The Hospital for Sick Children
Technology Assessment at SickKids (TASK)

FULL REPORT

A COST-EFFECTIVENESS ANALYSIS OF MATERNAL GENOTYPING TO GUIDE TREATMENT FOR POSTPARTUM PAIN AND AVERT INFANT ADVERSE EVENTS

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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List of Abbreviations

AAP	American Academy of Pediatrics
CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CNS	Central Nervous System
CPNDS	Canadian Pharmacogenomics Network for Drug Safety
CUA	Cost Utility Analysis
CYP2D6	Cytochrome-P450 2D6
EM	Extensive Metabolizer
FN	False Negative
HRQoL	Health Related Quality of Life
HUI	Health Utilities Index
ICER	Incremental Cost-Effectiveness Ratio
IM	Intermediate Metabolizer
INB	Incremental Net Benefit
MOHLTC	Ministry of Health and Long-Term Care
MRD	Most Responsible Diagnosis
NHB	Net Health Benefit
NICU	Neonatal Intensive Care Unit
non-UM	Non-Ultra rapid Metabolizer
OCCI	Ontario Case Costing Initiative
ODB	Ontario Drug Benefit Formulary
PM	Poor Metabolizer
PSA	Probabilistic Sensitivity Analysis
SF-6D	Short Form 6D
TP	True Positive
TTO	Time Trade Off
UM	Ultrarapid Metabolizer
WTP	Willingness-to-Pay

Executive Summary

BACKGROUND: The maternal and infant benefits of breastfeeding are numerous, however maternal exposure to medications during lactation raises concerns of infant exposure and may be an impediment to breastfeeding. Recent concerns about the safety of codeine, an analgesic commonly used after delivery, have arisen. Evidence suggests that mothers with an ultrarapid metabolizer phenotype may put their infants at risk for adverse events by producing more active metabolite, which is excreted into milk. Pharmacogenetic screening may be a valuable tool to identify such mothers, and avert adverse events.

OBJECTIVES: The objective of the study was to determine the incremental costs of genotyping to avert neonatal adverse events during maternal pharmacotherapy.

METHODS: A cost effectiveness analysis to determine the incremental costs of genotyping to guide codeine therapy compared to standard care to avert adverse events was performed. The base case was a prenatal patient whose metabolizer status was unknown, but who may require codeine analgesia after delivery. Parameter estimates and costs were ascertained from a concurrent clinical study, from the literature and expert opinion.

RESULTS: Pharmacogenetic screening resulted in a cost of $9,997 per adverse event averted or $2,173 per infant symptom day averted, when compared to standard care. The results were not sensitive to most variables in one way analysis, with the exception of the costs of a hospital admission. This study was limited by a small number of trials from which parameter estimates could be extracted and the very small number of adverse events reported in infants in the literature.

CONCLUSIONS: Although genotyping to guide pharmacotherapy was not cost saving, the cost to avert an infant adverse event may represent good value for money. It is not yet known whether implementation would be clinically viable, however these findings will have implications for new mothers and their health care providers world-wide.

1 Introduction

1.1 Background

While it has long been acknowledged that milk produced by mammals to feed their young is the ideal form of nutrition for their offspring, extensive research in humans in recent decades has verified the clinical advantages of human milk for both mother and her child across cultural, environmental, and geographic barriers (Johnson et al. 2012, Critch 2013, Ip et al. 2007, Horta et al. 2007, León-Cava et al. 2002). Owing to these well-established benefits, public health agencies and medical establishments around the world including the World Health Organization (World Health Organization 2001, Horta et al. 2007), Health Canada and the Canadian Paediatric Society (Critch 2013) and the American Academy of Pediatrics (AAP) (Johnson et al. 2012) recommend exclusive breastfeeding for all healthy infants for at least the first six months of life and continued breastfeeding for the first two years of life whenever possible.

The choice to continue breastfeeding can become complicated when maternal medication is required. In this scenario, the benefit-risk assessment is complicated by the potential for an unnecessary infant medication exposure weighed against the benefits of breastfeeding for both mother and child, since most drugs will reach human milk when ingested by the mother. Since success of breastfeeding is strongly related to initiation in the early hours of life, this issue is particularly critical for medications used to treat pain in the immediate post-natal period. Moreover, most new mothers will require some form of analgesia in the early days after delivering their child (Declercq et al. 2008). A number of medications are used to treat pain postnatally and fortunately, the medications used for acute analgesia after delivery have traditionally been considered safe for use in breastfeeding women (American Academy of Pediatrics Committee on Drugs 2001). More recently however, longstanding recommendations regarding codeine use in lactating women have been called into question following a report of a neonatal fatality in an infant whose mother had been taking acetaminophen with codeine (Koren et al. 2006). Subsequent to this report, the AAP statement was updated and the issue of codeine use in lactating women is discussed in detail with a more cautious approached being advised (Sachs and Committee on Drugs 2013).

The literature addressing the safety of codeine when used by breastfeeding mothers is scant and limited to case reports, a single prospective study and a review article (Davis and Bhutani 1985, Meny et al. 1993, Findlay et al. 1981, Naumburg and Meny 1988, Ito et al. 1993, Anderson et al. 2003). In a 2006 Lancet publication, a case of a neonatal fatality in an infant whose mother had been taking acetaminophen with codeine for postnatal pain was reported (Koren et al. 2006). As reported by the mother, the child's death was preceded by respiratory depression and lethargy, which prompted her to seek medical attention. The physician visit was unremarkable however, as the child had regained his initial birth weight and appeared to be thriving. After the child's death, genotyping was performed on the child, mother and extended family. The genotyping revealed that the mother was a Cytochrome P450 2D6 (CYP2D6) ultrarapid metabolizer (UM), producing higher amounts of morphine from codeine, and this morphine was excreted into the mother's breast milk. In addition, high amounts of morphine were found in the infant. The authors postulated that the high milk morphine level was the reason for the child's morphine intoxication and premature death. Subsequently, the FDA (US Food and Drug Administration 2007) and Health Canada (Health Canada Marketed Health Products Directorate 2008) issued public health advisories and label changes for codeine-containing prescription products. A similar report was also issued by the European Medicines Agency, where updated guidelines for codeine use were outlined (European Medicines Agency 2013).

Following this infant death, an observational cohort study of 72 mother-infant pairs was conducted (Madadi et al. 2009b). Women who reported using codeine while nursing were surveyed by standardized telephone interviews to determine the prevalence of infant adverse events, with specific attention to central nervous system (CNS)-related adverse events. Subjects were included if they had taken codeine at any time while breastfeeding but were excluded if they had taken codeine only as a cough syrup or had used sedative medications, drugs of abuse or alcohol concurrently with their codeine. Mothers of infants with CNS disorders were also excluded from the follow up procedure. The authors compared a number of characteristics between the symptomatic infant group and the asymptomatic group. Infant symptomatology was based on maternal report with 24% of the 72 mothers reporting symptoms in their infants. The maternal dose was found to be higher among the cases where infants had symptoms as compared to those who did not (1.62 ± 0.79 mg/kg/d vs 1.02 ± 0.54 mg/kg/d) and was statistically significant ($p=0.004$). The odds of maternal adverse effects were also significantly higher in the

symptomatic infant group as compared to the asymptomatic group (odds ratio 24.0, 95% confidence interval 6.0 to 96.4). The presence of maternal symptoms is highly relevant and may be an indication that there was greater systemic exposure, possibly related to her metabolic capacity. This higher maternal exposure may then result in higher drug concentrations in milk, and therefore, greater exposure to the nursing infant. Though there were no life-threatening events in this cohort, there were more emergency room visits among the symptomatic group as compared to the asymptomatic group (24% vs. 0%, p=0.002). The only case of respiratory depression was found in an infant whose mother was an UM. The findings from this study, together with the currently available literature (Madadi et al. 2008, Madadi et al. 2009b, Crews et al. 2014), suggest that there may be selected subgroups of infants who are more susceptible to the adverse effects of codeine though maternal milk. Infants may be uniquely susceptible to the effects of drugs because of their immature drug metabolizing capacity. That is, in the first weeks of life, they clear drugs less efficiently and therefore are prone to systemic drug accumulation. Moreover, there is an up-regulation of maternal drug metabolizing enzymes in the latter part of pregnancy and this has been shown for CYP2D6 specifically (Wadelius et al. 1997, Tracy et al. 2005). In the case of codeine, this may result in greater conversion to morphine in the mother near delivery as compared to her non-pregnant state.

It has long been known that human response to a drug is variable. In fact, for any drug, a population of exposed individuals will experience different rates of therapeutic responses as well as different rates of toxicities or adverse events related to treatment. These differences are largely attributed to the metabolism of drugs. The differences may be in conversion of the parent compound to the active drug, to toxic metabolites or maybe in the capacity to detoxify the active molecules. In the case of codeine metabolism, pharmacogenetics plays a critical role, as this prodrug is metabolized to its active metabolite, morphine by a highly polymorphic enzyme, CYP2D6. In fact, CYP2D6 plays a role in the metabolic pathway of some 25% of drugs (Evans and Relling 1999, Ingelman-Sundberg 2004, Eichelbaum et al. 2006). As a result of this polymorphism individuals will produce different amounts of morphine, depending on the presence and quantity of specific alleles encoding for the enzyme. This then translates into an individual's phenotype or metabolizer status. To date, over 100 allelic variants coding for the CYP2D6 enzyme have been identified in humans (Gaedigk 2013). These alleles encode for enzymes which have no activity, decreased activity, normal activity or increased activity.

Generally, individuals are categorized phenotypically as poor metabolizers (PM), intermediate metabolizers (IM) and extensive metabolizers (EM). More recently however, a UM phenotype has been identified and is predicted by genotype analysis in which the presence of alleles encoding for more than two active copies of the enzyme are detected (Ingelman-Sundberg et al. 2007, Gaedigk 2013). World-wide, there is significant variability in the prevalence of each these alleles and therefore CYP2D6 phenotypes are also highly variable around the world (Sistonen et al. 2007, Ingelman-Sundberg 2005, Ingelman-Sundberg et al. 2007, Teh and Bertilsson 2012, Cascorbi 2003, Llerena et al. 2009, Zanger and Schwab 2013, Zhou 2009a, Zhou 2009b).

For codeine, genotyping to identify the most common alleles resulting in non-functional, partially functional, or fully functional CYP2D6 enzyme is now possible. By performing such genotyping one could predict the metabolic phenotype of the individual tested and use this information to determine if an individual may produce unusually high or low serum concentrations of morphine. A higher plasma concentration will correspond to a higher incidence of central nervous system (CNS) depression, the primary adverse effect of morphine. Similarly, patients who are poor metabolizers will produce much less morphine and not experience therapeutic benefit at standard codeine dose (Lotsch et al. 2004). The measured world-wide prevalence of the UM phenotype ranges from 2 to 40% (Sistonen et al. 2007, Ingelman-Sundberg et al. 2007). The highest prevalence was noted in North Africa (40%) and 3% and 8% in European and American populations respectively (Sistonen et al. 2007) (Table 1.1).

