained pharmacists have to deal with the use of chemotherapy outside of a hospital environment. There is a perceived increase in the risk of patients taking their medications incorrectly (Banna et al., 2010, Chan and Ismail, 2014). We predict that handheld access to context-specific information on the use of these generally toxic

medications would be pertinent to community pharmacists who are not trained in the safe handling and dispensing of cytotoxic medications, and thus could help prevent errors and improve patient outcomes. Using a BOW, from development through testing to user acceptance, a CDS app containing curated and up-to-date Canadian data on oral chemotherapeutics was created for use within the Canadian community pharmacist's normal workflow. While filling prescriptions, pharmacists can, without difficulty, check for issues such as prescription errors, drug-drug interactions, treatments for co-morbidities, and medication side-effects. This study developed and tested the BOW methodology to formalize CDS app development, where a gap in the workflow has been identified by a healthcare provider and evidence-based knowledge is available to address this.

4.4. Methodology

4.4.1. BOW Model

We built a BOW Model consisting of two parts: one covering the governance of organizational changes and one covering the use of information technology (IT).

1. We utilized Lewin's Change Management Model (Burnes, 2004, Lewin, 1947), to alter roles and responsibilities in the organization of the development team by establishing a central leadership role for the healthcare provider in the CDS app creation process, and shifting the software development expertise on the team to a leading from below role (Bolden, 2011).

2. For the information architecture framework, we applied a three-tier client/server architecture as described by Eckerson (Eckerson, 1995), and others (Chu and Cesnik, 2000), to the storage, organization, and presentation of evidence-based medical data underlying CDS apps.

4.4.2. CASE STUDY

Forty-three monographs, representing the current state of use of oral chemotherapeutics in Canada, were created and curated by an oncology trained pharmacist. These included: the generic and trade names of medications, their classification, their indications and approved oncology uses, contraindications, precautions both for general and special populations, pregnancy and breastfeeding precautions, effects on fertility, side effects, drug interactions, metabolism, usual oral dosages, dose adjustments, excretion, unit dose availability, paths of administration and monitoring concerns. Risk levels were assigned to each drug to further warn of drug-drug interactions, therapeutic duplications, and dosages that are unsuitable for special populations. This was combined with data on drug interactions due to cytochrome P450 metabolism and p-glycoprotein efflux pump activity. Protocols and dose adjustment tables dealing with either myelosuppression or decreased liver function are also included. In keeping with the outline provided by a BOW, this work was done by the medical domain expert who was, in this case, an oncology trained pharmacist.

4.4.3. BOW MODEL APPLICATION

We tested the applicability of the BOW model by developing a CDS App to assist pharmacists in filling anti-cancer medication prescriptions.

1. A three-tier application was created through the development expertise using the following steps:
    a. A code repository was created on GitHub to allow for version control (van Rooij, 2014).
    b. An Entity-Relationship (ER) model was shaped based on the data provided by the pharmacist.
    c. A relational database, MySQL 5.5.32 for Debian Linux, was put in place based on a schema derived from the ER-Diagram.
    d. A Hypertext Preprocessor (PHP) server side Application Programming Interface (API) was developed to control access to the database and to provide the business logic layer for client requests.
    e. A PHP micro-framework based on the Silex framework was used for the web application server-side of the user and administrative views.
    f. The Database, API and Web Application Server were run on Ubuntu Linux 13.10 on Amazon Web Services (AWS) Elastic Compute Cloud (EC2).
    g. Hypertext Markup Language (HTML) 5, JavaScript and Cascading Style Sheets (CSS) were used to develop the web application client side, using the Twitter Bootstrap framework to facilitate User Interface (UI) design.

h. Cordova PhoneGap 2.3.0, a mobile development framework in JavaScript, was used for cross-platform functionality spanning iOS and Android. It was used for both the Graphical User Interface (GUI) design for the handhelds and access to data through the API.

i. Local data storage was handled through Cordova's database implementation to store data in Android's SQLite 3.7.11 for use on Android 4.1-4.4, and a SQLite 3.7.13 for use on iOS 7.

2. Direction of development, testing and signing off on interfaces and functionalities was performed by the pharmacist.
3. Curation of data was performed by the pharmacist.
4. Data integrity and Security were performed by the development team.
5. Installation Qualification (IQ) and Operational Qualification (OQ) were performed by the development team.
6. Alpha-testing (simulated operation testing by a potential user) was performed by the pharmacist.
7. Software updates, fixes and speed of response improvements were handled by the development team.
8. Validation and acceptance of updates were performed by the pharmacist.

Data curation and Performance Qualification (PQ) are ongoing activities performed by the medical domain expert, in this case the oncology trained pharmacist. Design Qualification (DQ) was provided by using a BOW model. For the web enabled interfaces,

JavaScript was used client-side to enhance the user experience and speed of the application.

4.5. Results

4.5.1. Creation of a BOW model

We created the BOW model for CDS app development. We built the view model based on Lewin's Change Management Model (Burnes, 2004, Lewin, 1947), to organize stakeholder's roles and responsibilities as shown in Figure 4.1, and worked through their interaction with the IT components as shown in Figure 4.2. For the IT architecture framework, the BOW model applied three-tier architecture as shown in Figure 4.3. The purpose of the organizational workflow and IT architecture was to create a system to convey complex information in an instant, appropriately organized and tailored for use in a time-constrained medical environment (Chong and Choi, 2005, Dang et al., 2008, Hussain et al., 2004).

In the BOW model developed in this study we strictly defined the roles of stakeholders and overall software architecture and divided them into their functional parts (Figures 4.1-4.3). The healthcare provider, as a medical domain expert, was the project lead and in control of all data organization, visualisation, presentation, acceptance and dissemination. The software development team, classified as application development expertise in the BOW model, worked on component development to support the aims of the healthcare provider, and parsed the data provided (by the medical domain expert) to

extract its semantics, in order to create a database schema. Additionally, the application development expertise provided an access point for the medical domain expert to autonomously edit and update the CDS data (Figure 4.4). The medical domain expert is similarly a medical domain user; consequently quality verification of user-interfaces and the cogency of the CDS app were achieved by iterative testing throughout the development.

The central axis of the software framework was the CDS app system's Application Programming Interface (API), as it connected a Relational Database Management System (DBMS) to a web application, providing both user and administrator interfaces. The DBMS housed the data, the API provided the business logic and powered the interfaces for adding, editing and displaying data. Together, these components formed a three-tier structure (Figure 4.3) (Chu and Cesnik, 2000, Eckerson, 1995).

4.5.2. BOW MODEL APPLICATION

A case study was used to test both the validity of the architect framework as well as the project management assumptions behind the BOW model. As per the BOW model, the project was directed by a medical domain expert. An app was developed to provide decision support to community pharmacists in safely filling anti-cancer medication prescriptions.

Comprehensive, curated and relevant data on 43 oral chemotherapeutic medications available in Canada were implemented for use on handhelds. The oncology pharmacist provided the evidence-based data, which was well-formed, making parsing of

the data easier (Chen and Liou, 2014) because it was rule-based and had a high degree of data organization (e.g. medication monographs, dosing adjustment rules, cautions, interactions etc.). Exploiting this particular property, entity relationships, classes, and logic rules were derived (Chen and Liou, 2014). The software development team created the components of the BOW models' three-tier architecture.

The first tier's GUIs consist of views from both workstations as well as handheld Android and iOS devices. For the second tier an API was created, which, through a web server processed the requests to the data from the various GUIs. The third tier housed the DBMS allowing for the storage of, and transactions to, the oral chemotherapeutic data.

The software has specific forms and views for both user and administrative roles. Web interfaces were made available through www.oralchemotherapy.ca. On handhelds, view-only data is made available on devices based on either Android (smartphone, tablet) or iOS (iPhone, iPod, iPad) platforms. Figure 4.5 shows the dedicated CDS app interface for the oral chemotherapeutic drug acitretin on an Android platform. A single relational DBMS provides the main content for every instance of the toolset. A unique instance of the database is downloaded on handhelds to provide a local data copy for offline data use; this copy of the content is stored directly on the smartphone or tablet and assures access to data in the absence of a Wi-Fi or mobile signal. Changes to the DBMS are reflected simultaneously on a website and, in the presence of a mobile or network connection, as an available update on their mobile counterparts. Updates are pushed with a user prompt when a connection becomes available.

4.6. Discussion

We developed and applied a BOW to app development (Figure 4.5), providing a re-usable model for future development of healthcare apps. In our test-case we involved an oncology-trained pharmacist as the healthcare provider, to create a system to make relevant data on oral chemotherapeutics available on handhelds for use by Canadian community pharmacists. In keeping with the amount of display available on handhelds and to not overwhelm the user with extraneous data, our test-case was focused on pharmacists' use within a regional (Canadian) context. An administrative interface was built to allow the healthcare provider to autonomously edit and update the source data (Figure 4.4). The app system links data from medication monographs to interactions, dose adjustments and protocols. Once tested and validated by a large group of end-users (in this case, hospital and community pharmacists), this app could be presented on handhelds, and oral chemotherapeutic knowledge could be incorporated in the day-to-day workflow of community pharmacists (Figure 4.5) (Sullivan et al., 2014).

In order to increase stakeholder engagement, we altered the software development process (Burnes, 2004, Dickson et al., 2012, Lewin, 1947). In addition to an architect framework, BOW is a project management model where the healthcare provider becomes the leader of the software development project rather than a client to it (Bolden, 2011). In doing so, our BOW addresses common issues affecting the success of electronic healthcare system development such as sensitivity to the medical context, development issues, equipment selection, and uptake and maintenance (Al Mallah et al., 2010, Cooley et al., 2012, van Rooij and Marsh, 2011). Additionally, it ensures known facilitators such

as ease of use, reliability, and integration in the day-to-day workflow (Cooley et al., 2012, van Rooij et al., 2015c).

In our test-case, the application of the generic BOW model made it possible for an oncology-trained pharmacist to guide the development of a CDS app, and create a system to upload and edit evidence-based data to be integrated into pharmacy decision-making processes regarding the dispensing of anti-cancer drugs. Furthermore, as a user in the healthcare field directed the development of the software's abilities, we expect this to benefit uptake and dissemination of our test app in Canadian pharmacy settings once tested and validated by a large team of end-users (Chong and Choi, 2005, Damodaran, 1996, Hussain et al., 2004). Based on the BOW model's implementation in our oral chemotherapy app development case study, we believe this mHealth approach to be generalizable across similar situations, where specific medical frontline workflows would benefit from tailored decision support integration.

4.6.1. LIMITATIONS

The BOW model's architecture framework is not completely independent of the corresponding implementation, as currently mobile application development has few choices in development tools. In addition, medical data is inherently complex and as research continues, or fine-tuning based on clinical outcomes becomes available, new guidance will emerge (Al Mallah et al., 2010, van Rooij and Marsh, 2011, van Rooij et al., 2012); hence a CDS app can never truly be completed without becoming obsolete (Charani et al., 2013). This necessitates ongoing updates to any medical app, but even more so for CDS apps that are used to help healthcare providers determine an appropriate

medical course of action in real-time settings (Charani et al., 2013). Thus a healthcare provider's commitment is necessary to keep a CDS app system up-to-date (Chong and Choi, 2005, Damodaran, 1996, Hussain et al., 2004). The development of an app for healthcare, even with the inclusion of a healthcare provider at the development stage, does not preclude the need for regulatory approval from country-specific agencies before the app can be used in a healthcare setting. A generic model for app development does not automatically guarantee regulatory approval, and the quality of input data and quality of testing and validation are crucial to app success. Finally, CDS apps developed through a BOW model will, like most apps, need some modifications to continue functioning when major operating system revisions occur on handheld platforms.