Table 1.1: Prevalence of Ultra-rapid Metabolizer Status Around the World

Region	Prevalence of Ultrarapid Metabolizer Phenotype
North Africa	40%
Middle East	12%
America	8%
Europe	3%
Central/South Asia	2%
East Asia	2%

Based on Ingelman-Sundberg 2007 (Ingelman-Sundberg et al. 2007) and Sistonen 2007(Sistonen et al. 2007)

Recent years have brought about an upsurge in research potential in genomics, with scientists having now sequenced the full human genome (Levy et al. 2007, Ledford 2007) and an increasing understanding of specific gene functions. The availability of genotype information is sure to lead to a better understanding of human health and disease and have world-wide impact. While a better knowledge of genes can help us to understand mechanisms or predisposition to human disease a subset of genomics is focused on understanding human response to drugs, this is known as pharmacogenetics. The core aim of pharmacogenetics is to determine which genes are responsible for both drug metabolism and drug mechanism of action. In understanding the specific genes involved, scientists are better able to understand patient response to drugs and why responses may differ across populations, allowing clinicians to tailor pharmacotherapy for individuals, thus leading to improved response, minimizing the likelihood of side effects and improving health outcomes overall. The improved health outcomes and fewer side effects may lead to fewer visits to the doctor or the emergency room which may translate into reductions in health service use and potential savings to payers. However, pharmacogenetic testing itself is not without costs. To date, economic evaluations of particular pharmacogenetic tests to guide treatment are limited. Though economic evaluations of pharmacogenetic screening strategies are increasing, there remains substantial heterogeneity across studies. Moreover, they are often lacking in quality or clear perspectives on their importance in policy decisions (Vegter et al. 2008, Beaulieu et al. 2010, Wong et al. 2010). Before pharmacogenetic testing is incorporated into routine medical care it is critical that its cost-effectiveness be examined.

1.2 Research Objectives

The primary objective of this study is:

1. To determine the incremental costs of CYP2D6 pharmacogenetic testing compared to standard care in averting neonatal CNS depressive adverse events during maternal treatment for postnatal pain from a societal perspective.

The secondary objectives are:

2. To describe the utilization rates of opioid analgesics in the postnatal ward at an urban teaching hospital in Toronto and to determine if these rates changed after a Health Canada warning pertaining to the use of codeine in lactating women.

2. To measure levels of anxiety and HRQoL before and after drug therapy is completed, among a group of women who have not received genetic screening information prior to commencing post-partum codeine therapy.

3. To estimate health state utility before and after drug therapy is completed among a group of women who have not received genetic screening information prior to commencing post-partum codeine therapy.

2 Methods

This work includes a series of studies culminating in a CEA performed by decision analysis. The initial study involved a medical record review to establish the prevalence of use of various analgesics in the postnatal ward at St. Michael's hospital in Toronto. This was the site of a clinical study where the proposed intervention of CYP2D6 screening to guide analgesic treatment was conducted. Within the clinical study patient anxiety and HRQoL were measured while other data was used to inform some of the model inputs for a CEA. Finally, a decision analysis model was employed to evaluate cost-effectiveness.

2.1 Determination of Analgesic Utilization Rates in the Postnatal Ward

One of the primary parameter estimates required for the decision model is an estimate of the rate of opioid use by postnatal patients. In an attempt to better inform this value, the rates of various analgesics used by the study population were ascertained from medical records at an Ontario hospital. The study population for the decision model was defined as any patient receiving pharmacotherapy for analgesia postnatally. To determine the utilization rates of codeine and non-codeine containing analgesics in this population a separate retrospective medical record review was undertaken. This record review was conducted at St. Michael's hospital in order to optimize internal validity and to best represent the base case population of patients delivering a child in Ontario. The review did not lead to any practice changes in the clinical study and did not interfere with standard care at the hospital. No intervention or additional contact with patients or healthcare practitioners at the hospital was required.

Sampling consisted of women delivering a liveborn singleton child at St. Michaels Hospital, Toronto. Sampling was restricted to singleton births as multiple births are more likely to be premature, experience neonatal complications or difficulty feeding, and are less likely to initiate breastfeeding at birth. Such deliveries are also more likely to result in admission to the neonatal intensive care unit and physician practices as it relates to analgesic administration may be affected by the morbidity of the child. Only the medication administered in the postnatal ward was recorded; labour and delivery charts were not evaluated for this review.

The medical records of each of the subjects in the data file were retrieved such that details about medication used, dose and frequency of use could be recorded. Subjects were identified only by their encounter number, a unique ID assigned to each hospital admission, and no patient identifiable information was recorded in the dataset used in this analysis. The results of the utilization rates of codeine and opioids in this medical record review would be used to inform the parameter estimates for the proceeding decision model.

2.2 Clinical Study

As part of evaluating the cost effectiveness of the proposed genotyping strategy a clinical study was undertaken to determine the values for parameter estimates and costs needed to populate the model. The study initially set out to evaluate the intervention against a comparator group not receiving the intervention. As there were ethical concerns with having subjects at a single site be randomized to either genotyping or not, to prevent patient concerns that they may not be getting optimal care, and to minimize interference with standard care at the sites, treatment was allocated consecutively rather than randomly. The first phase of the study recruited only subjects in the comparator group, that is, subjects who would not have genotyping prior to medication administration. All patients at a single site were subjected to the same procedures during the recruitment period (between December 1, 2009 and November 30, 2011). That is, the cohort representing standard care was recruited and followed first and the cohort of patients receiving the screening strategy were to be recruited subsequently. Owing to extremely low adverse event rates, upon completion of recruitment in the standard care group the study team decided not to continue with prospective recruitment of the intervention arm as it was deemed impractical to continue with the second arm of the trial. This apparent decrease in adverse events was attributed to clinical practice changes in the months immediately preceding the study initiation and during the study period. Specifically, clinicians became much more cautious about whom they were prescribing codeine to, and the duration of treatment was restricted to the shortest possible clinically effective dosing regimen. These changes occurred throughout the Toronto academic hospitals in response to the fatal adverse event and subsequent Health Canada warning about exerting caution when administering codeine to breastfeeding women.

2.2.1 Study Design

The resulting study was a single arm, observational cohort design consisting of all women at St. Michael's Hospital, Toronto who required codeine for pain relief after a caesarean section delivery. Only patients with a scheduled caesarean section were recruited. Medication dosing was guided by the hospital protocol. These subjects did undergo genotype screening, to determine maternal metabolizer status, but this information was not available prior to dosing and was not used to modify or guide pharmacotherapy.

2.2.2 Subjects

Subjects were recruited from St. Michael's Hospital in Toronto. This hospital was designated as the control site, where only retrospective screening of maternal genotype was performed and pain management proceeded according to standard care.

To follow is the inclusion criteria for this cohort among consenting participants:

- subject was able to provide saliva sample for CYP2D6 analysis
- subject delivered her child by caesarean delivery
- subject was requiring codeine treatment in the first 24hours after delivery
- subject had initiated and intended to continue breastfeeding their infants
- willing to participate in follow-up interviews, medical chart extraction
- able to complete follow-up interviews in English

In addition, if any one of the following exclusion criteria were present the subject was not included in the study:

- the subject was taking other medications known to be associated with sedating side effects (including benzodiazepines, muscle relaxants, psychotropic medications)
- the subject was taking, or addicted to, other opioids and/or illicit drugs
- either mother or child does not survive delivery
- the child was admitted to NICU or special care nursery
- either mother or child is transferred out to another facility

2.2.3 Study Procedures

In this observational cohort, only patients who had already delivered a child and required codeine for pain relief after delivery were approached for participation. After consenting, subjects provided a saliva sample which was used for the CYP2D6 screening. Subjects in the cohort were informed that results of the genetic testing would take several weeks and therefore would not provide immediate benefit to help them make treatment decisions for this particular delivery.

All study procedures are shown in Figure 2.1 and data collection timelines shown Table 2.1. Briefly, the State-Trait Anxiety Inventory (Spielberger 1977, Spielberger et al. 1983) and the Short-Form 36v2 (Ware, Jr. 1996, Ware, Jr. et al. 2008) was used to assess maternal anxiety levels and health related quality of life (HRQoL) before and after drug therapy. A patient tracking sheet was used for patients to self-report medication use and infant medical status or adverse event after discharge. Patients were also asked to complete a health service use and cost diary to record health services use throughout the duration of drug therapy and for the duration of any adverse event and its resolution.

Figure 2.1: Study procedures

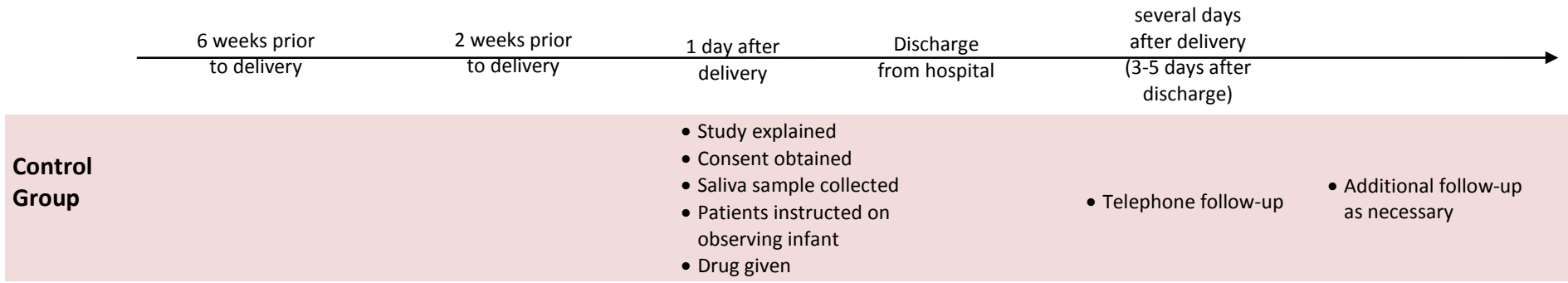


Table 2.1: Data Collection Time Points

Timing	Comparator Group
6 weeks prior to delivery	N/A
Approximately 1 day after delivery of healthy newborn and prior to discharge	• maternal demographics by chart extraction • baseline maternal medical information by chart extraction (obstetric history, medical conditions) • baseline infant medical information by chart extraction (medical conditions, birth weight, gestational age) • SF-36v2 (one-week recall) • State-Trait Anxiety Inventory
Several days after discharge	• Patient medication and breastfeeding tracking sheet (patient self-report) • Infant medical status or adverse events (maternal report) • SF-36v2 (one-week recall) • State-Trait Anxiety Inventory
After treatment completed	• Health service use questionnaire (patient self-report)

In Ontario, oral analgesia may be commenced in the hours after delivery. When mothers are prescribed analgesia they may also be sent home with the analgesics prescribed in hospital. All mothers were instructed to observe infants for symptoms of sedation, poor latch or feeding, difficulty breathing or limpness. Mothers were provided diaries with cues to assist them in observing their infants, track breastfeeding progress and maternal medication consumption. In order to determine patient-level costs associated with health services use subjects were given the "*Patient Health Services Use and Cost Diary*" to take home. This was used to record all health services use for the duration of the study and to ascertain health services use attributable to adverse events in the child. The clinical study coordinator recorded details about maternal and infant health after delivery and prior to discharge on standardized data collection forms by medical record extraction. This data collection included maternal and infant health status, infant weight at birth and at discharge, abnormalities, vital signs and maternal medication details. In

addition, in order to assess quality of life and maternal anxiety levels subjects self-administered the generic health survey, one-week recall (SF-36v2) and the State-Trait Anxiety Inventory (STAI). The SF-36v2 is commonly used to measure HRQoL, and because the questionnaire encompasses many important areas such as mental, physical, pain and vitality domains it is ideal in this particular population.

Once mothers were home, approximately a week after discharge, a single follow-up interview was conducted over the phone by the study coordinator. During the interview, maternal and infant health outcomes, details of medication and doses used, maternal side effects and magnitude of analgesia were recorded. If, during the follow-up interview, the study coordinator detected any reason for concern, arrangements were made for a study physician to visit the subject in her home to examine the infant or the mother was given instructions to take the child to the doctor or emergency room immediately. Also during this follow-up interview, subjects were reminded to complete the health service use diary, the second SF-36v2 one-week recall survey, and STAI questionnaires and return them via the self-addressed stamped envelope they were given prior to discharge.

2.2.3.1 Duration of Follow-Up

The follow-up assessment consisted of a single telephone call to the mother in the days immediately following discharge from hospital (approximately a week). Since follow-up relied on a team member being able to reach the mother directly, there was some flexibility in the precise interval between birth and the follow-up interview. So that all details regarding health service utilization and medication consumption were collected, data collection continued until subjects completed their analgesic medication. In cases where an adverse event was noted in the infant, data collection continued until the infant had recovered. As drug therapy for post-partum pain is relatively short, and because adverse events were expected to occur within the period of treatment or shortly thereafter, the follow up duration was several days longer in any subject with an adverse event but long-term follow-up was not conducted.

2.2.4 Safety

Any adverse events were brought to the attention of the telephone interviewer or noted by physician upon follow-up were referred, as appropriate, for medical attention. Subjects also had

24-hour access to a physician in the event that they had any concerns regarding their treatment or their infant.

2.2.5 Statistical Analysis of Clinical Study Data

For analysis of clinical data the software package R was used (2014)(R Core Team 2014). Univariate analysis was used to describe the characteristics of the enrolled subjects such as gravidity, parity, maternal age, dose and duration of codeine use, infant sex, weight and gestational age.

2.2.5.1 Quality of Life Analysis (Short Form 36 version 2)

For subjects that completed the Quality of Life questionnaires, the Short Form 36 (SF-36v2) data were entered into Quality Metric's scoring software (2010) and overall summary scores as well as individual component, physical and mental scores were generated and summarized for the group. For subjects who completed both before and after treatment questionnaires, the pre and post scores were compared by a paired student's t-test to determine if there were differences between the time points.

2.2.5.2 SF-6D Score Analysis

The SF-36v2 scores were converted into SF-6D, a preference-based index measure of health, using algorithms developed at the University of Sheffield (Brazier and Roberts 2004, Kharroubi et al. 2007, McCabe et al. 2006) and are based on a population of individuals from the United Kingdom. Subjects who complete the SF-36 can be classified in to one of the health states described by SF-6D and a set of preference weights can be applied. The SF-6D utility scores were summarized and compared across the two interview time points with a paired student's t-test when subjects had completed both questionnaires.

2.2.5.3 State-Trait Anxiety Inventory Score Analysis

Similar to the SF-36v2 scores, subjects completed the State-Trait Anxiety Inventory (STAI) questionnaires. In some cases these questionnaires were also completed before and after treatment. Subject responses were entered into excel and scored manually based on the scoring guidelines from the developer of the scale. Summary scores for each time period were generated and scores before and after treatment were compared by paired student's t-test.

2.2.5.4 Regression Analysis

In cases where both the pre-treatment and post-treatment surveys were available for the same subject (paired data) a difference in the HRQoL summary scores, State, Trait and SF-6D scores was computed for each set of paired data. These scores were then analyzed by ordinary least squares (OLS) regression against several possible covariates to determine if any of the covariates could explain the differences in the values. The covariates considered were maternal age, total codeine dose, gestational age at birth and gravidity because these were the variables believed to most likely have an effect on the outcome, the change in survey scores over time. Equation 1 shows the proposed model.

Equation 1: Ordinary least squares regression model

$$Difference\ Score = \beta_0 + \beta_1 Total\ CodeineDose + \beta_2 Gestational\ Age + \beta_3 Gravidity$$

2.2.6 Ethics

The clinical study was presented to a Scientific Review committee at the Hospital for Sick Children where scientific merit was assessed. This research posed little risk for harm to the subjects since there was no significant change to normal practice. The only inconvenience to subjects was the time required to complete the data collection forms and the possible minimal discomfort of collecting a saliva samples. All biological fluid samples were barcode labeled and the genetic screening facility did not have any information about the patient or her identity. This clinical study and the amendments for the economic evaluation and retrospective medical record review received approval from the Research Ethics Board of St. Michael's Hospital.

2.3 Cost-Effectiveness Analysis

The primary objective of this work was to determine whether genotyping prior to delivery to guide treatment choice for analgesia was cost-effective. A cost-effectiveness analysis (CEA) was conducted from societal and health care system perspectives to compare two treatment

options, namely genotyping prior to delivery to guide treatment choice for analgesia as compared to standard care. Standard care consisted of no routine genotype testing and pharmacologic management of analgesia at the discretion of clinicians. This analysis was performed on a hypothetical cohort of prenatal patients who had not yet delivered their child and were anticipated to require treatment for analgesia after delivery.

2.3.1 Perspective

This economic evaluation was investigated from both a societal and health care system perspective. Specifically the societal perspective was that of the population of Ontario, should such a new strategy be implemented. The societal perspective included all direct health care costs including costs to the publicly funded health care system (cost of the screening procedure and emergency room visits or inpatient hospital care resulting from adverse events) and to private payers, as well as out-of-pocket costs to the subjects (direct health care costs) and loss of productivity to the subjects and their family or caregivers (indirect) resulting from an adverse event. Analysis from the perspective of the health care system was also performed. This perspective included all costs to the publically funded health care system such as costs of the screening procedure, emergency room visits or inpatient hospital care but did not include patient out-of-pocket or lost productivity costs (detailed in Section 2.3.9).

2.3.2 Time Horizon

The CEA had a time horizon beginning from the point of the intervention, the prenatal genotype screening procedure four to six weeks prior to delivery, to the resolution of any adverse events occurring, typically less than one month after delivery. This time horizon was chosen to reflect the expectation that the adverse events associated with drug treatment will occur during treatment or shortly thereafter and will be relatively short-lived. Analgesic treatment for perinatal pain is required only for a few days and mothers are asked to note and report any adverse events in their infants to their clinicians immediately. The differences between the two strategies are therefore expected to occur within this relatively short time horizon.

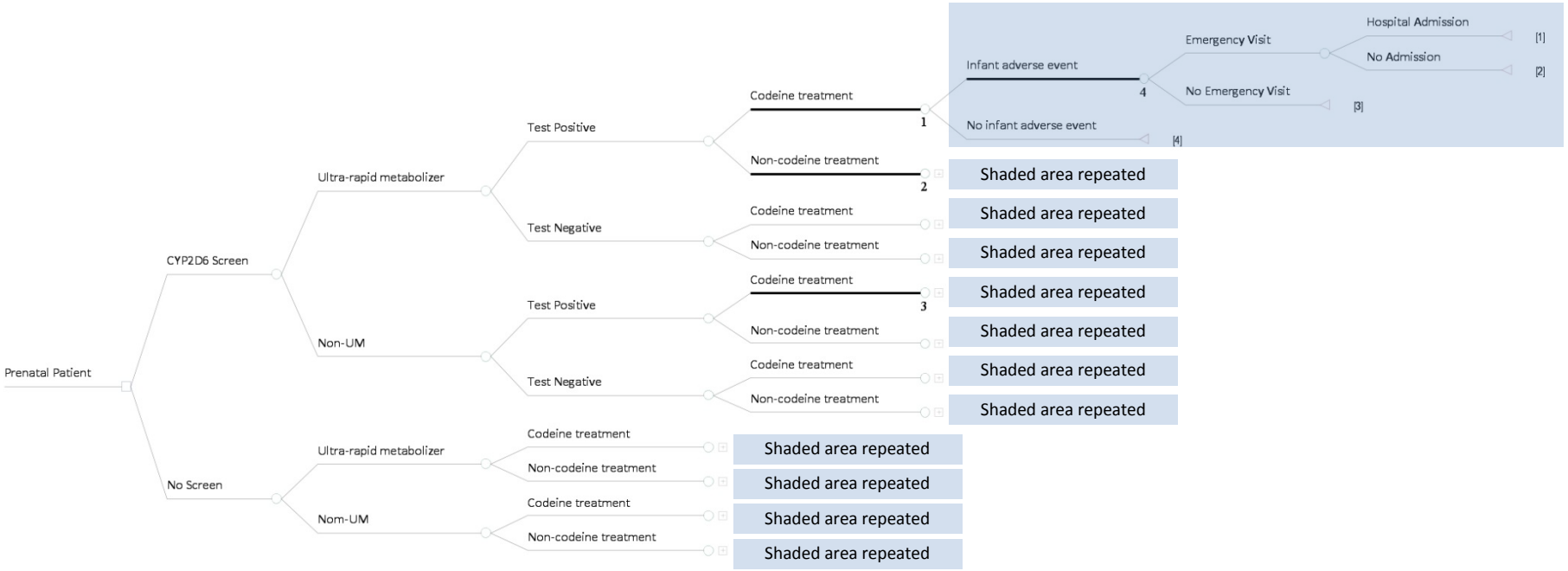
2.3.3 The Model

A decision model (Figure 2.2) was created to determine the expected values of costs and effectiveness of the proposed intervention (genotyping to guide pharmacotherapy) as compared

to standard care of no genotyping and administration of analgesics as per local practice patterns, in averting infant adverse events. Local practice patterns are dependent on the prescribing habits and discretion of the attending physician. In general, all patients who require analgesia are prescribed acetaminophen/opiate combination every four hours as needed. Nurses administer such medication and patients will decide, based on their pain, whether they would like the medication at any particular point. In addition, patients are given self-medication packages of non-opiate analgesics, containing single compound tablets of acetaminophen and ibuprofen, which they can administer to themselves as needed.

The decision model is shown below (Figure 2.2). It begins with the base case and the decision node followed by a series of pathways that could occur in the course of the intervention or standard care. Each of the pathways includes a number of intermediate chance nodes and the variables are used to assign probabilities to the branch (Table 2.2). Each pathway ends at a terminal node represented by either “hospital admission” or “no admission”, the outcome of the infant in the mother-child pair at the end of the time horizon for this analysis.

Figure 2.2: Decision model schematic



2.3.4 Base Case

The base case was a prenatal patient whose CYP2D6 status was unknown but who may have needed to be prescribed codeine containing analgesics for pain relief after delivery and planned to breast feed her child. Other than the codeine used for delivery pain, she was not taking any other narcotic, sedative or psychotropic medications which may have similar adverse effects on the breastfed infant. The tree followed an episode of care and terminated upon completion of pharmacotherapy for postnatal pain relief and resolution of any adverse events. The episode of care began at the prenatal testing phase in which a sample was taken at one of the routine prenatal visits. Patients were then prescribed analgesics by the delivering physician and analgesia was administered by nursing staff once patients were admitted to the postnatal floor. Both mother and child were followed and monitored for adverse events by the health team while in the hospital. Once at home, mothers observed and reported any adverse events in her child to her physician or took her child to the emergency room. In Ontario, nearly all patients will not know their CYP2D6 status as the test is not currently clinically available. In addition, nearly all women plan to breastfeed their children and most will require some form of analgesia after delivery. As such, this base case definition will encompass the vast majority of women having a child in Ontario.