4.7. Conclusions

We developed a generic model to build CDS apps. In this instance we used a test-case aimed to improve the safe handling, dispensing and use of oral chemotherapeutics outside of the hospital setting. Through a secure web-based administrator interface, oncology trained pharmacists can curate the data as new oral chemotherapeutic agents or guidance on their use becomes available. Once tested and validated for accuracy of content, using this CDS app, community pharmacists could actively apply current evidence-based knowledge on safety and standards in the use of oral chemotherapeutics.

The CDS app and website are linked to the same data source; however handhelds can be used as a standalone whenever network or mobile connections are not available (e.g. rural settings) (Skillman et al., 2014). If there are changes or updates to the source

data during this time, pharmacists will be alerted to an automatic update as soon as a connection becomes available again. This brings knowledge to the bedside at the touch of a button.

The test CDS app was developed on the re-usable BOW model. We envision that the generic template provided by our BOW model could be applied to other healthcare scenarios where having instant access to complex and dynamic evidence-based knowledge would be vital for improving patient outcomes. Moreover, the genesis of a separate software package based on the model developed here could enable non-technical users to create fully functioning mobile CDS apps by themselves, akin to the way in which Blogs allowed laypersons web publishing (Horter et al., 2014). We believe that the model presented here can help spur the growth of evidence-based medicine adoption by lowering the barrier to entry for healthcare providers looking to use mHealth to address known knowledge gaps (Finkelstein et al., 2012, Skillman et al., 2014). More case studies are needed to assess the feasibility of disruptive innovation based on the BOW model (Schwamm, 2014).

4.8. Future Perspectives

Although certain therapies have been proven to be efficacious, they are not being used in clinical settings. Clinical decision support systems can help to move local recommendations and guidelines to healthcare providers so they can integrate them in their decision making processes when providing care for patients (dos Santos et al., 2014). The aim is to do this in manner which helps to improve both the quality and safety

of the care delivered (Cresswell et al., 2012). CDS development will be increasingly initiated by healthcare providers in a "user pull" model (Cresswell et al., 2012), as opposed to a vendor “push” of prepackaged and ill-fitting solutions. Stakeholder engagement is essential, and significant pre-processing on medical data will become a prerequisite. Indeed, this role is already predicted for pharmacists in the translation of pharmacogenomics (Owusu-Obeng et al., 2014). Current approaches such as support vector machines and decision trees are already deployed (Kureshi et al., 2014, van Rooij et al., 2015c); in addition, CDS data needs to be locally applicable and devoid of clutter. Further, any CDS apps developed using the BOW model need to undergo robust curation of the input data and extensive field testing before being submitted to country-specific regulatory agencies for approval to use in healthcare settings. In mHealth, CDS constitutes a higher level objective of medical data usage with significant potential impact. We predict that standardized medical app development involving end users, like in the model presented here, will grow rapidly in the near future.

4.9. Executive Summary

4.9.1. BACKGROUND

- Clinical decision support (CDS) mobile applications (apps) may show the greatest promise when created by and for frontline clinicians, as they identify and address shortcomings in their current workflow.

- This study aimed to create and test a generic model that makes it possible for healthcare providers, who are domain experts, to guide the development of CDS apps, as they create a system to upload and edit evidence-based data to be integrated into decision making processes.

4.9.2. METHODOLOGY

- Organizational Change Management was combined with a three-tier IT architecture, separating medical data from engineering concerns, to enable healthcare providers to lead CDS app development.
- Testing the validity of the model, a specific CDS app was developed to make up-to-date information on oral chemotherapy agents available to Canadian pharmacists.

4.9.3. RESULTS

- The Bridging Opportunities Work-frame (BOW) model was created.
- The BOW model strictly defines the roles of stakeholders and overall software architecture in order to stimulate development and implementation of CDS apps.
- Using a BOW, a CDS app was developed based on Canadian oral chemotherapy use.

4.9.4. DISCUSSION

- Healthcare provider generated and curated data, presented on pharmacists' cue using handhelds has the potential to translate into application of evidence-based medicine in emerging medication use, or novel treatment regimens.

- The BOW model increases stakeholder engagement by altering the software development process so that healthcare provider becomes the leader of the software development project rather than a client to it.
- The use of the BOW addresses common issues affecting the implementation success of electronic healthcare systems.

4.9.5. CONCLUSION

- The BOW model presents a re-usable, potentially disruptive innovation approach to CDS app development.
- Globally applicable, the BOW model allows regional healthcare providers to direct the process of placing decision support information onto handhelds.

4.9.6. FUTURE PERSPECTIVES

- CDS development is a high value activity in mobile medical app development, and subsequently will experience rapid growth in the near future.
- Rather than using a "one size fits all" commercial off the shelf solution, healthcare providers will actively be involved in the development of CDS apps for their own domains and locales.

4.10. Author Contributions

T van Rooij initiated the project, developed the model, website and mobile app, drafted the manuscript and reviewed the final draft; S Rix designed the oral chemotherapy monographs, contributed to the manuscript and reviewed the final draft; JB

Moore contributed to the development of the website and mobile app, contributed to the manuscript and reviewed the final draft; S Marsh supervised the project, contributed to the manuscript and reviewed the final draft.

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4.11.3. Competing Interests

The authors declare that they have no competing interests.

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4.13. Figures

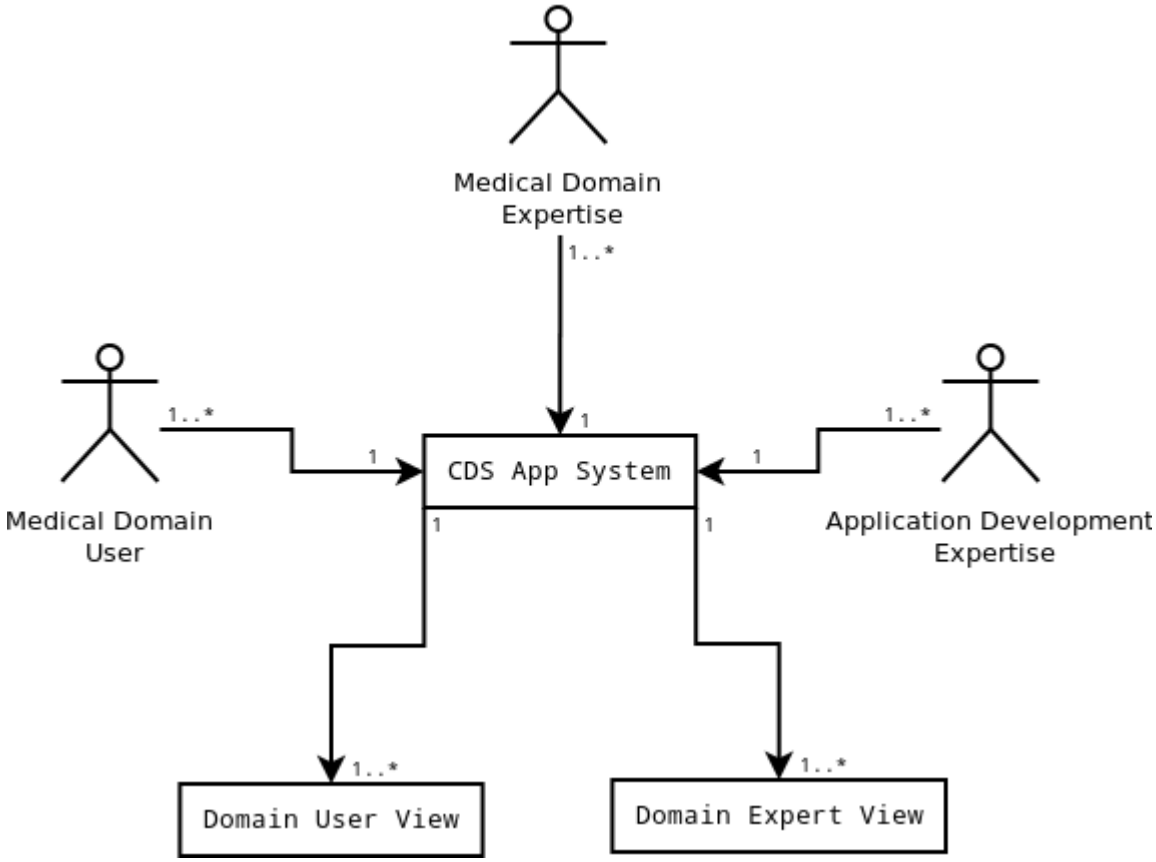

Figure 4.1. A view of the stakeholders in a clinical decision support (CDS) mobile application (app) context when organized according to the Bridging Opportunities Work-frame (BOW) model. The medical domain expert is the main driver of the application development. The expert identifies the opportunity, i.e. the gap in the current workflow that would benefit from the introduction of clinical decision support, and provides the curated knowledge that needs to be implemented into the CDS app system to help improve decision making.

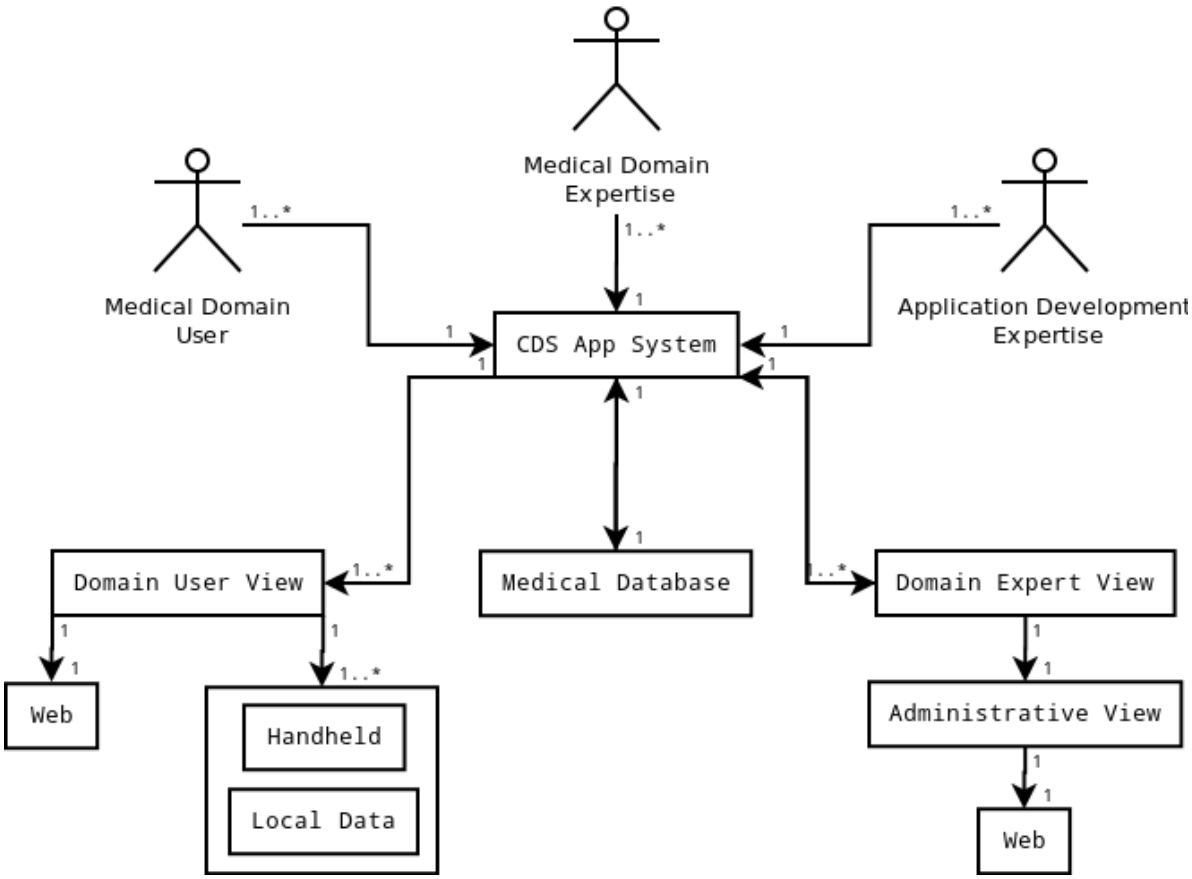

Figure 4.2. Building on the outline shown in Figure 4.1, stakeholders' actions, functional components, and overall data flow are further defined. Clinical Decision Support (CDS) data is contained in a centralized transactional database (DB) which connects to both web views and to the mobile user counterpart through the CDS app system. An instance of the DB is offloaded onto the handheld for offline use. Changes to the DB are reflected in handhelds after an update cycle, as the model does not presume that network access will be continuous (Berner et al., 2006). The web-based administrator interface allows the medical domain expert(s) to upload, edit and assure correctness of data stored in the DB. Through the CDS app system, end-users have either a website or handheld view of the medical data stored in the DB, as a source for their decision making.