2.3.5 Strategies

For this decision analysis, the decision node, represented by a square, represents the two strategies being compared. These are:

1. Pharmacogenetic screening prior to the anticipated birth with the results of the screening available prior to delivery. Following delivery analgesic prescribing is clinician-driven as per local practice patterns guided by the attending physician. Women who require codeine for pain relief after delivery are prescribed codeine provided they test negative for the UM phenotype. Women who test positive for the UM phenotype are given only non-codeine analgesics while breastfeeding.

2. The second strategy represents current standard care. That is, no pharmacogenetic screening is given to patients and analgesia administration after delivery proceeds by

clinician orders and as per local practice patterns. Specifically, patients are given codeine when warranted.

The chance nodes and branch probabilities of the model include the probabilities of being a true positive (an UM), screening positive for UM, using codeine analgesics, infant adverse events as reported by the mother, adverse events requiring emergency room visits, and adverse events resulting in hospitalizations (Figure 2.2). Following the decision node of screening or not is the first chance node whereby a patient is truly a UM or not. The second chance node, seen only in the screening arm, is the chance that the patient screens positive or screens negative. Following this the model proceeds along the same path for all patients regardless of strategy. The next chance node is that patients will either take a codeine containing analgesic or not. During the administration of the analgesic, mothers continue to breastfeed their children. All patients are asked to report any adverse events or concerning changes in their child to a healthcare provider. The next chance node is that of an adverse event or not. If there is no adverse event during the follow up interval the child is considered well. If there is an adverse event then the next chance node represents the mother's choice to take the child to the emergency room or not. If the mother does not take the child to the emergency room then the child is assumed to recover at home. If a child is brought to the emergency room he or she may or may not be admitted. If the child is not admitted, the child is assumed to be released well, terminating that arm of the tree. This terminates all arms of the tree.

Each tree pathway ends in a terminal node which is populated by two values: 1) the average costs for an individual following that particular pathway expressed in 2014 dollars and 2) the average effectiveness for an individual following that particular pathway, in terms of the presence or absence of an adverse event or the duration of an adverse event. A pathway can be described by the subject UM status, analgesic use, test results, rate of adverse events, hospitalization and hospital admissions. Each of these events has a cost associated with it. Post hospital discharge costs were not captured in this model as it was assumed that there were no long term sequelae experienced by infants following admission for an adverse event. The costs for all the pathways in each strategy were summed to determine total costs for the strategy.

2.3.6 Outcomes

For the purposes of this decision analysis two effectiveness measures were evaluated.

1) The adverse event rate in infants

2) The number of symptom days in infants

Specifically, the adverse events were CNS depressive events, as this is the adverse event attributable to codeine and its metabolites (i.e. morphine) and for which the patient may require medical attention. These may include lethargy, increased sleepiness, not waking for feeds, slow or shallow breathing, poor suck or cyanosis in the lips or digits. Morbidity, characterized by symptom days, is included as an alternate outcome measure in the model assessment. In reality, the distribution and severity of adverse events are expected to vary across the population as will the sequelae. This may be a result of varied doses, individual susceptibility and differences in maternal or clinician behaviours in response to an observed event. The model included average values as point estimates for the base case analysis, while sensitivity analysis was used to evaluate outcomes when base case estimates are varied. Each pathway in the model contains a terminal node. The CEA analysis is run twice, once with each effectiveness measure. The values assigned depend on the events occurring along a particular pathway. Adverse events were assigned a one if present and a zero if absent for a particular pathway. The mean number of symptom days in the clinical study was 4.6 days, and therefore symptom days were set at 4.6 days when an adverse event occurred in a particular pathway and zero if not.

2.3.7 Populating the Model

The model was populated with estimates obtained from a number of sources. The probability estimates and the ranges of estimates are shown in Table 2.2. A systematic literature search was used to identify relevant citations which may yield estimates for these values. In addition a retrospective medical record review (see Section 2.1) and a clinical study (see Section 2.2), provided values to support some of these estimates. Where literature values and the clinical study were unable to provide appropriate estimates, expert clinical judgement/opinion from members of the thesis advisory committee was used to complement the values used in the model.

Table 2.2: Model Probability Inputs

Parameter	Variable name	Base Case Estimate	Source	Minimum	Maximum	Distribution for PSA
Probability of being UM	pUM	0.08	(Sistonen et al. 2007, Ingelman-Sundberg et al. 2007, Kohlrausch et al. 2009, Cascorbi 2003)	0.01	0.4	Beta
Probability of being a non-ultrarapid metabolizer (non-UM)	pNonUM	1-pUM				
Probability of testing positive for UM, given UM (True Positive)	pTest+|UM	0.99	Laboratory measures; (Almoguera et al. 2010, Fleeman et al. 2011, Fleeman et al. 2010)	0.70	1	Fixed
Probability of testing negative for UM, given UM (False Negative)	pTest-|UM	1-(pTest+|UM)	Laboratory measures; (Almoguera et al. 2010, Fleeman et al. 2011, Fleeman et al. 2010)			
Probability of testing positive for UM, given non-UM (False Positive)	pTest+|nonUM	1-(pTest-|nonUM)	Laboratory measures; (Almoguera et al. 2010, Fleeman et al. 2011, Fleeman et al. 2010)			

Parameter	Variable name	Base Case Estimate	Source	Minimum	Maximum	Distribution for PSA
Probability of testing non-UM, given non-UM (True Negative)	pTest-|nonUM	0.999	Laboratory measures; (Almoguera et al. 2010, Fleeman et al. 2011, Fleeman et al. 2010)	0.7	1	Fixed
Probability of receiving codeine given subject is screened and tests positive UM	pCodeine|test+	0	Expert Opinion	0	0.01	Fixed
Probability of non-codeine analgesia given subject is screened and tests positive UM	pNonCodeine|test+	1-pCodeine|test+	Expert Opinion			
Probability of codeine, given subject tests negative UM	pCodeine|test-	0.6584	(East et al. 2007)	0.4155	0.825	Beta
Probability of non-codeine, given subject tests negative UM	pNonCodeine|test-	1-pCodeine|test-				
Probability of codeine (not tested)	pCodeine	0.6584	(East et al. 2007); medical record extraction	0.4155	0.825	Beta
Probability of non-codeine (not tested)	pNonCodeine	1-pCodeine				
Probability of an adverse event, given non-codeine (metabolizer status unknown)	pAE|NonCodeine	0	(Lam et al. 2012, Ito et al. 1993)	0	0.03	Beta
Probability of no adverse event, given non-codeine (metabolizer status unknown)	pWell|NonCodeine	1-pAE| NonCodeine				
Probability of an adverse event, given codeine use and UM	pAE|Codeine_UM	0.6667	(Madadi et al. 2009b)	0.2174	1	Beta
Probability of no adverse event, given codeine use and UM	pWell|Codeine_UM	1-pAE| codeine|UM				
Probability of an adverse event, given codeine use and non-UM	pAE|Codeine_nonUM	0.2174	(Madadi et al. 2009b)	0.021	0.3077	Beta

Parameter	Variable name	Base Case Estimate	Source	Minimum	Maximum	Distribution for PSA
Probability of no adverse event, given codeine use and non-UM	pWell|Codeine_nonUM	1-pAE|codeine |nonUM				
Probability of emergency room visit with AE	pEmerg|AE	0.1143	(Madadi et al. 2009b, Lam et al. 2012)	0	0.2343	Beta
Probability of no emergency room visit with AE	pNoEmerg|AE	1-pEmerg|AE				
Probability of hospital admission with Emerg visit, given AE	pAdmit|Emerg_AE	0.9	Expert Opinion (Dr. Shinya Ito)	0.75	1	Beta
Probability of no hospital admission with Emerg visit, given AE	pNoAdmit|Emerg_AE	1-pAdmit| Emerg_AE				

2.3.8 Probabilities

As shown in Table 2.2, in the screening strategy it was assumed that the rate of codeine use is 65.84% in patients who screen as non-UM based on East et al. (East et al. 2007) as well as values from the utilization survey. It is recognized that these individuals could, in fact, be UM if the test result is a false negative. Because the laboratory test performance is not perfect, some error exists and the test sensitivity and specificity are built into the model. It was assumed that in patients who screen as UM positive there was no use of codeine, or any opioid analgesic. Again, owing to the possibility of test error, these patients may not be true UM. The chance nodes in the model lead to a number of other branch probabilities including the probabilities of screening positive for UM, being a true positive (an UM), using codeine analgesics, observing an adverse event in the infant, the probability of the child going to the emergency room or being admitted to the hospital (Figure 2.2). These values were ascertained from previously published data obtained in the literature search as well as from the clinical study population. The prevalence of metabolizer status was retrieved from the literature. The proportion of patients using codeine and other pain medications was determined from the literature and the results of the utilization survey (Section 2.1) were used to establish the ranges. Rates of adverse events, including emergency room visits and hospitalizations were determined from both the published literature and the clinical study. The completion of pharmacotherapy for postpartum analgesia and resolution of any adverse events signified the termination point (terminal node, indicated by triangle) for each pathway in the model. This model evaluated only the first occurrence of analgesia for postnatal pain, that is, the medications initially prescribed in the hospital after delivery. It is theoretically possible that mothers could require analgesia at some point in the future while still breastfeeding, but after the immediate neonatal period, and potentially expose infants to analgesics through milk again. However, subsequent analgesic use is beyond the scope of this decision analysis and was not addressed in the model.

Since, not all infant adverse events may be associated with a maternal UM phenotype, a probability of adverse events among the non-UM patients was built in to the model. In addition, it was assumed that there were no CNS adverse events in mothers taking non-opioid analgesics and a small range was built in for sensitivity analysis.

2.3.9 Costs

Costs are calculated along each pathway of the model. The costs of interest are costs to the public health care payer, costs to private payers, out of pocket costs by the patient and lost productivity for the patient and/or their caregivers Broad categories of costs and the associated perspective are shown in Table 2.3.

Table 2.3: Costs Categories Considered

Perspective		Cost Items	Category
Societal	Health Care System	Public Payer Costs	
		Genotyping analysis	intervention
		Saliva sample preparation	intervention
		Sample packaging and shipping to analytical laboratory	intervention
		Drug treatment for post-partum analgesia	intervention
		Unscheduled visits to physician	direct health care costs
		Laboratory tests	direct health care costs
		Emergency department visit	direct health care costs
		Hospital Admission	direct health care costs
		Patient Costs	
		Medication (or co-payments)	direct health care costs
		Feeding supplies (or co-payments)	direct health care costs
		Lactation consultants	direct health care costs
		Other health professionals (nurses, social work) (or co-payments)	direct health care costs
		Midwife visit (or co-payments)	direct health care costs
		Caregiver costs (aides, babysitters	direct health care costs
		Transportation to physician visits	indirect costs
		Parent days missed from work to accompany infant	indirect costs
		Third Party Insurer	
		Medication costs	direct health care costs
		Feeding supplies	direct health care costs
		Lactation consultants	direct health care costs
		Other health professionals (nurses, social work)	direct health care costs

Any costs incurred as a direct result of the study procedures which would not be part of routine care were excluded from costing. Costs are presented in 2014 Canadian dollars. The data sources for the items considered including resource use and the individual price of items in this analysis are shown in Table 2.4.