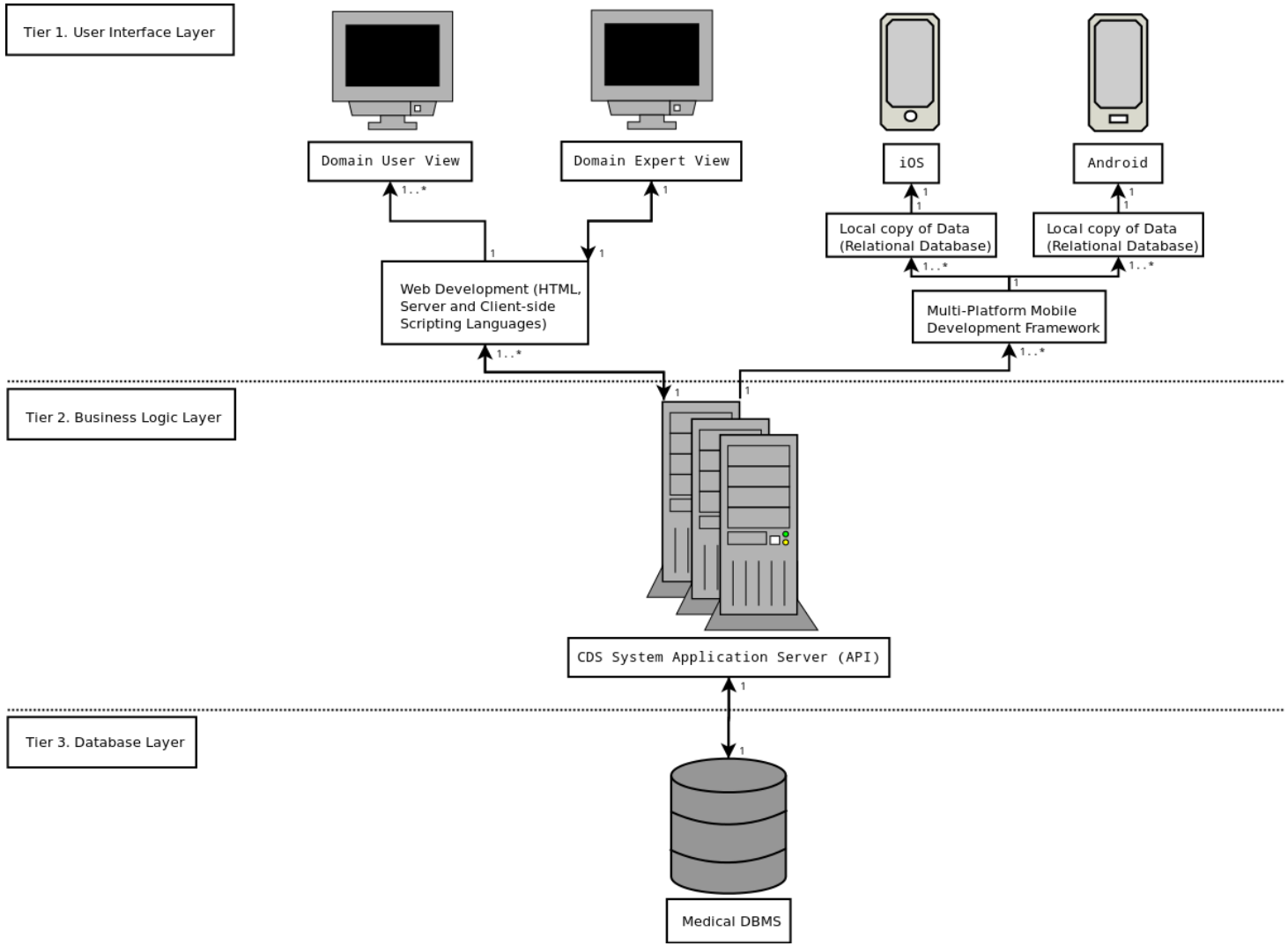

Figure 4.3. The Bridging Opportunities Work-frame (BOW) software architecture components organized in a three-tier model. The architect framework's goal is to enable mobile tools to deliver decision support at point-of-care, in order to improve the use of medications, or the selection of treatments.

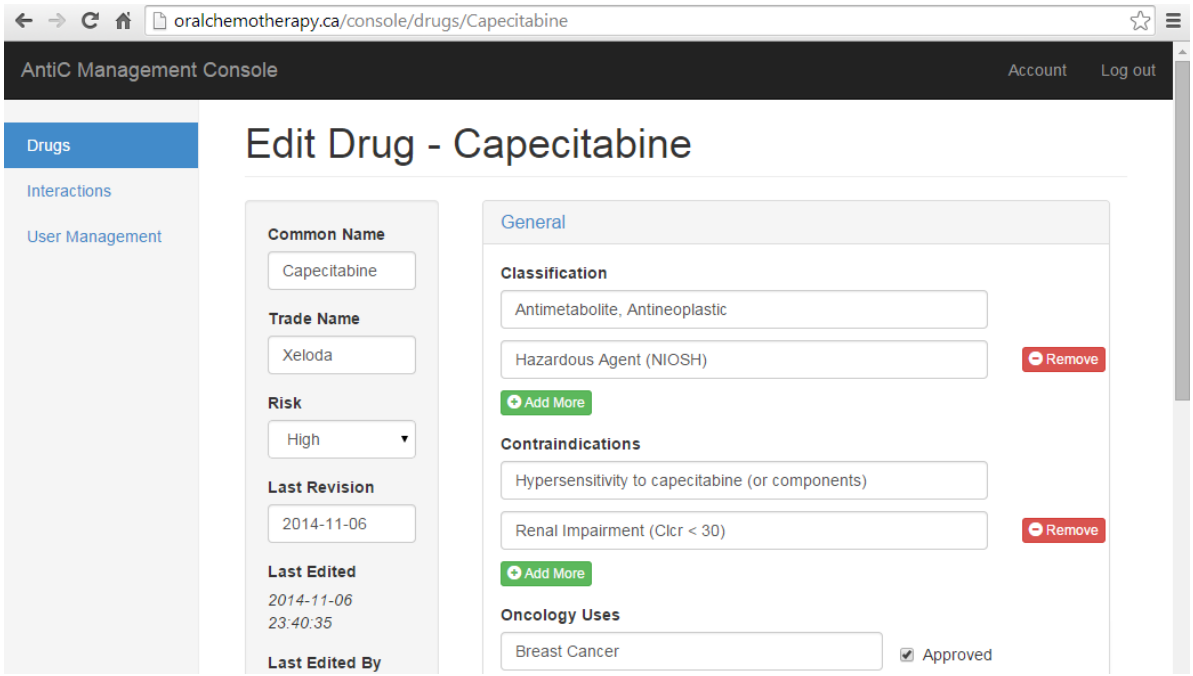

Figure 4.4. The Bridging Opportunities Work-frame (BOW) model calls for an administrator interface. This figure shows the administrator console for use by the healthcare provider in our test-case. The web-based interface allows real-time updates for adding and making changes to stored data.

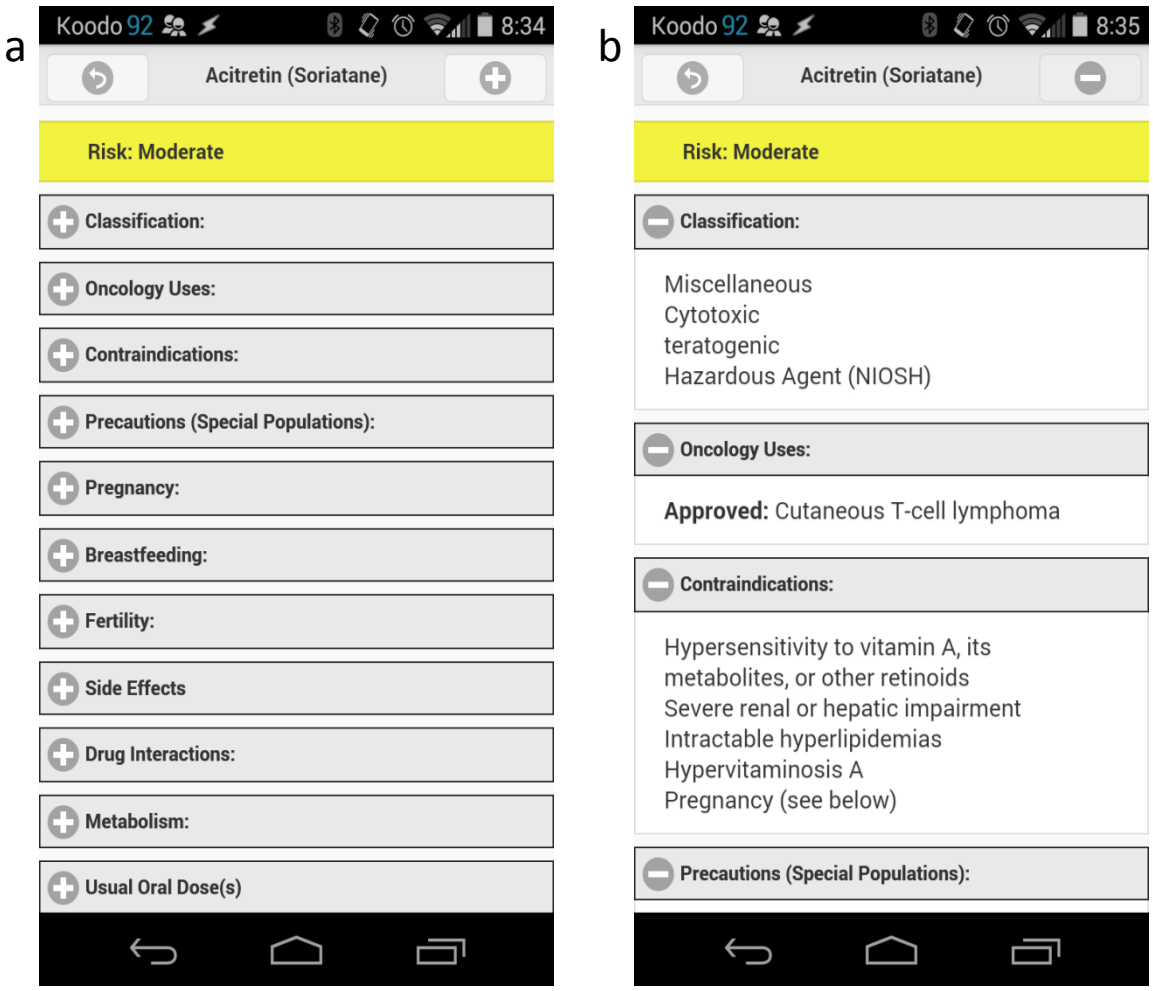

Figure 4.5. The Bridging Opportunities Work-frame (BOW) model is designed to create clinical decision support (CDS) mobile applications (apps). This figure demonstrates the clinical interface of our test-case app on an Android platform. Two views are shown based on our test-case; (a) high level headings grouping available data that are consistent across categories; (b) subcategories can be opened independently to drill down to additional information.