Table 2.4: Cost items, Sources and Unit Prices

Cost Item	Variable Name	Volume Source	Base Case Volume	Unit Price Source	Base Case Unit Price	Base Case Cost	Minimum	Maximum	Distribution for PSA
Intervention									
Test cost (genotyping analysis)	cTesting	One event for each subject in intervention strategy	1	Personal communication (C. Ross)	$150.00	$150.00	$90.00	$1300.00	Gamma
Post-test consult with Physician Specialist	cCounselling	One event for each subject in intervention strategy	1	Physician Schedule of Benefits (Ministry of Health and Long Term Care 2013)	$167.00	$167.00	N/A	N/A	Fixed
Test Preparation costs	cTestPrep	Excluded	0		$0.00	$0.00	N/A	N/A	N/A
Sample Shipping costs	cShipping	One event for each subject in intervention strategy	1	Courier published rates	$64.89	$64.89	$17.64	$72.93	Uniform
Codeine Tablet	cCodeineUnit			Ontario Drug Benefit Formulary (Ontario Ministry of Health and Long-Term Care 2014)	$0.0524	$0.3980	N/A	N/A	Fixed
	qCodeineUnit	Drug Utilization Study	7.5954				0.5	18	Gamma
Additional Analgesics Used (as polytherapy with opioids)	cAddAnalgesic			Ontario Drug Benefit Formulary (Ontario Ministry of Health and Long-Term Care 2014)	$0.2244	$1.1500	N/A	N/A	Fixed

Cost Item	Variable Name	Volume Source	Base Case Volume	Unit Price Source	Base Case Unit Price	Base Case Cost	Minimum	Maximum	Distribution for PSA
	qAddAnalgesic	Drug Utilization Study	5.1284				0.5	18	Gamma
Other Analgesics Used (non opioid only users)	cOtherAnalgesic			Ontario Drug Benefit Formulary (Ontario Ministry of Health and Long-Term Care 2014)	$0.2244	$0.9615	N/A	N/A	Fixed
	qOtherAnalgesic	Drug Utilization Study	4.2847				0.5	17	Gamma
Pharmaceutical Dispensing fee	cDispense	Excluded	0		$0.00	$0.00	N/A	N/A	
Adverse Event									
Patient Out-of-Pocket costs for adverse event	cPatientOutofPocket	Excluded	0		$0.00	$0.00	N/A	N/A	
Call by parent for help or consultation to TIS	cHelpCall	One for each adverse event case	1	Hancock et al. (Hancock et al. 2008)	$42.00	$42.00	$10.00	$78.00	Gamma
Ambulance	cAmbulance	One for each case going to emergency room	1	Ontario MOHLTC (Ontario Ministry of Health and Long-Term Care 2012)	$240.00	$240.00	N/A	N/A	Fixed
Emergency Room Visit	cERVisit	One for each case going to emergency room	1	OCCI (2014)	$278.38	$278.38	$6.50	$1769.95	Gamma
Cost of Emergency Physician in the ER	cER_Physician	One for each case going to emergency room	1	Physician Schedule of Benefits (Ministry of Health and Long Term Care 2013)	$97.60	$97.60	N/A	N/A	Fixed

Cost Item	Variable Name	Volume Source	Base Case Volume	Unit Price Source	Base Case Unit Price	Base Case Cost	Minimum	Maximum	Distribution for PSA
Parent lost productivity costs for Day missed from work/usual activities to be in Emerg with child	cLostProdDay	One day of wages for each case going to emergency room	1	Statistics Canada (Statistics Canada 2014b, Statistics Canada 2014a)	$250.23	$250.23	$194.83	$525.26	Gamma
Hospital Admission	cHospAdmit			OCCI (2014)	$6,865.32	$6,865.32	$6.50	$387,058.59	Gamma
	qAdmitDays	One for each case admitted	5.1				1	169	Gamma
Cost of in-patient physician visit for day one	cAdmit_PhysDay1	One for each case admitted	1	Physician Schedule of Benefits (Ministry of Health and Long Term Care 2013)	$196.28	$196.28	N/A	N/A	Fixed
Cost of in-patient physician visit for subsequent days	cAdmit_PhysSubs			Physician Schedule of Benefits (Ministry of Health and Long Term Care 2013)	$58.80	$58.80	N/A	N/A	Fixed
	qAdmit_PhysSubs	Average days of admission (qAdmitDays) less one	4.1				N/A	N/A	
Parent lost productivity costs for Day missed from work/usual activities to be in hospital with child	cAdmit_LostProdDay	Average days of Admission		Statistics Canada (Statistics Canada 2014b, Statistics Canada 2014a)	$250.23	$250.23	$194.83	$525.26	Gamma

2.3.9.1 Intervention Costs

This intervention being evaluated is a single genotype test on each prenatal patient. This particular CYP2D6 gene test is not commercially available for routine medical care and in Canada is used only in research settings. Analysis was performed at the University of British Columbia. The testing is based on the AutoGenomics Infiniti platform which initially tests for the presence of specific alleles. This is then followed with polymerase chain reaction and gel electrophoresis to detect for possible duplications. The price of the testing of $150 was determined from costs incurred during the clinical study (Colin Ross, personal communication) and included sample extraction, analytical kits and reagents. Sample preparation and storage costs were not included as the sample, once obtained, is sent directly to the analytical laboratory. Shipping costs were determined from an average cost to ship a package from Toronto to Vancouver by courier based on published courier company rates. No additional human resource costs (personnel) were included as the time required to retrieve a sample was minimal. Commercially available testing kits were also sought out, and the prices of such commercial testing kits were ascertained for use in establishing the ranges of costs relevant for sensitivity analysis.

During the hospital stay, codeine containing analgesics and other analgesics such as ibuprofen and naproxen are administered as individual tablets to the patients by the ward nurses based on prescriptions ordered by the attending physician. Patients can choose to take the analgesic based on their perceived need at the time of dosing. The mean number of tablets used during the hospital stay was determined by medical record extraction as part of the retrospective review (Section 2.1) and the clinical study (Section 2.2). While in hospital, patients who did not require codeine containing analgesia were given a medication self-administration package. This package contains tablets of acetaminophen, ibuprofen and stool softeners which patients are instructed to take on an as need basis. Once discharged, if patients continued to require codeine containing analgesics they were given a small supply of tablets to take home not exceeding four days of dosing. The number of tablets used by the patients after discharge was reported by the mother upon follow-up. Patients were asked to record each tablet taken in a diary in real time and the information was subsequently collected in a follow up telephone interview by the clinical study

team. The mean of the total number of tablets used in hospital plus the number of tablets sent home with the mother was used to inform the volume of use parameter estimate in the model.

The unit cost of the analgesics administered was determined from the Ontario Drug Benefit formulary (ODB) (Ontario Ministry of Health and Long-Term Care 2014). The costs of analgesics were calculated by multiplying the unit cost of each tablet by the volume of tablets dispensed as described above. For the base case analysis the average dose of analgesics used by subjects at the participating institution was used.

2.3.9.2 Direct Health Care Costs

The mean cost of hospital emergency room visits (ambulatory) and admissions (acute inpatient) for serious adverse events including respiratory distress, cyanotic attacks, newborn affected by maternal medication and a number of other categories (Table 2.5) were determined from the Ontario Case Costing Initiative (OCCI) (2014).

Table 2.5: OCCI List of Most Responsible Diagnoses (ICD-10) Used for Costing of Inpatient and Emergency Ambulatory Care (2010-2011)

Most Responsible Diagnosis Code	Description	Mean Cost Emergency Care	Mean Cost Inpatient Care
P040	Fetus & newborn affected by maternal anaesthesia and analgesia	N/A*	$4,275
P041	Fetus & newborn affected by other maternal medication	$282	$3,534
P220	Respiratory distress syndrome of newborn	$281	$17,407
P228	Other respiratory distress of newborn	$394	$2,950
P229	Respiratory distress of newborn, unspecified	N/A*	$4,489
P282	Cyanotic attacks of newborn	$333	$3,455
P283	Primary sleep apnoea of newborn	N/A	$8,200
P284	Other apnoea of newborn	$260	$3,110
P285	Respiratory failure of newborn	$315	$2,460
P288	Other specified respiratory conditions of newborn	N/A*	$2,450
P289	Respiratory condition of newborn, unspecified	$178	$4,756
P922	Slow feeding of newborn	$234	$3,205
P923	Underfeeding of newborn	$203	$6,354
P928	Other feeding problems of newborn	N/A*	$4,283
P929	Feeding problem of newborn unspecified	N/A	N/A*
P948	Other disorders of muscle tone of newborn	$282	N/A*
P949	Disorder of muscle tone of newborn, unspecified	$281	$13,964
P962	Newborn withdrawal therapeutic drug use	$394	$4,275
	Totals	$257	$6338

* When a diagnostic code had fewer than 5 cases the mean costs could not be shown, however the costs of those cases are included in the total mean values for either Emergency or Inpatient Care

The list of most responsible diagnoses (MRD) retrieved from OCCI for costing of inpatient and ambulatory emergency care visits of an infant who may have experienced an adverse event is shown in Table 2.5. The average total cost of an emergency room visit and the average total cost

of an admission for all individuals with the specified MRD codes (see Table 2.5 above) were used for the base case. As the most recent values available were for the 2010-2011 fiscal year, reported values were inflated to 2014 values using the Canadian Consumer Price Index for health care in Ontario for the previous three years (Statistics Canada 2014c). Inflated values were used to populate the model and are reflected in Table 2.4.

2.3.9.3 Productivity Costs

Despite the fact that mothers on maternity leave may not have had actual income losses, any time spent at the hospital with a child during their stay for an adverse event was deemed to be a productivity loss to the mother. In order to account for this productivity loss, an average wage in the Province of Ontario for females of childbearing age was allocated to each adverse event for the duration of the hospital stay. Average wages were obtained from Statistics Canada (Statistics Canada 2014b, Statistics Canada 2014a).

2.3.10 Valuation

Unit cost sources are outlined in Table 2.4. A unit cost for each item was multiplied by the quantity reported to obtain a total for each expense type per subject. Specific formulas for cost items and their variable names are outlined in (Appendix A).

An average cost for a patient in each pathway of the model was computed and then total expected costs for each strategy of the decision model was calculated by summing the costs of all branches in that strategy. These costs included intervention costs, direct health care costs and direct patient costs. A formula to sum all the relevant costs for a particular pathway was created and in at the terminal node for each pathway (Appendix B).

2.3.11 Populating Outcome Terminal Values

The primary outcome measured in the model was adverse events in the infant, specifically CNS depressive adverse events. Adverse events are CNS-related changes noted and reported by the child's mother. Any contact with a health care provider regarding an adverse event would be used as corroborating information to substantiate the mother's claims. The terminal nodes were populated with two possible effectiveness measures to account for the outcome of interest and were used in two separate base cases cost-effectiveness analyses. The primary outcome was the presence (or absence) of adverse events indicated in the terminal node by a one or a zero.

Secondarily, the average duration of adverse event, 4.6 days, was used as a terminal node value in order to compute costs per symptom day. Pathways describing an adverse event were recorded with the terminal value of 4.6 while those without were recorded as a zero.

2.3.12 Assumptions

In order to clearly define the base case patient a number of assumptions were required. These assumptions were used to guide model development and better define the population to which this analysis is relevant.