5. ANTIC: A PRACTICE TOOL FOR THE SAFE USE OF ORAL CHEMOTHERAPEUTICS BY COMMUNITY AND HOSPITAL PHARMACISTS

This chapter has been peer-reviewed and published in its entirety through SAGE Journals:
Tibor van Rooij, Serena Rix, and Sharon Marsh. AntiC: A Practice Tool for the Safe Use of Oral Chemotherapeutics by Community and Hospital Pharmacists. Canadian Pharmacists Journal/Revue des Pharmaciens du Canada, 2015, 148(3) 118-124. doi:10.1177/1715163515578454

5.1. Problem

"Kate" has an order for capecitabine 2000 mg po bid. Is this the correct dose for "Kate"? Perhaps you are the pharmacist in a busy community pharmacy or maybe you are processing orders in a hospital, but without a comprehensive oncology background, how do you ensure you are processing these prescriptions appropriately?

5.2. Background

With an increasing number of chemotherapeutic agents available in oral formulations, it is essential to have the necessary prescribing/dispensing information in a readily accessible format, which can be interpreted easily and quickly. The case outlined above demonstrated the necessity for such an instrument as neither the prescribing physicians nor the pharmacists processing the order were aware of the potential harm to the patient.

The urgency of this issue was initially identified when "Kate" was admitted to hospital via the emergency room for complications of metastatic breast cancer and "at home" medications were ordered. Hospital policy issues a 30-day automatic stop order for all medications, except opiate analgesics, antibiotics and other medications needing more frequent assessment. Oral chemotherapeutic agents, however, are not classified in this group, so this order was processed with a 30-day stop date. Neither the physicians nor the pharmacists involved were aware this medication is prescribed within the strict

parameters of a chemotherapy protocol, including specific start and stop dates. Thus, a serious problem had been identified and a solution needed to be found.

5.3. Development of the practice tool

The resolution came in three stages. Initially, chemotherapeutic drugs were identified in the hospital computer system and flagged for further evaluation. Monographs were produced for each of the oral chemotherapeutic agents available in Alberta. These were made in a standardized one-page format so the information required was quickly retrieved (Figure 5.1). Doses, indications, common side effects and drug interactions were included as well as basic pharmacokinetics to identify if dose adjustments were necessary for renal or hepatic insufficiency. We also devised a CYP drug interaction table and outlined commonly used chemotherapeutic protocols, as well as including NIOSH classification (BC Cancer Agency, Bragalone, 2011, Canadian Pharmacists Association, 2011, Cancer Care Ontario, Connor et al., 2014b, Lacy et al., 2009, NCI Common Toxicity Criteria (Version 4), 2009, P-glycoprotein drug interactions, QTc Interval Prolonging agents, Tatro, 2013).

Another component to the problem is not all the medications classified as chemotherapy have the same risk if dosed inappropriately. We wanted to stratify the risk so the pharmacist would be able to identify which agents warranted the greatest concern. A literature search was performed to determine if this had been done previously, but nothing was found, so we risk stratified based on perceived complexity of dosing regimens and potential harm to patient if the medication was incorrectly prescribed

(Table 5.1). If more detailed information was required, the pharmacist was referred to the CPS, or other drug information.

5.4. Website development

The second stage was the creation of the website. Training tools for community pharmacists have been shown to have a significant impact on pharmacist confidence in dispensing oral chemotherapeutics (Charpentier et al., 2012). A serendipitous conversation at the University of Alberta resulted in a collaboration to transfer this information onto an interactive website, thus enabling dissemination of the information to a wider audience, and www.oralchemotherapy.ca was born (Figure 5.2). The website provided the same information as the monographs, but had links to pages listing CYP drug interactions and the chemotherapeutic protocols for each drug.

5.5. Mobile Application development

The third phase of the project was achieved when the opportunity arose to transform the website into an application (app), making the information available via a handheld device such as a smartphone or tablet. This development resulted in the AntiC app (Figure 5.3). The oralchemotherapy.ca website infrastructure was modified to connect with the AntiC app. This allows all the information on the website to be accessed at the bedside. A template was created for the app, which is compatible with both Apple and Android devices (van Rooij et al., 2015b). This template format allows a pharmacist

or other non-computer expert to add and manage the data. There are obvious advantages to this system. Data is inputted by personnel with administrative access, who are familiar with the drug names and understand the relevant medical terminology, thus reducing the risk of error. Also, the template can be re-used for other data sets such as psychiatry medications or antibiotics. Therefore it is relatively simple and inexpensive to build other apps using this template, which may also be used to access local information, such as regional or provincial formularies.

Another unique feature of this system is that adding to, or editing the database on the website, will automatically confer the changes to the app the next time it is connected to the internet, thus saving time and reducing the risk of transcription error. Finally, the app can be used even in the absence of a network connection, allowing pharmacists to access data regardless of their location.

5.6. Clinical use of the practice tool

In the case of "Kate" if you look at the entry for capecitabine on the website (Figure 5.1; http://oralchemotherapy.ca/drugs/Capecitabine) you will see this medication is coded in the high-risk category, and therefore has the potential to cause patient harm if dosed incorrectly. We see the dose is protocol dependent. In this case we are using capecitabine as a single agent for metastatic breast cancer. Referring to the protocol (Figure 5.4) we note the usual dose for single agent capecitabine for metastatic breast cancer is 1000-1250mg/m^2 po bid x 14 days in a 21-day cycle. "Kate" is ~ 1.6 m^2, so 2000mg is a suitable dose providing there have been no prior dose modifications.

However, the drug should be dosed x 14 days in a 21-day cycle, so a definite stop date should have been indicated. This information would have to be verified by obtaining the start date and dose using the provincial drug record (if available) or by contacting the originating pharmacy or prescriber, or from medication containers. If "Kate" is still in your care beyond day 21 and is unable to return to the prescriber, you will need to contact them to determine how to proceed to the next cycle.

Assuming "Kate" is not in acute renal failure (the monograph states capecitabine is renally cleared; Figure 5.1) and "Kate" is not suffering from febrile neutropenia, serious side effects of the drug, or disease progression, then it should be safe to proceed for the remainder of the 14 days. If there is any doubt it is always prudent to contact the prescriber for further direction. As it is likely a hospital admission would result in the prescribing of new medications, we should also perform a drug interaction check, using the website or app (Figure 5.5).

Using "Kate" as an example, we have demonstrated how a non-oncology pharmacist can navigate the necessary triaging steps with ease, and process chemotherapy orders with confidence.

We encourage systems to flag oral chemotherapeutic agents and direct the user to the website or app, where the necessary information is available to dispense the medications correctly, paying particular attention to the high and intermediate risk medications. Although the website/app may not be able to solve all the possible problems

encountered when prescribing/dispensing oral chemotherapy, we can alert the pharmacist to potential issues and encourage further follow-up if they are still uncertain.

We plan to provide some instruction in the form of on-line tutorials, for example we will provide cases, on the website homepage (http://oralchemotherapy.ca), similar to "Kate's", where you have the opportunity to resolve the drug-related problems using the website. There is also an opportunity to request the mobile app, and to provide feedback (http://oralchemotherapy.ca/about) so we can improve the service to better fit the needs of the users.

5.7. Limitations

Although creating an updatable app and website is a powerful method of disseminating information quickly and efficiently, it is not without drawbacks. There is a need to update the technology as new operating systems become available, and ensuring the data is continually updated and accurate.

Only medications licensed for use in Canada are included, with Canadian specific data. It is also important to acknowledge oncology is a specialized area of practice. However, pharmacists in non-oncology environments are expected to handle these medications, with limited training. No website or mobile app can replace knowledge or education, and this is not the intention. AntiC is merely a tool designed to provide information in a concise and convenient format.

5.8. Next steps

The next phase of the project will be a testing/dissemination one. We are asking pharmacists to test the website/app, assess the information, and provide feedback. The system is currently being tested at a community hospital pharmacy in Edmonton and any edits will be incorporated into the database fueling the website and app immediately. We also welcome feedback from pharmacists across Canada.

For education, we will continue to provide training through the website, including a streamlined triage process for non-oncology trained pharmacists. One proposed training mechanism is to devise a series of questions to be answered pre- and post- using the information provided on website or app and determine if there is an improvement in the quality of the responses. We also propose to introduce this as workshops that would include all aspects of oral chemotherapy use, including monitoring side effects and how and when to adjust doses safely.

Future work includes a plan to devise and test a tool to determine the risk stratification of oral chemotherapeutics. This will ensure the stratification process is reproducible and robust for the rapid assessment of newly approved drugs.

5.9. Conclusion

In conclusion, we identified a need to ensure safer dispensing of oral chemotherapy. The information to do this was incorporated into an updatable website and

mobile app specifically designed to help the pharmacist achieve this in an efficient, user-friendly manner.

5.10. Disclosures

5.10.1. Roles

SR initiated the pharmacy project, designed the monographs, contributed to the manuscript and reviewed the final draft; TvR initiated the informatics project, developed the website and mobile App, contributed to the manuscript and reviewed the final draft; SM supervised the project, contributed to the manuscript edits and reviewed the final draft.

5.10.2. Financial acknowledgements

TvR was supported by an Alberta Innovates Doctoral Graduate Student Scholarship and an Antoine Noujaim Graduate Scholarship.

5.10.3. Conflict of Interest

None

5.10.4. Acknowledgements

The input from James B. Moore, and the 2014 CMPUT401 (Software Process and Product Management) AntiC team, is greatly appreciated.

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5.12. Table

High Risk	Moderate Risk	Low Risk
Busulfan (Myleran®)	Abiraterone (Zytiga®)	Anastrozole (Arimidex®)
Capecitabine (Xeloda®)	Acitretin (Soriatane®)	Bicalutamide (Casodex®)
Chlorambucil (Leukeran®)	Afatinib (Giotrif®)	Cyproterone (Androcur®)
Cyclophosphamide (Procytox®)	Anagrelide (Agrylin®)	Exemestane (Aromasin®)
Estramustine (Emcyt®)	Axitinib (Inlyta®)	Flutamide (Euflex®)
Etoposide (VePesid®)	Bexarotene (Targretin®)	Letrozole (Femara®)
Fludarabine (Fludara®)	Bosutinib (Bosulif®)	Medroxyprogesterone (Provera®)
Lapatinib (Tykerb®)	Dasatinib (Sprycel®)	Megestrol (Megace®)
Lenalidomide (Revlimid®)	Erlotinib (Tarceva®)	Nilutamide (Anandron®)
Lomustine (CeeNU®)	Everolimus (Afinitor®)	Tamoxifen (Nolvadex-D®)
Melphalan (Alkeran®)	Gefitinib (Iressa®)	
Methotrexate (Trexall®)	Hydroxyurea (Hydrea®)	
Procarbazine (Matulane®)	Imatinib (Gleevec®)	
Sunitinib (Sutent®)	Mercaptopurine (Purinethol®)	
Temozolomide (Temodal®)	Nilotinib (Tasigna®)	
Thalidomide (Thalomid®)	Pazopanib (Votrient®)	
	Sorafenib (Nexavar®)	
	Thioguanine (Lanvis®)	
	Tretinoin (Vesanoid®)	
	Vorinostat (Zolinza®)	

Table 5.1. Risk stratification of available oral chemotherapeutic agents in Canada. Over 75% of oral chemotherapy medications fall into the high or moderate risk categories. Parameters considered for risk category included: multiple administration routes, multiple dosing regimens, potential for drug-drug interactions, high potential for toxicity, and if there was high potential that the toxicity would be life-threatening (BC Cancer Agency, Bragalone, 2011, Canadian Pharmacists Association, 2011, Cancer Care Ontario, Connor et al., 2014b, Lacy et al., 2009, NCI Common Toxicity Criteria (Version 4), 2009, P-glycoprotein drug interactions, QTc Interval Prolonging agents, Tatro, 2013).

5.13. Figures

Capecitabine **(Xeloda)**	
Risk	**High: consult clinical/oncology pharmacist**
Classification	Antimetabolite Cytotoxic
Oncology uses (*Approved by Health Canada)	*Breast Cancer Pancreatic cancer *Colorectal cancer
Contraindications	Hypersensitivity to capecitabine (or components) Renal Impairment (Cl_{cr} < 30)
Precautions (Special populations)	Pediatrics: Safety & efficacy have not been established Elderly (> 65): may be more sensitive: consider dose reduction DPD deficiency: may require dose reduction
Pregnancy **Breastfeeding** **Fertility**	Category: D Not recommended May impair fertility
Side Effects (**Clinically significant** & frequent: >10%)	**PPE**, dermatitis, rash **Diarrhea, nausea**, **vomiting, stomatitis**, abdominal pain, anorexia, decreased appetite, constipation Cardiotoxicty, edema Hyperbilirubinemia, ↑LFT's, myelosuppression Fatigue, pain, fever, paresthesia, dyspnea, eye irritation
Drug Interactions Metabolism: hepatic **Inhibits:** CYP 2C9 (s)	**Avoid: natalizumab, pimecrolimus, tacrolimus (top), live vaccines** ↓**effect of capecitabine:** echinacea ↑**effect of capecitabine**: denosumab, trastuzumab ↑ **Effect of:** CYP 2C9 substrates, leflunomide, warfarin Caution with other anti-neoplastic agents (unless per protocol)
Usual Oral Dose(s)	Refer to protocol
Dose Adjustments Excretion: renal	Renal Cl_{cr}: 30-50 mL/min: 75% < 30 mL/min: contraindicated Dialysis: no data available Hepatic dysfunction: moderate: no adjustment severe: no data available Myelosuppression/toxicities: dose adjust per protocol or dose adjustment for myelosuppression
Available	Tablets 150 mg & 500 mg
Administration	Oral: Do not crush tablets. Take with water, 30 mins after food
Monitoring	Disease progression & toxicities. (NCI Common Toxicity Criteria) Labs (each cycle): Renal function, LTFs, CBC (diff) INR if on anticoagulants

Figure 5.1. Example of a one-page monograph with information for capecitabine, a common oral chemotherapy agent with a high risk of toxicity. In addition to the risk categories, further information including contraindications, common associated toxicities, and monitoring requirements are included (BC Cancer Agency, Bragalone, 2011, Canadian Pharmacists Association, 2011, Cancer Care Ontario, Connor et al., 2014b, Lacy et al., 2009, NCI Common Toxicity Criteria (Version 4), 2009, P-glycoprotein drug interactions, QTc Interval Prolonging agents, Tatro, 2013).

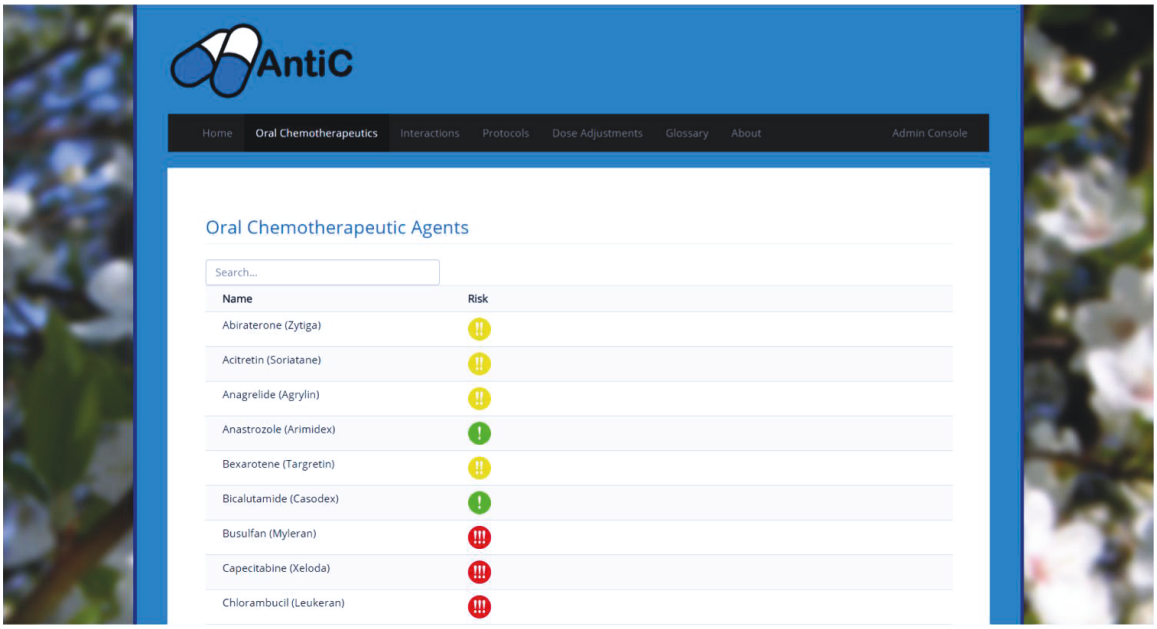

Figure 5.2. Screenshot of Antic website Oral Chemotherapeutics page (http://oralchemotherapy.ca/drugs). Users can click on the drug of interest for more information.

Figure 5.3. AntiC Android Application.

Capecitabine Protocols	Use	V	Dose	Days of cycle	Days	# Cycles
Capecitabine (single agent)	Metastatic Breast	1	1000 mg/m^2	1-14	21	
Capecitabine (single agent)	Metastatic Breast	2	1250 mg/m^2	1-14	21	
Capecitabine (single agent)	Colorectal	1	1250mg	1-14	21	
Bevacizumab-**capecitabine (XELOX)**	Colorectal	1	850 mg/m^2 bid	D1 (pm) - D15 (am)	21	
Bevacizumab-**capecitabine (XELOX)**	Colorectal	2	1000mg/m^2/bid	1-14	21	
Capecitabine-Docetaxel	Breast	1	1250mg/^{2} bid	1-14	21	DP/toxic
Capecitabine-Docetaxel	Gastric	1	1000mg/m2 bid	1-14	21	9 cycles/DP/toxic
Capecitabine-Docetaxel	Gastric	2	1000mg/m2 bid	1-14	21	DP/toxic
Capecitabine-Docetaxel	Gastric	3	825mg/m^2 bid	1-14	21	DP
Capecitabine-Docetaxel	Gastric	4	1250mg/m^2 bid	1-14	21	6 cycles/DP
Capecitabine-Gemcitabine	Pancreatic	1	650mg/m2 bid	1-14	21	24wks/DP
Capecitabine-Gemcitabine	Pancreatic	2	830mg/m2 bid	1-21	28	DP/toxic
Capecitabine-Ixabepilone	Breast	1	1000mg/m^{2}bid	1-14	21	DP/toxic
Capecitabine-Lapatinib	Breast	1	1000mg/m2 bid	1-14	21	DP/toxic
Capecitabine-Trastuzumab	Breast	1	1250mg/m^2	1-14	21	DP/toxic
Capecitabine-Trastuzumab	Breast	2	1250mg/m^2	1-14	21	
Capecitabine (CAPOX)	Biliary	1	1000mg/m2 bid	1-14	21	
Capecitabine (CAPOX)	Pancreatic	1	1000mg/m2 bid	1-14	21	DP or toxic
Capecitabine (CAPOX)	Pancreatic	2	750mg/m^2/bid	1-14	21	DP or toxic
Cisplatin-**capecitabine**	Esophageal	1	1000mg/m2 bid	1-14	21	DP or toxic
Cisplatin-**capecitabine**	Gastric	1	1000mg/m2 bid	1-14	21	DP or toxic
Epirubicin-cisplatin-**capecitabine** (ECX)	Esophageal	1	625mg/m2 bid	1-21	21	up to 8
Epirubicin-oxaliplatin-**capecitabine** (EOX)	Esophageal/Gastric	1	625mg/m2 bid	1-21	21	up to 8
Gemcitabine-**capecitabine**	Biliary	1	650mg/m^2 bid	1-14	21	DP or toxic
Gemcitabine-**capecitabine**	Pancreatic	1	650mg/m^2 bid	1-14	21	DP/tox. M 24wks
Gemcitabine-**capecitabine**	Pancreatic	2	830mg/m2 bid	1-21	28	DP or toxic
Gemcitabine-docetaxel-**capecitabine**	Pancreatic	1	750mg/m^2 bid	1-14	21	
Gemcitabine-docetaxel-**capecitabine**	Pancreatic	2	500mg/m^2 bid	1-14	21	DP or toxic
Irinotecan-**capecitabine**	Esophageal	1	1000mg/m^2 bid	1-14	21	DP or toxic
Irinotecan-**capecitabine**	Esophageal	2	1000mg/m^2 bid	1-14	21	up to 24 weeks
Irinotecan-**capecitabine**	Gastric	1	1000mg/m^2 bid	1-14	21	DP or toxic
Irinotecan-**capecitabine**	Gastric	2	1000mg/m^2 bid	1-14	21	24 weeks
Capecitabine (XELOX)	Colorectal	1	1000mg/m^2 bid	1-14	21	8 cycles
Capecitabine (XELOX)	Colorectal	2	1000mg/m^2 bid	D1 (pm) - D15 (am)	21	
Capecitabine (XELOX)	Colorectal	3	850 mg/m^2 bid	D1 (pm) - D15 (am)	21	
Trastuzumab-cisplatin-**capecitabine**	Gastric	1	1000mg/m^2 bid	1-14	21	DP/toxic

Figure 5.4. Screenshot of protocols for capecitabine.

Interactions:

Interaction	Compound	Enzyme Effect
Increases effect of	Carvedilol	-
Increases effect of capecitabine	Cimetidine	-
Avoid concomitant use	Clozapine	-
Increases effect of capecitabine	Denosumab	-
Increases effect of	Diclofenac	-
Decreases effect of capecitabine	Echinacea	-
Increases effect of	Fosphenytoin	-
Decreases effect of	Inactivated vaccines	-
Increases effect of	Lacosamide	-
Increases effect of	Leflunomide	-
Avoid concomitant use	Live vaccines	-
Avoid concomitant use	Natalizumab	-
Increases effect of	Ospemifene	-
Increases effect of	Phenytoin	-
Avoid concomitant use	Pimecrolimus	-
Increases effect of capecitabine	Roflumilast	-
Avoid concomitant use	Tacrolimus (topical)	-
Increases effect of capecitabine	Trastuzumab	-
Increases effect of	Warfarin	-
Increases effect of	CYP2C9	Substrate
Other Interactions	n/a	-

Figure 5.5. Screenshot of drug interactions table for capecitabine from http://oralchemotherapy.ca/drugs/Capecitabine.