1. Women exclusively breastfeed their children during the interval of drug use. Deviations in breastfeeding patterns for any reason were not accounted for in the model.
2. Patients who test positive for the UM phenotype did not take any codeine or other opioid containing analgesic.
3. Physicians did not prescribe codeine or any other opioid containing analgesic to women who tested positive for UM phenotype.
4. Patients who are not UM were considered non-UM and were assumed to have a similar rate of adverse events as one another since they do not produce excessive morphine as compared to an UM.
5. Rates of opioid-related adverse events did not differ for male and female offspring.
6. Infants were born at term, were healthy at birth (without obvious malformations) and had normal birth weight.
7. Unless proven otherwise, CNS depressive events noted in the child for were assumed to be due to exposure to medications in maternal milk (i.e. unless a clinician makes an alternate diagnosis the effects in the child are assumed to be related to the drug).
8. The opioid analgesic being used is Tylenol #3, with each tablet containing 30 mg of codeine and 325 mg acetaminophen.
9. Women were prescribed 2 tablets every 4 hours as needed, however the base case will assume a dose equivalent to the mean dose noted in the clinical study and medical record review.
10. Adverse events included only CNS depressive events such as sedation, lethargy, irregular breathing, decreased alertness, and poor feeding.
11. Subsequent exposure to opioid analgesics was not accounted for in this model.
12. Only the first postnatal adverse event in the infant is accounted for in this model.

13. No maternal adverse events were included in the model.

2.3.13 Incremental Cost-effectiveness

Cost-effectiveness was expressed in terms of the incremental cost-effectiveness ratio (ICER), calculated from folding back the model. Thus, the incremental cost-effectiveness ratio is the additional cost per unit of outcome, in this case, the adverse event averted or symptom day averted. Using Monte Carlo simulation as part of a PSA (a point estimate and 95% confidence interval were generated for ΔC and ΔE and the ICER.

2.3.14 Uncertainty

Sensitivity analysis was performed to evaluate the robustness of the results and to assess the effect of uncertainty around the parameter estimates and model assumptions.

Deterministic parameter uncertainty was performed by a series of one-way and two-way sensitivity analyses. One-way sensitivity analysis was performed for all parameter estimates within a reasonable range based on values obtained from the literature in order to determine if the findings were sensitive to any of the variable estimates. Specifically, one-way sensitivity analysis was conducted to determine if small changes in a parameter estimate changed the decisions of the model. The ranges used to vary parameters in the sensitivity analysis were ascertained from the literature (Table 2.2). Reasonable ranges were defined after systematic and thorough reviews of the literature. When literature estimates were not available, data from the clinical study and consultation with clinical experts were utilized (Table 2.2).

Probabilistic parameter uncertainty evaluation followed the deterministic sensitivity analysis. Probabilistic sensitivity analysis (PSA) was conducted using Monte Carlo simulation modelling to address the limitations of deterministic sensitivity and to assess the effect of multiple sources of uncertainty existing simultaneously in the model. In this method of PSA all variables were varied simultaneously and the model was run one thousand times. Distributions were assigned to each parameter and each simulation randomly selected a value from within the distribution of all of the variables included in the PSA (Table 2.2 and Table 2.4). By calculating expected values of costs and effectiveness for each group with each iteration, the PSA generated a mean and 95%

CIs of expected values for costs and for outcomes for the two strategies, as well as point estimates and 95% CIs for incremental costs and incremental effects and the ICER. Results of the PSA were displayed graphically in a cluster diagram.

2.3.15 Analysis of Perspectives

The model was analyzed from two different perspectives, the societal perspective and the health care payer perspective. The model itself is not changed or manipulated for each of these perspectives; however the cost formulae at the terminal nodes, which represent the total costs for each pathway, were adjusted to reflect only costs relevant to the specific perspective.

2.3.16 Scenario Analyses

Scenario analysis was performed to understand how the results would change with different selected populations. Specific populations were chosen because they were believed to have different rates of adverse events which could impact on the cost- effectiveness of the testing intervention and subsequently may shed light on whether some populations may be more or less likely to benefit from genotyping. In this case the scenario analysis included four two distinct groups:

i) Specific Ethnic Group

Certain ethnic populations have a relatively high prevalence of UM phenotype and therefore are expected to have a higher risk of adverse events. In this scenario the probability of UM phenotype (pUM) in the base case was estimated at 0.4, with a range of 0.12 to 0.45, which would approximate a North African population (Sistonen et al. 2007). This rate is among the highest currently identified world-wide.

ii) Caesarean Section Deliveries

Mothers with surgical deliveries are more likely to experience pain and therefore more likely to use opioids. With a high likelihood of requiring codeine after delivery, this group may be more likely to benefit from a screening strategy which would avert adverse events. In the utilization study the rate of opioid use was higher in this group (as compared to vaginal deliveries) and published literature suggests the same (East et al. 2007, Greene et al. 1999). Moreover, infants born by caesarean section may be more prone to adverse events in the days after birth.

In this scenario probability of codeine use in the base case (pCodeine) was estimated at 0.93, with a range of 0.78 to 1. The probability of an adverse event in nonUM patient was increased to 0.2174, with a range of 0.0210 to 0.6670.

3 Results

3.1 Analgesic Utilization Rates in the Postnatal Ward

In order to determine the rate of codeine and other analgesics used at St. Michaels Hospital in Toronto a retrospective medical record review of a 4-year interval of postnatal medical records was conducted. The survey results are shown below. A total of 973 medical records were evaluated

Table 3.1: Overall Opioid Utilization Rates (January 2007 to June 2011)

	n=973	Percent of All Patients
Any Opioid Use	436	44.81%
Any Codeine (with or without other opiates)	377	38.75%

Among all medical records of patients in the retrospective review, close to 45% of new mothers at St. Michael's Hospital used at least one opiate overall, with 38.75% of the population receiving codeine specifically. This translates into 86.37% codeine use among the opioid exposures. This included both patients who used codeine as their only opioid as well as those who may have used codeine and another opioid as well.

3.1.1 Utilization Rates by Specific Drug and Mode of Delivery

Though the vast majority of patients using opioids used codeine alone, some patients were exposed to codeine with another opioid or only another opioid (Table 3.2).

Table 3.2: Specific Opioids Used by New Mothers at St. Michael's Hospital Among All Medical Records Surveyed

Specific Opioid	Number Exposed (N=973)	Percent of Total Surveyed
Codeine alone	348	38.75%
Oxycodone	48	4.93%
Codeine + oxycodone	21	2.16%
Morphine	7	0.72%
Codeine + morphine	5	0.51%
Codeine + hydrocodone	2	0.21%
Codeine + oxycodone + morphine	1	0.10%
Hydrocodone	1	0.10%
Hydromophone	1	0.10%
Nalbuphine	1	0.10%
Oxycodone + morphine	1	0.10%

As shown the most common opioid or opioid combination used was codeine alone at close to 39% (Table 3.2). This was followed by oxycodone use alone at close to 5% of the total population. When multiple opioids were used, patients generally did so consecutively. That is, patients were not consuming multiple opioids at the same time but rather would be switched from one to another based on clinical need or physician discretion

To determine if opioid use varied by mode of delivery, either vaginal or caesarean section the opioid use by delivery is described below (Table 3.3).

Table 3.3: Prevalence of Opioid Use by Mode of Delivery

Mode of Delivery	Number Using Opioids	%
Caesarean Section	349/439	79.5%
Vaginal	87/534	16.3%
Total	**436/973**	**44.8%**

As shown in Table 3.3 the vast majority of opioid use was among women who delivered by Caesarean Section, with over 79% of patients who had a caesarean section requiring the use of opioids and approximately just under 10% of women with vaginal delivery who used opioids. This was significantly different by Chi square analysis ($p<0.001$).

3.2 Clinical Study

3.2.1 Demographics of Enrolled Subject

The clinical study included a total of 238 mother-infant pairs taking codeine while breastfeeding in the immediate postpartum period. Within this cohort, 5 mothers reported adverse events in their infants. The demographics of the subjects are shown in

Table 3.4, with the adverse events compared against the asymptomatic group.

Table 3.4: Demographics and Codeine Dosing Among 238 Mother-Infant Pairs

	Adverse Events (n = 5)	**Asymptomatic Infants (N=233)**	**p-value**
No. days taking codeine (mean ± SD)	4.8 ± 2.6	2.5 ± 1.6	0.01*
Total amount of codeine used (mean mg/kg ± SD)	5.1 ± 2.4	3.2 ± 2.5	0.08*
Infant's gestational age at delivery (weeks)	38.6 ± 1.1	39.1 ± 1.4	0.44*
Infants birth weight (g)	3392.4 ± 584.4	3403.1 ± 510.1	0.96*
Non-Caucasian	100% (5/5)	62% (143/230)	0.1†

*Wilcoxon signed-rank test
†Fisher's exact

As shown the mothers of symptomatic infants were taking their codeine for longer than the mothers of the asymptomatic infants (p=0.01) and were exposed to a higher per kg dosage, though this did not reach statistical significance (p=0.08). Other demographic characteristics such as gestational age at birth, birth weight and ethnicity were not different between the two groups.

3.2.2 Health-related Quality of Life Scores

A total of 145 HRQoL surveys were completed among subjects in the clinical study, with 109 surveys completed at recruitment (pre-treatment), 36 subjects who returned the follow-up surveys (post-treatment), and 33 subjects for whom the paired data could be compared and statistically analyzed.

Table 3.5 shows the summary and component scores for the SF-36v2 surveys for both measurement time points, when both surveys were completed by subjects. Data were compared by paired student's t-test.

Table 3.5: Summary Scores for SF-36v2 (n=33)

	Pre-Treatment (mean ± SD)	Post Treatment (mean ± SD)	p-value*
Physical Component Score	31.89 ± 10.04	40.15 ± 9.46	**0.0008**
Mental Component Score	52.53 ± 11.00	48.24 ± 10.55	**0.017**
Physical Functioning	28.75 ± 12.05	40.03 ± 11.58	**0.0002**
Role Physical	30.78 ± 11.19	34.55 ± 10.78	0.132
Bodily Pain	36.42 ± 12.35	43.10 ± 10.50	**0.024**
General Health	54.417 ± 7.14	54.54 ± 8.60	0.949
Vitality	44.32 ± 9.00	46.09 ± 7.04	0.325
Social Function	38.87 ± 12.71	36.27 ± 11.6	0.319
Role Emotional	47.79 ± 12.2	46.79 ± 11.67	0.625
Mental Health	48.93 ± 8.32	48.87 ± 9.58	0.963

*Paired student's t-test

Results of the HRQoL surveys indicate that several scores did not change significantly between the two time points. The physical component score, the physical functioning score and bodily pain score showed a statistically significant improvement from pre-treatment to post-treatment (Table 3.5). The mental component score also showed a change between survey timepoints.

3.2.3 SF-6D Scores

An SF-6D score was calculated for all completed SF-36v2 surveys, to generate an estimate of utility at each time point. Results of the SF-6D are summarized in Table 3.6, and comparisons made by student's t-test.

Table 3.6: Summaries of the SF-6D Scores (n=33)

	Pre-Treatment (mean ± SD)	Post Treatment (mean ± SD)	p-value*
SF-6D (standard gamble method)	0.57 ± 0.11	0.63 ± 0.11	**0.052**

*Paired student's t-test

The SF-6D Scores increased over time. That is, the subjects estimated utility was increased after they returned home and had completed their analgesic treatment, though this did not reach statistical significance.