6. DISCUSSION

6.1. General Discussion

Currently eHealth presents a rapidly expanding effort to improve the quality and safety of healthcare. In healthcare delivery, eHealth uses ICT to try to optimize healthcare system access and usefulness. Recent advancements in wireless technologies and novel genomic discoveries may have brought technology tool development for use at PoC to a tipping point (McHattie et al., 2014). We created models that can bring insights from scientific endeavours in the laboratory, as well as established evidence-based knowledge, to physicians, nurses and pharmacists. We translated and optimized medical knowledge, and created two pipelines to put filtered and applicable information into the hands of healthcare providers so they can utilize it in patient care (Figure 6.1). We focused on decisions regarding medication selection and treatment plans, as well as the safe use of medications.

In eHealth there is a need to build interconnected pipelines. These are pipelines that can capture data, such as genomic Big data, store new knowledge derived from this data, and deliver benefits to patients through optimized treatments. In other words, these are pipelines that carry, filter and transform medical data to be ultimately applicable at PoC. This study fits within an overall effort to connect the bench to the bedside by creating more seamless eHealth pipelines. In building re-usable CDSS components this study addressed known stumbling blocks in the uptake and implementation of CDS within eHealth (Crews et al., 2012, Marsh and van Rooij, 2009, van Rooij and Marsh, 2011, van Rooij et al., 2012).

Currently many evidence-based healthcare practices are not implemented. In order to improve access to, and application of, medical evidence, this study created models to solve complex problems in the construction of eHealth pipelines. In this study we created three eHealth model methodologies and one mHealth application: the Comprehensive Analysis and STORage (CASTOR) model described in Chapter 2 (Bouffard et al., 2010), the augmented Fast and Frugal Tree (FFT) model described in Chapter 3 (van Rooij et al., 2015c), the Bridging Opportunities Work-frame (BOW) model described in Chapter 4 (van Rooij et al., 2015b), and the AntiC mobile CDS application described in Chapter 5 (van Rooij et al., 2015a). The three different models (Chapters 2-4) provide CDSS component solutions that can be used in the translation of evidence-based knowledge for use by healthcare providers. In addition, this study created a three-tier mobile CDS application named AntiC for use by hospital and community pharmacists to assist in the safe dispensing and use of anti-cancer medications in pill form (oral chemotherapeutics).

We concentrated on building CDSS pipeline components for ease of use of genomic data, as well as for evidence-based practices regarding medication use. We built re-usable models for two eHealth pipelines, one pipeline is focused on medication selection (CASTOR and FFT) and the other pipeline is focused on medication safety (BOW and AntiC) (Figure 6.1).

We developed our models to be generalizable; we wanted them to be universally applicable but regionally applied. To that end they are also standardized i.e. our models are uniform and consistent throughout. This was done because we wanted other multi-

disciplinary teams to be able to re-use and apply our models as CDSS components when building the same or similar eHealth pipelines.

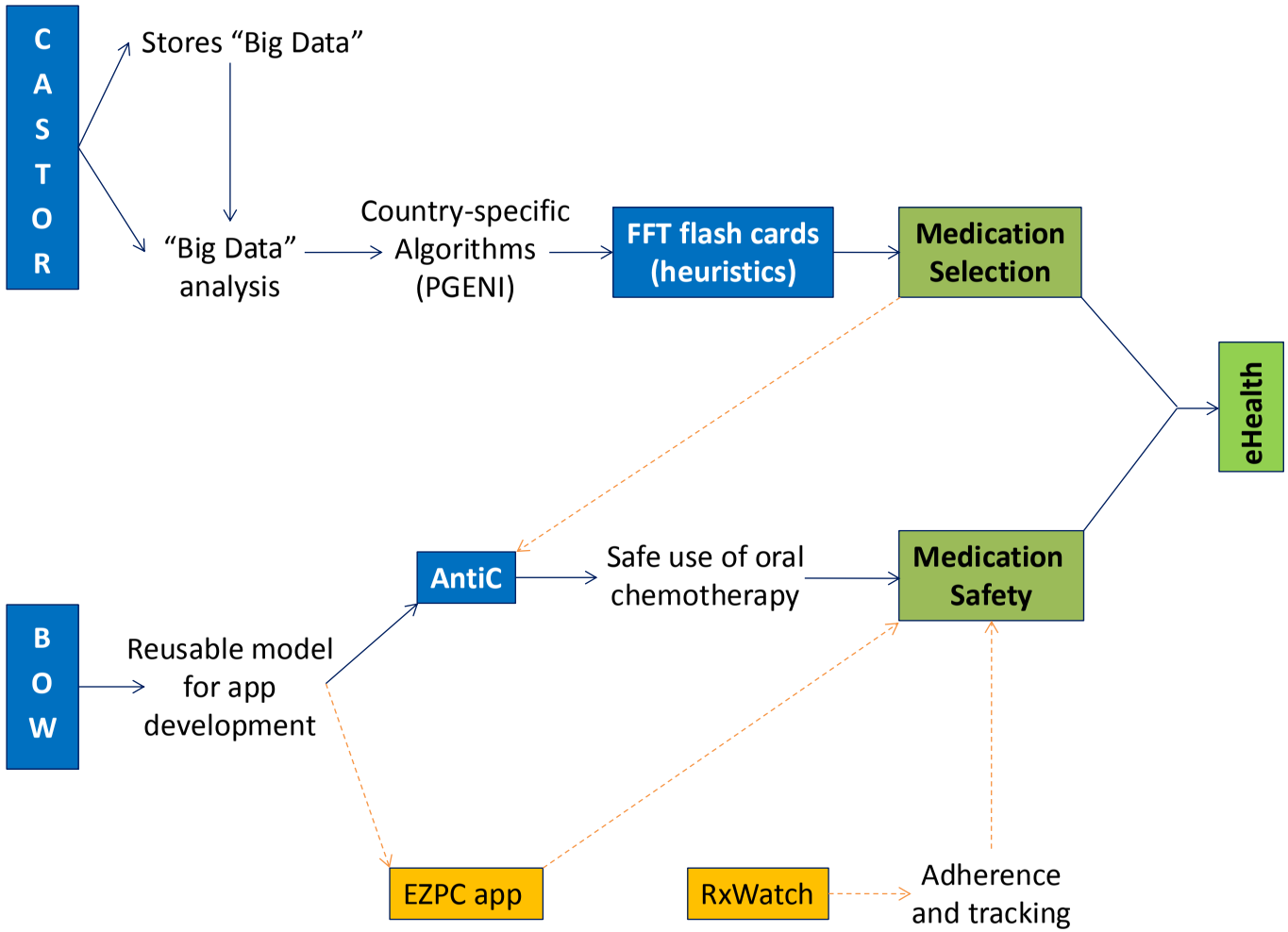

Figure 6.1. Project summary.

6.1.1. MEDICATION SELECTION PIPELINE

Big Data and complex genomic guidelines can benefit from database architecture and heuristic approaches as an implementation strategy. Both are necessary components in the automation of pharmacogenomic data processes to enable decision-support for medication selection. The Comprehensive Analysis and STORage (CASTOR) project and the Fast and Frugal Tree (FTT) model (Chapters 2 and 3) present the creation of active CDS focused on linking data storage and analysis with interpretation and visualisation of both pharmacogenomic data and guidance. CASTOR and the FTT model are part of an eHealth pipeline (Figure 6.1)

6.1.1.1. Data storage and analysis

In the Comprehensive Analysis and STORage (CASTOR) project presented in Chapter 2 we created a model for dealing with molecular genetic evidence, its focus is on the process of storing and analyzing genomic data along with patient demographics to better understand the correlation between the two (Bouffard et al., 2010). This is an important step in the overall process of personalized medication selection, towards the goal of CDS implementation. It allows data from genomic studies to be analyzed in a patient-context to extract meaning from vast amounts of data. This is important as it can elucidate the genetic mechanism by which treatments can be enhanced (e.g. by applying genetic pre-dispositions of patients, or patient populations to medication selection). In CASTOR we created a model to incorporate genomic datasets into an eHealth pipeline. Modern genomic datasets can be huge, and are an example of Big Data (Denny, 2014), and their storage and interpretation is crucial to the pursuit of personalized medicine. It

has been predicted that the medical informatics-based application of personalized medicine will greatly benefit from advances in Big Data management (Merelli et al., 2014). The storage and analysis of these large genomic data files is an ongoing concern in bioinformatics and numerous open problems exist when it comes to analyzing and storing this data (Niu et al., 2009).

For historical reasons, genomic technologies often put out files that are formatted to be human readable. This practice leads to unnecessary repetition in files and increases overall file-size. These files are called flat text files and the data in them is organized in a sequential format. This creates a problem. In sequential access, one needs to read all the preceding data first in order to reach any point anywhere in the data. This is akin to a book where in order to read a passage one would be forced to read all the preceding text every time the passage is read. Rather than addressing this problem, most current solutions use expensive hardware to cope with this inherent shortcoming. Many forego the use of databases altogether by claiming that the data is simply too big. However, additional computational hardware leads to an added expense and takes up more physical space, which is a hindrance to uptake. We addressed this barrier through the CASTOR model (Chapter 2). The model consists of multiple parts. We altered these large genomic data files to be machine readable only and changed them into the binary format preferred by computers. In doing so, the same information fit into a much smaller file. This makes moving these files around easier and also helps when uploading the data to a database.

For speed of access reasons, we parsed these files. Parsing breaks up files into smaller meaningful parts e.g. the name of a particular region of interest in the genome

and the corresponding measured value. After we parsed the data we stored it in a local database on a hard disk. The improvements we made in CASTOR led to faster analysis times.

Using CASTOR, genomic data was stored in a commonly available and inexpensive database, and additionally it was simultaneously optimized for computer-aided analysis. Our test showed that, when looking at the speed of statistical analyses commonly performed in Genome Wide Association Studies (GWAS), we could compete in a direct way with more bulky and expensive hardware/software combinations.

Although CASTOR houses genomic data in a database with a small footprint, it does not come at the price of data-loss or decreased performance in analysis capabilities. This finding was echoed by Sebastian Dorok from the University of Magdeburg's School of Computer Science, who in 2013 in his master's thesis entitled: *Towards Genome Analysis on Modern Database Systems*, concluded that CASTOR's specialized data structure approach was advantageous and helped to improve analysis performance, when compared to other commonly used object-based and relational databases, including among others GIMS, Atlas, BioWarehouse, and dbBlast (Dorok, 2013).

CASTOR can be used in pharmacogenomics projects to archive and process SNP data that can come from a variety of sources. The CASTOR model can be used to store data originating from Microarray Chips and whole genome sequencing, such as data generated by and through Affymetrix' Genome-Wide Human SNP Array, Thermo Fisher TaqMan SNP Genotyping Assays, Agilent Human Genome CGH+SNP Microarrays, Pacific Biosciences' SMRT sequencing, Illumina's Infinium HD, and Sequenom's

MassARRAY iPLEX/ iPLEX. These technologies can be used to generate data from a whole range of genomic research projects, including oncology, cardiology and psychiatry related studies. Furthermore CASTOR can be used to store the outcomes of personalized SNP sequencing for future healthcare use. In both these cases some additional parsing may be required as formats are likely to change somewhat between technologies. CASTOR provides a model to store information and filter knowledge from vast amounts of pharmacogenomic data, and in doing so, is a functional part of the CDSS pipeline that aims to improve medication selection. However, CASTOR requires expertise in database management to be installed.