3.2.4 State-Trait Anxiety Inventory Scores

Table 3.7 displays the result scored from the completed STAIs surveys.

Table 3.7: Summary of State-Trait Anxiety Inventory Scores (n=33)

	Pre-Treatment (mean ± SD)	Post Treatment (mean ± SD)	p-value*
State score	34.81 ± 9.43	32.74 ± 10.88	0.27
Trait scores	32.19 ± 7.68	32.93 ± 10.74	0.70

*Student's t-test

The mean pre-treatment and post-treatment state and trait scores were unchanged indicating that the subjects' level of anxiety around the time of delivery and the subjects' anxiety levels in general were not different before and after their analgesic treatment.

3.2.5 Quality of Life, Anxiety and Utility Score Changes Over Time

An OLS regression analysis was performed on the difference in HRQoL summary scores, State score, Trait score and SF-6D scores for all subjects where both pre and post treatment surveys were completed (n=33). The covariates in each of the models were total codeine dose, gravidity and maternal age and the dependent variable was the difference between the pre and post treatment scores. The general equation for the regression was described in Equation 1 (p.15).

Table 3.8: Summary of Linear Regression Analysis for Differences in HRQoL, State, Trait and SF-6D Scores

Difference Score	F-statistic p-value
SF-36 Physical Component	0.778
SF-36 Mental Component	0.318
State Score	0.875
Trait Score	0.865
SF-6D	0.762

As none of the summary statistics for each of the regressions was statistically significant the individual results are not shown (Table 3.8).

3.3 Cost-Effectiveness Analysis

3.3.1 Base Case Analysis

The base case analysis for the primary outcome of adverse events is shown in Table 3.9. The findings indicate that the screening option costs approximately $521 per case while the no screen choice was less costly at $175. There were 0.0346 fewer adverse events per case in the screening arm, resulting in a cost per adverse event averted of $9,997.43.

Table 3.9: Base Case Cost Consequence Analysis for Adverse Events

Strategy	Cost Per Case	Adverse Events Per Case	Cost-Effectiveness Ratio
Screen	$520.95	0.1339	
No Screen	$174.72	0.1656	
Increment	$346.23	- 0.0346	**$9,997.43**

The same analysis was conducted with the outcome measure of symptom days. A mean number of 4.6 symptom days was assumed for each adverse event (Table 3.10).

Table 3.10 Base Case Cost Consequence Analysis for Symptom Days

Strategy	Cost per Case	Symptom Days per Case	Cost-Effectiveness Ratio
Screen	$520.95	0.6158	
No Screen	$174.72	0.7751	
Increment	$346.23	- 0.1593	**$2,173.35**

When evaluating by symptom day the model indicated that the incremental cost per symptom day averted was $2,173.35 and the incremental effect was 0.159 symptom days per case.

3.3.2 Deterministic One-Way Sensitivity Analysis

A series of one-way sensitivity analyses was performed on most variables for both outcomes. Plausible ranges were determined and outlined in the methods section (Table 2.2). Results of the one-way sensitivity analysis, presented in Table 3.11, indicate that the model was sensitive only to a single variable: the cost of a hospital admission. When hospital admission costs associated with a severe AE were greater than $104,000 per stay, the screening strategy became cost saving. The model decision did not change upon varying any of the other variables within the specified ranges. That is, screening did not become cost saving. When the probability of codeine use was varied to lower than 0.53 the screening strategy became dominated, it cost more money and had lower effectiveness.

Table 3.11: One-Way Sensitivity Analysis of All Model Variables

Variable	Range	Threshold Value	Preferred Strategy
Probabilities (range: 0-1)			
UM	0.0100 – 0.400	None	No Screen
Test specificity	0.7000 – 1.000	None	No Screen
Test sensitivity	0.7000 – 1	None	No Screen
Codeine use rate	0.4155 – 0.0825	None	No Screen*
Codeine use rate, tests negative for UM	0.4155 – 0.0825	None	No Screen
AE for UM	0.2174 – 1.000	None	No Screen
AE for nonUM	0.0210 - 0.3070	None	No Screen
AE, non-codeine users	0 – 0.0300	None	No Screen
Emergency room visit	0 – 0.2340	None	No Screen
Admission to hospital from emergency room visit	0.7500 -1	None	No Screen
Costs			
Pharmacogenetic Screen	$90.00 - $1300.00	None	No Screen
Sample Shipping	$17.64 – $72.93	None	No Screen
Codeine Tablet	$0.01 – $0.50	None	No Screen
Additional analgesics used, other than opioids	$0.01 – $1.00	None	No Screen
Help call to drug information service	$10.00 – $78.00	None	No Screen
Emergency room visit	$7.00 – $1770.00	None	No Screen
Parent Lost Productivity Day	$194.83 – $262.63	None	No Screen
Hospital Admission	$7.00 - $387,059.00	>$104,000	No Screen (below threshold)
Quantities			
Codeine Tablets	0.5 – 18	None	No Screen
Other Analgesic Tablets	0.5 – 18	None	No Screen
Days of Admission	1 – 169	None	No Screen

AE= Adverse event
UM=Ultrarapid Metabolizer
*Screening strategy is dominated below p=0.53

3.3.3 Probabilistic Sensitivity Analyses

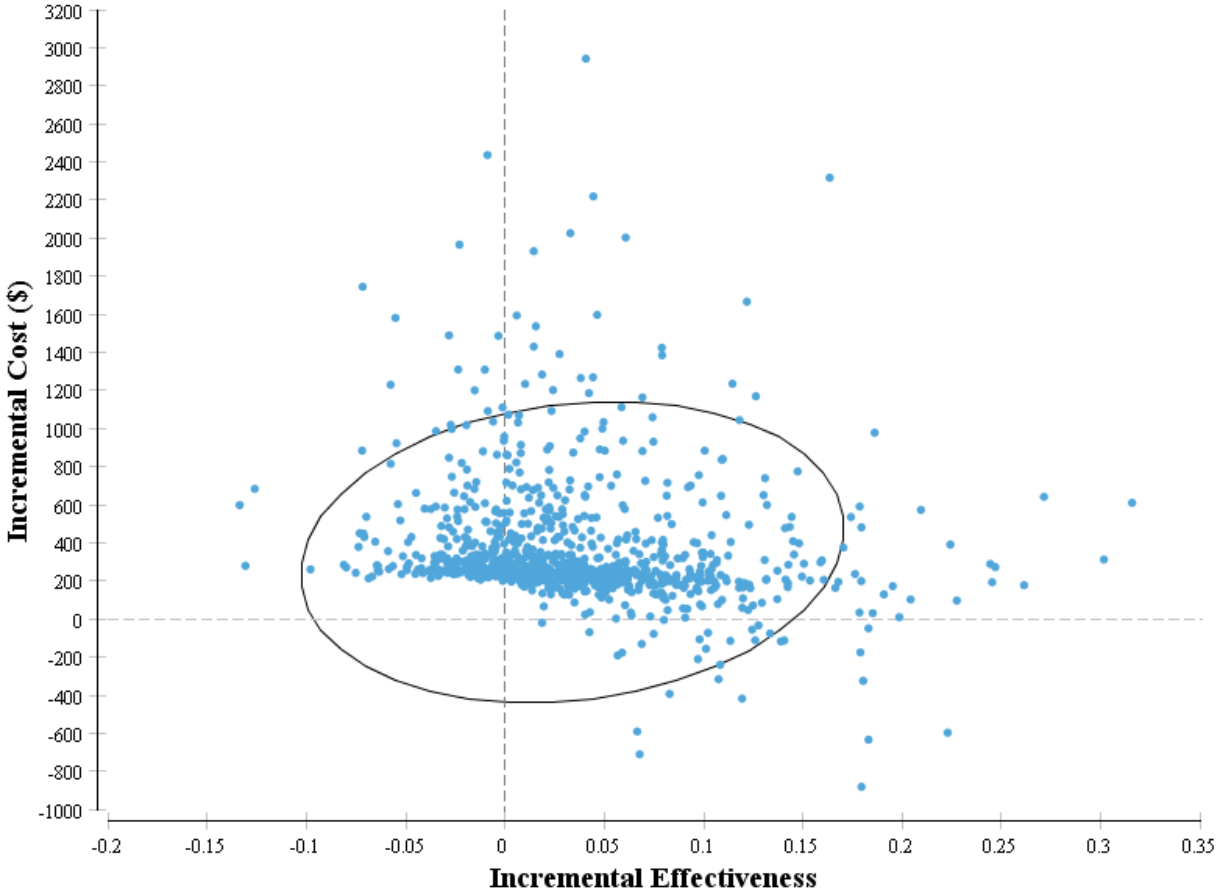
The PSA analysis evaluated all uncertainties simultaneously in a stochastic manner. Table 3.12 shows the results of the mean values of the costs and outcomes for each strategy as well as their respective confidence intervals obtained from the PSA for the adverse event outcome.

Table 3.12: Results of Probabilistic Sensitivity Analysis for Base Case

Strategy	Mean Cost per Case (95% CI)	Mean Adverse Events per Case (95% CI)	Cost-Effectiveness Ratio
Screen	$537.09 ($241.78, $1670.63)	0.1339 (0.0543, 0.2518)	
No Screen	$183.73 ($12.15, $1137.30)	0.1687 (0.0691, 0.3095)	
Incremental	$353.36 (-$55.14, $1235.91)	- 0.0339 (-0.0566, 0.1785)	$10,432.73