Although CASTOR can take advantage of storage and server capacity in the Cloud, it does not require it; its small footprint and reasonable cost make it possible to house it directly in hospitals and clinics, where it may be easier to get ethics approval and oversight, as patient-data does not have to leave the physical premise to be analysed.

CASTOR has been disseminated to the Ontario Institute for Cancer Research (OICR) and the Université de Montréal Beaulieu-Saucier Pharmacogenomics Centre where further development on the framework has taken place. Efforts have included the use of MySQL (an open-source database) to generate the database schema, and development towards the integration of CASTOR with PLINK. PLINK is a free, open-source whole genome association analysis toolset (Purcell et al., 2007).

Because our focus was on pipeline development leading to CDS implementation, the CASTOR model provides an easy to apply alternative for genomic data storage and application geared towards the translational needs of healthcare providers. Once data is

stored in CASTOR, its output, for example, genomic data that helps to explain differences in drug response in patients, can be linked to inform clinical guidance based on this data, which then can subsequently be visualized for use in regionally-specific medication selection, as shown in the FFT model (Chapter 3).

6.1.1.2. Data interpretation and visualization

As part of the global project, the Pharmacogenomics for Every Nation Initiative (PGENI) we automated the use of up-to-date genomic information for appropriate medication selection in the developing world. We modified and applied the fast and frugal tree methodology (FTT) to provide automated decision support to the PGENI (van Rooij et al., 2015c).

In low and middle income member states PGENI strives to include known and experimentally derived pharmacogenomic data in the process of medication selection on a population basis, rather than by individualized testing, which is cost prohibitive in many countries (Roederer and McLeod, 2010). Data collection is currently ongoing in the PGENI project. Once Microarray Chip Data (Genome-Wide Human SNP Array 6.0) has been gathered on SNPs in multiple populations, they can be stored and analysed in CASTOR and automated and visualized through FFTs for population specific medication selection across the PGENI member states. Both the CASTOR model and the FFT model have been disseminated to the international PGENI project. Linking the CASTOR model to the FFT model is set to complete a medication selection pipeline.

FFTs are further down the pipeline from CASTOR (Figure 6.1), and closer to the healthcare provider. FFTs are described in Chapter 3. We modified the FFT heuristic to

standardize pharmacogenomic algorithms and flow-charts created by PGENI. Although these algorithms and flow-charts were correct, prior to this standardization, they were hard to interpret. Healthcare providers operate in time-constrained settings so tools for the use in this environment necessarily need to be concise, accurate and easy to use. FFTs use heuristics, which are a seemingly simple but powerful way of organizing data for decision-making. Heuristics can provide shortcuts through large or complex data in order to reach a solution to a problem faster. We used FFTs as a heuristic to simplify and synthesize complex genomic guidance data to ready it for regionally-specific medication selection decision making purposes.

FFTs are an example of the use of heuristics in the form of decision trees. Many different types of decision trees exist but what makes the FFT so useful is that it splits the data by a series of yes/no questions where one of answers always leads to a direct recommendation. The other answer may require yet another question to establish a recommendation. This process continues until there are no more questions left. This FFT approach is intuitive for decision making in high-throughput and time-constrained environments such as a clinic, as it allows getting to recommendations in a very short time through very few steps.

There is great tension between speed and accuracy of medical decision making in clinical settings. This is where CDS can aid in the decision making process and be a useful tool to assist healthcare providers in a timely fashion. Indeed FFTs, drawn as a schematic on a piece of paper, have been successfully used in pediatrics, cardiology, and emergency medicine, as well as in diagnosing depression (Fischer et al., 2002, Jenny et

al., 2013, Marewski and Gigerenzer, 2012, Todd and Gigerenzer, 2000, Wegwarth et al., 2009).

We augmented FFTs to be able to contain pharmacogenomic decision data for ultimate use in medication selection by clinicians in developing countries. Our augmented FFTs allow for regionalized application of the pharmacogenomic data in PGENI against self-described (by the patient) membership in ethnic or tribal backgrounds. Our study also found that FFTs are conducive to automation. We showed how the FFT could be relatively easily transformed by software in a series of automated flash cards for use by healthcare providers. By answering questions on the flash cards a clinician could potentially apply complex pharmacogenomic data in an easy routine to rationalize medication selection.

Our study presents the first medical automation of FFT use for CDS. Our model is generalizable, which means that any augmented FFT tree can be automated. Automation has many advantages, it allows for rapid updates should the FFT change, for instance because of new knowledge or fine-tuning of genomic-algorithms underlying the guidelines or flow charts that inform FFTs. It also keeps data consistent across different user sites. Furthermore, automation of FFTs extends the reach of this evidence-based translation. Compared to paper-based approaches, dissemination through technology is more rapid and consistent to (remote) regional settings. In the PGENI project, automated FFTs can be extended to provide decision-support using wireless mobile networks (mHealth), alongside the use of internet access.

Increasing the efficient use of available data for healthcare, our FFT model created a simplified and powerful model to effectively integrate pharmacogenomics into the clinical workflow of medication selection by providing concise access to pertinent medical data through software.

6.1.2. MEDICATION SAFETY PIPELINE

Not all complex or large data can benefit from heuristics like the FFT, sometimes the application of data needs a different strategy. This is the case in the application of passive decision support through the creation of CDS apps, in the safe use and dispensing of medications. The Bridging Opportunities Work-frame (BOW) and AntiC mobile application (Chapters 4 and 5) present an mHealth model and its subsequent application in the creation of regionalized passive decision support. BOW and AntiC are part of an eHealth pipeline (Figure 6.1) but are focused on medication safety rather than medication selection.

6.1.2.1. mHealth model

Regionalization of medical data is important to provide relevant and meaningful support in the day-to-day workflow of healthcare providers. Rather than interfaces teeming with information, concise data that is directly applicable in a local context is preferable when making decisions (Drohan et al., 2009). The BOW model (Chapter 4) provides a novel work-frame whereby healthcare providers can direct the process of creating their own regional mobile CDS applications (van Rooij et al., 2015b). Healthcare providers, as experts in their field, can identify the need for CDS and the evidence-based

data that requires translation to a specific workflow within a regionalized healthcare setting (Bright et al., 2012, Drohan et al., 2009).

In the BOW model, healthcare providers direct a team effort on implementation of relevant localized data, and assure meaningful interfaces when creating CDS apps. This provides a safeguard to ensure that only curated and concise data will be implemented, and that visualisation of the data meets workflow expectations. The BOW model achieved this by applying Change Management (Burnes, 2004, Manchester et al., 2014) to alter the organization of the development team.

Using Change Management, roles and responsibilities in the multi-disciplinary development team were modified from a traditional model whereby the healthcare provider had a client-role in the project, to a model that reflected the importance of the healthcare provider in the overall development process. In the new model the healthcare provider becomes the co-director of the project with the ICT expert. This new role is invaluable to the project's app development, as the healthcare provider's expertise in accuracy and applicability of data is the focus of providing decision support for medication safety. Healthcare providers know their own work environment and are aware of local knowledge, information, and workflow needs. This change in roles furthermore allows software developers to focus on implementation as they do not have to assess the use or validity of data or present implementation strategies.

Apart from changing the management structure, the BOW model also formalizes the informatics infrastructure. It applies a three-tier computer architecture, normally reserved for larger eHealth projects. This was done because this specific architecture fits

the requirements for CDSS development. CDSS development requires that data storage, data interpretation and data presentation activities are separated. In addition BOW's architecture added cloud-computing, both to store medical data in a centralized database and to visualize data through an application server. Cloud-computing provides an easy and inexpensive way to access considerable computing resources. The use of cloud-computing in CDS apps for medication safety is an appropriate use of the cloud in healthcare where it uses EBM knowledge only. Therefore the fact that the resources exist outside the healthcare organization is not an ethical concern in this case, as it would be with patient data. For uninterrupted use on wireless mobile devices, the BOW model provides a local copy of the data on smartphones, tablets, iPads, and iPhones. This is in case they are used by healthcare providers outside a wireless or Wi-Fi zone. In this way mobile devices can be used as a standalone whenever network or mobile connections are not available (e.g. rural settings). Any updates that occur to the data during this time are made available from the centralized database as soon as a connection to the network becomes available again.

The architecture also contains a web-interface for healthcare providers to access the data from a laptop or desktop. To keep data current, a laptop or desktop can also be used to securely log in to an administrator interface, which can be used to issue updates to the data stored in the database. This interface does not require specialized technology know-how. Upon saving, the data it is automatically reflected in all connected devices.

The BOW model's computer architecture is generalized (not bound to a specific use case) and uses open standards (not tied to a specific vendor). However, mobile

application development as a whole currently has few choices in development tools. Another limitation to the use of open standards is that development for Apple products does require a specific license. However, Apple products are commonly used by healthcare providers (Ventola, 2014), and were included because the BOW model, although regionally applied, aimed to be universally applicable. Furthermore, both Android and iOS apps will need some modifications to continue functioning when operating systems are updated.

The BOW's computer architecture enables structured, effective CDSS implementation. It allows for rapid and applicable data exchange, the ability to keep data current by the healthcare provider, and accessibility on multiple commonly used mHealth platforms (e.g. smartphone, tablet, iPad, iPhone). In combination, the management and computer architecture methodology in BOW addressed known requirements for CDSS development such as applicable regional data in a curated and concise format, ease of use, meaningful interpretation and visualisation of data, equipment selection, fit within the workflow, real-time access and updates, and healthcare provider oversight and involvement. The BOW model is furthermore generic and can therefore maximize software re-use. It can be re-applied to different use cases, as a CDSS component for the creation of novel CDS apps for medication safety.

6.1.2.2. CDS app

A recent surge in the approval and use of oral chemotherapeutics has made it possible for cancer patients to take their medications at home. Consequently, non-oncology trained pharmacists are now educating patients on the safe handling and use of

these generally toxic medications. Without ready access to all the pertinent information for the safe use of oral chemotherapy, issues such as drug-drug interactions from treatments for co-morbidities and side-effects become serious safety concerns (Allen and Williamson, 2014, Collins and Elsaid, 2011, Foulon et al., 2011, Geynisman and Wickersham, 2013, Given et al., 2011, Hammond et al., 2012).

In our implementation case study, the application of the BOW model (Chapter 4) created a CDS app for use by non-oncology trained pharmacists in safe dispensing and use of oral chemotherapeutics. This passive CDS app is called AntiC (Chapter 5), and supports both Android and iOS operating systems (i.e. AntiC works on smartphones, tablets, iPhones and iPad, but it also works on laptops and desktops through a website) (van Rooij et al., 2015a). The BOW model made it possible for an oncology pharmacist to co-lead the development of AntiC and for the development team to create a system to store, upload, edit and visualize evidence-based data for pharmacy based decision-making. As a re-usable CDSS component, the BOW model sped up the development of the CDS app and the project validated the feasibility of the work-frame (although more studies are needed for further validation). A complete CDSS was developed comprised of a mobile application, web-based applications and a centralized application server and a database. As per BOW, AntiC is a three tier application with 3 versions in the presentation layer (a public website, an administrator-access website for adding and modifying medication data, and the AntiC app), a logical layer for processing commands to the database (e.g. show me the dose adjustment for Afatinib given that the problem is

toxicity), and a data storage layer (AntiC uses MySQL as a transactional, relational database).

An entity-relationship model (ER model) for oral-chemotherapeutic data was created, to describe the data and the relationships within, so that curated data provided by the pharmacist could be stored in the database. The system subsequently parsed and stored all the relevant EBM data related to oral chemotherapeutic medications e.g. monographs, protocols, and dose adjustments.

After information on oral chemotherapeutic agents was standardized throughout the CDSS, it was made to have the same look and feel, independent of technology or operating system. Furthermore, all medications contain the exact same sub-categories e.g. known indications, drug interactions, special population warnings etc. Providing data in a concise and standard format reduces cognitive complexity in use, which means that actionable data can be located faster and with less mental effort. Furthermore, iterative development, beta testing, refinements and quality control could be done more rapidly because an oncology pharmacist was part of the multi-disciplinary development team.

AntiC provides multiple ways to access the same data. For instance, on the website, medications can be browsed alphabetically or by typing in a partial name (i.e. the website will respond with all medications that fit the search string). Another example is dose adjustments access on the smartphone, dose adjustments can be accessed from within oral chemotherapeutic medications or directly from a dose adjustment tab.

AntiC is an example of a regionalized app as it handles Canadian oral chemotherapeutics exclusively. This is a benefit to Canadian pharmacists as the data will

be consistent with medications availability, nomenclature, and will indicate Health Canada approval status. This further means that there is no visual clutter or superfluous data that is not pertaining to the Canadian context.

Content is stored directly on the smartphone or tablet in a local copy of the database so that pharmacists can access oral chemotherapy related information even if they work in settings without a Wi-Fi or mobile signal. This improves accessibility to content. AntiC can be maintained and remain relevant, while medical knowledge evolves and new medications become available. Through a secure web-based administrator interface, oncology trained pharmacists can curate the data as new oral chemotherapeutic agents or guidance on their use becomes available. Furthermore, based on the fact that the data now resides in an updatable database, more interactive features can be added if the CDS would require it. However, this would require more software development. Upgrades in operating systems on either Android or iOS may need the involvement of specialized developers to keep the application running.

Using the AntiC CDS app, community pharmacists can, through smartphones, tablets, iPhones, or iPads, actively apply current evidence-based knowledge on safety and standards in the use of oral chemotherapeutics, thus strengthening their level of assessment and pharmaceutical care when filling prescriptions of these generally toxic medications. The proposed use of AntiC by pharmacists is described in Figure 6.2.

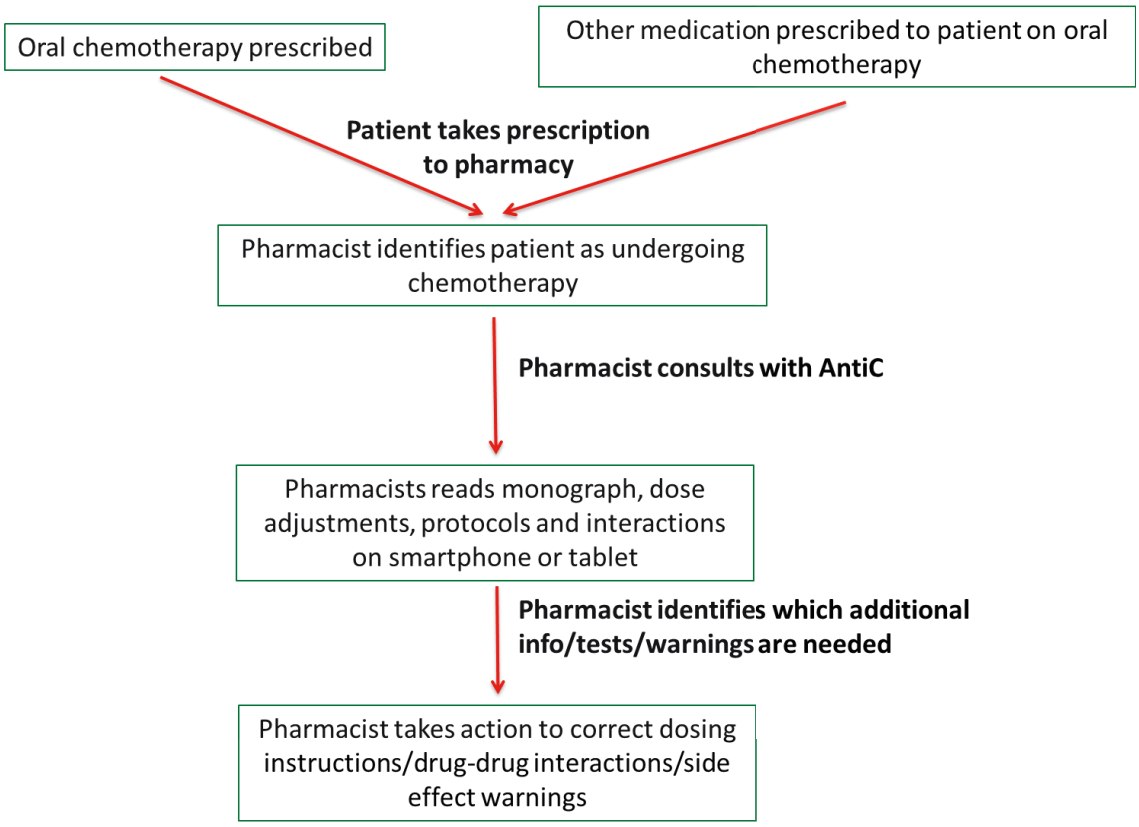

Figure 6.2. CDS can be used to provide patient-specific advice. AntiC can be used by pharmacists to provide an additional level of assessment in medication evaluation leading to greater patient safety.

6.1.3. RE-USABLE CDSS PIPELINE COMPONENTS

The component based approach in this study maximizes software re-use for the development of CDSS. It furthermore allows for customization of the software system's content and application according to the needs of new projects. In this manner, re-usable components can save time and effort required to create active and passive CDS for medication selection and safety. The published models for the novel CDSS components in this study provide the necessary detail for other multi-disciplinary teams to be able to re-use and apply the software techniques, computer architecture designs and project organization toolsets when building the same or similar eHealth pipelines for CDS. Not only can these components be re-used in the context they were originally developed in, but novel combinations of the CDSS components of this study may also be possible, as they all provide targeted (e.g. individual, local, regional) approaches. For instance, cross-over potential exists between the medication selection and medication safety pipelines described here, as depicted in Figure 6.1. It may be feasible to use the FFT model to encode heuristics for CDS apps regarding safety of complex medication regimens involving polypharmacy, as research has indicated a possible algorithmic approach to this problem (Grando et al., 2012). Furthermore, heuristics were also used to identify the cause of postoperative retching (e.g. polypharmacy, overfeeding) in children that underwent surgical intervention for gastro-esophageal reflux disease (GERD) (Cook and Blinman, 2014). These are examples where medication safety CDS could re-use FFTs developed for medication selection CDS. This overlap and feasible cross-use of CDDS components in medication contexts is not surprising, as the ability to filter

complex data to present simpler, meaningful results, in a targeted context, is a shared characteristic. These re-usable CDSS components provide toolsets to reduce the time needed to assess a multitude of complex scenarios, which has wide application in real-world medical CDSS development (Kilsdonk et al., 2013, Marewski and Gigerenzer, 2012).

6.2. Conclusions

The mechanism the delivery of preventative, personalized, and predictive modes of medicine have in common is that they all require more advanced use of ICT to become established medical realities (McHattie et al., 2014). The three models developed in this study (Chapters 2, 3, and 4) improved access to resource and data compendiums to obtain, understand, transform, and apply health information with direct relevance to patients and providers in a regional context. We developed a novel database structure for storing and analyzing data (Chapter 2) (Bouffard et al., 2010), and augmented fast and frugal decision trees to improve medication selection (Chapter 3) (van Rooij et al., 2015c). We developed a work-frame whereby healthcare providers can direct the process of creating their own regionalized CDS applications (Chapter 4) (van Rooij et al., 2015b). To test this work-frame we developed a CDS system comprised of a mobile application, web-based applications and a centralized server and database (Chapter 5) (van Rooij et al., 2015a).

This study developed and disseminated re-usable CDSS components of two eHealth pipelines, medication selection (CASTOR, FFT) and medication safety (BOW,

AntiC) (Figure 6.1). Both of these pipelines dealt with the problem of what and how much health information should be gathered from different heterogeneous data sources, how this data should be stored and represented internally in automated systems, and how it should be analyzed, synthesized, interpreted, and presented to healthcare providers for access and ease of use.

6.3. Future directions

Two different mHealth projects involving the creation of decision support apps for use by healthcare providers, as well as by patients, using the BOW model developed in Chapter 4, are planned.

6.3.1. EZPC, A MOBILE CDS APPLICATION FOR PALLIATIVE CARE

Based on the BOW model's re-usability it will be applied to create a regionalized CDS app for use in palliative care (Figure 6.1). To that end a multi-disciplinary team has been formed at the Grey Nuns Hospital in Edmonton, Alberta to develop the Edmonton Zone Palliative Care (EZPC) app. This team of healthcare providers and ICT experts will develop an evidence-based decision support tool for palliation in end of life care organized around (often off-label) medication use for the symptom management of indications such as pain, anxiety, constipation, depression, dyspnea, and seizures. It is envisioned that the EZPC app will be used for training practices in hospitals, as well as by nurses who serve community needs outside the hospital, in outpatient settings.

Practices and organization of palliative care vary across Canadian Provinces and therefore local context is a requirement to maintain usability of the CDS app to be built. The focus of EZPC will be narrower than AntiC, as the applicability will be confined to Alberta only, with data included on insurance coverage of medications, which can be a factor in accessibility for patients. A regional focus will increase the usefulness of this app and subsequently it is anticipated that this will lead to enhanced uptake and use of this CDSS component for CDS in palliative care.

6.3.2. Rx Watch, Smart Watch technology for medication adherence

Non-compliance to medication dosing can lead to unnecessary failure of treatment, toxicities and even hospitalization (Routledge et al., 2004). With increasing numbers of medications taken per patient, a greater chance of error and mix-up arises; especially in the elderly where often the complexity of regimens increases (Gallagher et al., 2007). Furthermore, in oncology, strict adherence to oral chemotherapy dosing is often a matter of life and death (Landier et al., 2011).

We are assembling a multi-disciplinary team for an mHealth project called Rx Watch, to try to improve patient adherence (Figure 6.1). The BOW model's re-usability, will be applied to create active patient-support apps for medication adherence. The patient interface is envisioned for use on a smart watch, which is a watch-like wearable device that supports the use of mobile apps. Worn on the wrist; the smart watch could give a patient continuous access to an active support app. The app could prompt patients to take the appropriate pill at the appropriate time, by showing a picture of the actual pill, with an alarm. A patient could then confirm, using the smart watch, that a specific

medication was taken. With permission of the patient, this feedback would allow the pharmacy to monitor adherence wirelessly. Through this mHealth project patients could be alerted to take their medications, and pharmacists could provide an additional level of assessment by having access to information on patients' medication use in their own homes.

6.4. Future Perspective

Building on the progress in organization and storage of medical data that started around the millennium in EHRs, and its related eHealth interventions and pipelines, personalized and patient-centric medicine is becoming increasingly mobile. Ultimately, using the models developed here as an interpretive and computational framework to deliver support at PoC should enable clinicians to make faster and more accurate decisions to improve their use and selection of medications. Ministries of Health in developing countries will eventually have access to curated, pharmacogenomics-based decision trees specific to their countries to improve the use and selection of medications at no extra cost to their healthcare systems (Chapters 2 and 3), and non-oncology trained pharmacists will be better informed about oral chemotherapeutics, preventing deleterious issues such as adverse drug reactions (Chapters 4 and 5). Smartphone and tablet use for regionally applicable CDS, suited for integration in the day-to-day workflow of healthcare providers, is becoming commonplace (Saint-Elizabeth, 2015), and the re-usable BOW model (Chapter 4) will enable standardized, formalized mHealth apps to be developed for future use at PoC.

6.5. References

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