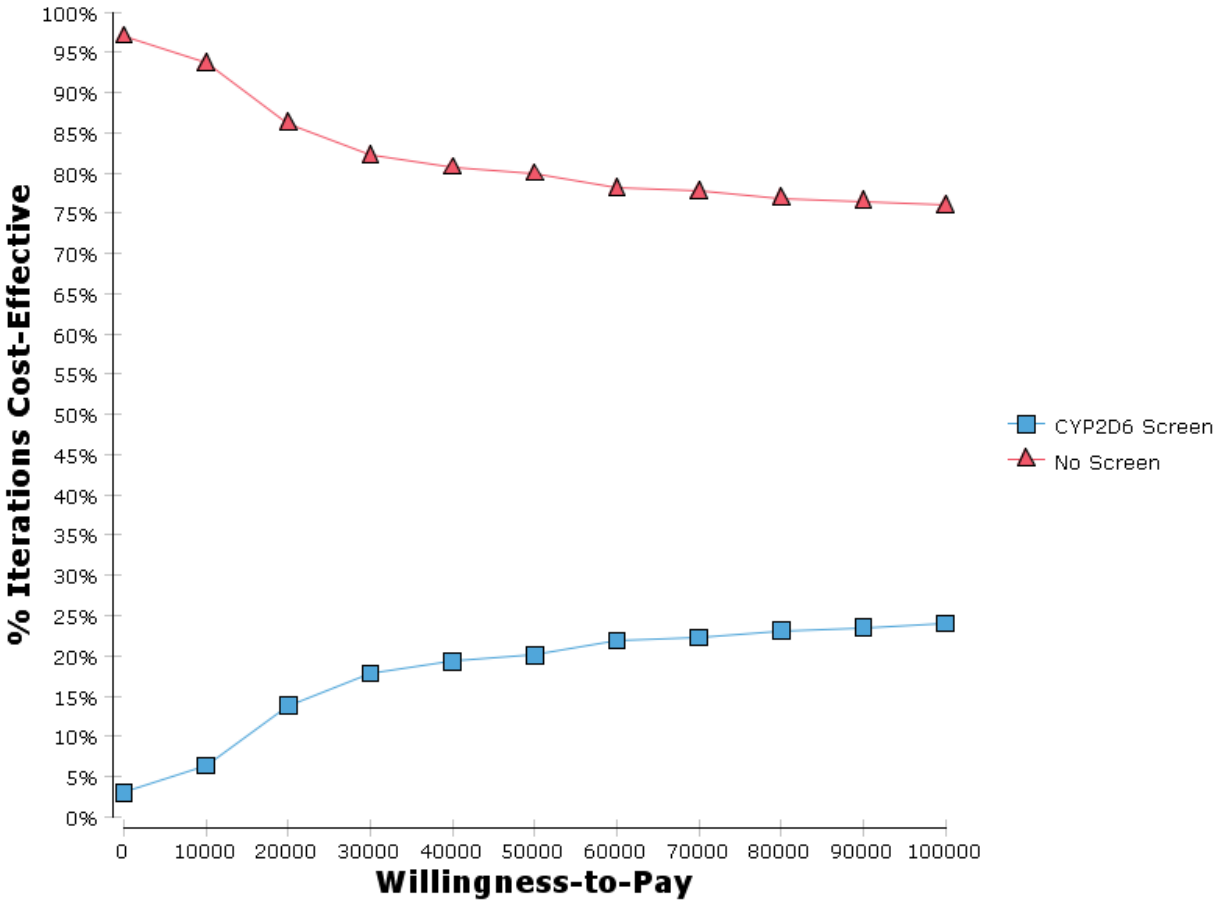
Results of the PSA are shown in the scatter plot below (Figure 3.1), where each point represents an ICER for the specified incremental cost and incremental effect. The ellipse around the scatter represents a 95% confidence interval. This scatter plot shows that the incremental costs are nearly always positive, i.e. screening costs more than standard care, but that the incremental effects are also often positive, more adverse events are averted, with 75% of the scatter in the quadrant where both costs and adverse events averted are positive.

Figure 3.1: Probabilistic Sensitivity Analysis Plot of ICERs for Adverse Events Averted



The result of the PSA was used to generate a CEAC, displaying the proportion of time each of the strategies was cost effective at a variety of WTP thresholds, shown in Figure 3.2.

Figure 3.2: Cost-Effectiveness Acceptability Curve for Adverse Event Outcome



3.3.4 Health Care Payer Perspective Analysis

The analysis shown thus far has been from the societal perspective. The base case analysis was therefore repeated from a health care system perspective, which excluded any patient or caregiver costs resulting from an adverse event (Table 2.3, p.27). Results of the findings from this perspective are detailed and described below. The base case analysis for the adverse event outcome is shown in Table 3.13. The findings are similar to those shown with the societal perspective. The screening strategy cost just under $500 per case and the no screen strategy cost 147.78 per case. There were the same number of fewer adverse events, 0.0346, which can be expected since the change in perspective modified only cost inputs and not probability inputs. The ICER was $10,157.31 per adverse event averted.

Table 3.13: Base Case Cost Consequence Analysis for Adverse Events Health Care System Perspective

Strategy	Cost Per Case	Adverse Events Per Case	Cost-Effectiveness Ratio
Screen	$499.55	0.1339	
No Screen	$147.78	0.1685	
Increment	$351.76	- 0.0346	**$10,157.31**

A PSA was also used to evaluate the cost-effectiveness from the health care perspective. After 1000 iterations of the decision model, mean and incremental costs and consequences were calculated and are shown in Table 3.14.

Table 3.14: Results of Probabilistic Sensitivity Analysis for Base Case from Health Care System Perspective

Strategy	Mean Cost per Case (95% CI)	Mean Adverse Events per Case (95% CI)	Cost-Effectiveness Ratio
Screen	$497.91 ($235.54, $1,512.59)	0.1309 (0.0512, 0.2400)	
No Screen	$145.60 ($10.32, $907.69)	0.1656 (0.0683, 0.3017)	
Incremental	$352.31 (-$10.45. , $1186.31)	- 0.0346 (-0.1682, 0.0440)	$10,173.61

The results of this analysis are similar to the societal perspective analysis. There are only minimal dollar value differences in the mean costs, incremental costs and mean ICER. As a result of the similarities the remaining analyses on the model were all performed from the societal perspective.

3.3.5 Scenario Analyses

The model was re-run with alternate scenarios, the first being for a target population of patients with a high UM rate and the second for a target population of women undergoing caesarean section deliveries. In the first scenario the probability of UM was estimated at 0.4, with a range of 0.12 to 0.45 (Sistonen et al. 2007). No other variables were altered. The results of the decision analysis for this high UM group is shown below (Table 3.15). Overall the screening strategy would cost $476.27 and the standard care, $272.11, an incremental cost of $204.15. The average cost per adverse event averted, the ICER was $1182.82 in this scenario. This value is markedly lower than the base case values and reflects the fact that, with a higher prevalence of UM, a greater number of adverse events are being averted by screening.

Table 3.15: Cost-Consequence Analysis of Adverse Events Averted for High UM Phenotype Scenario

Strategy	Cost per Case	Adverse Events per Case	Cost-Effectiveness Ratio
Screen	$476.27	0.0906	
No Screen	$272.11	0.2632	
Incremental	$204.15	- 0.1726	**$1182.82**

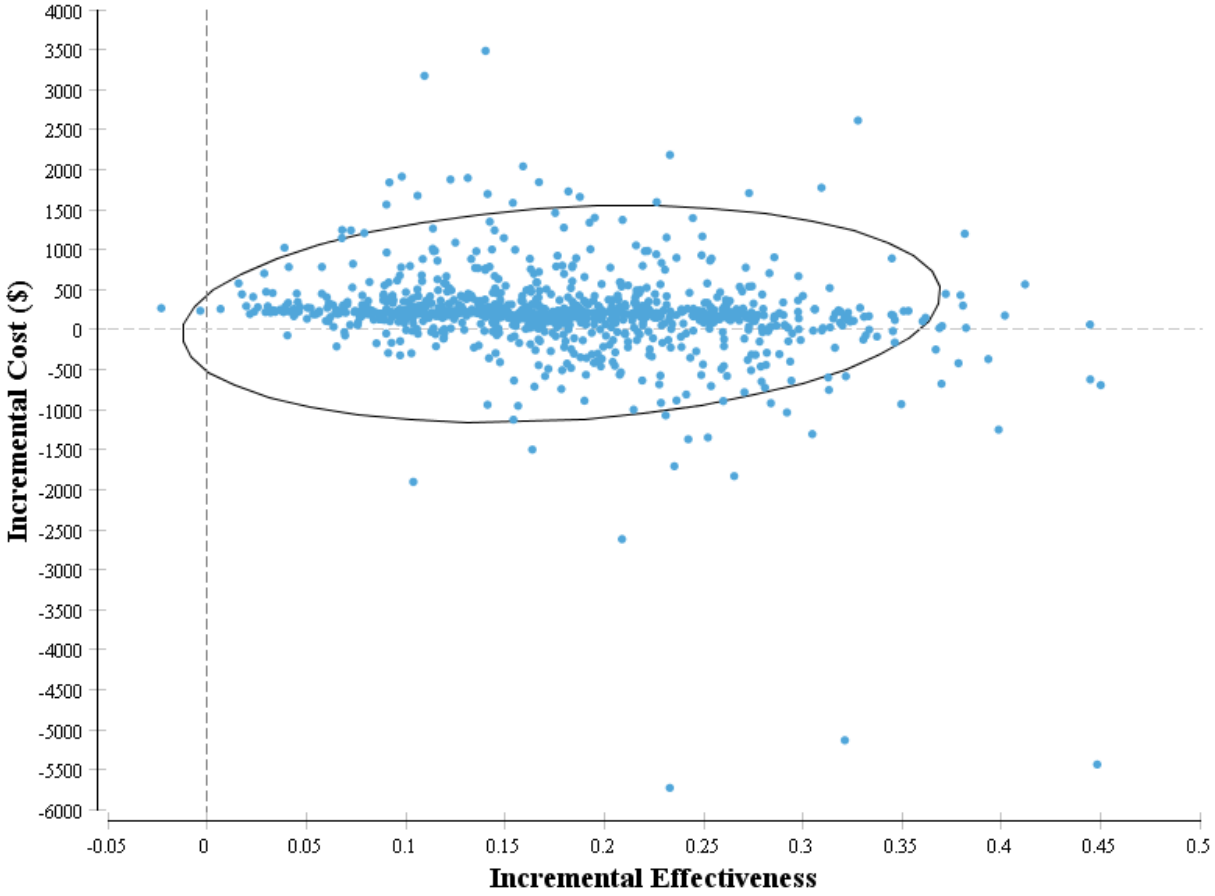
A PSA was also explored for this scenario. Mean estimates and 95% confidence intervals of the costs and outcomes obtained from the PSA are shown in Table 3.16 .

Table 3.16: Results of Probabilistic Sensitivity Analysis for High UM Scenario

Strategy	Mean Cost per Case (95% CI)	Mean Adverse Events per Case (95% CI)	Cost-Effectiveness Ratio
Screen	$479.46 ($235.70, $1524.12)	0.0877 (0.0345, 0.1603)	
No Screen	$287.11 ($22.53, $1572.36)	0.2619 (0.1196, 0.4323)	
Incremental	$192.35 (-$664.15, $1142.56)	-0.1743 (-0.3455, -0.0353)	$1,137.56

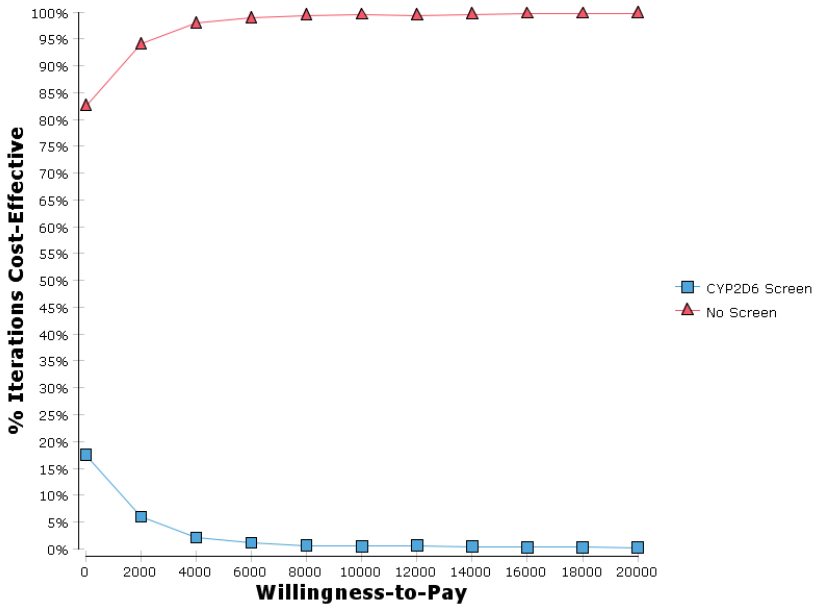
Graphical results of the PSA for the high UM scenario (Figure 3.3) show a shift in the scatter. The incremental effectiveness is now almost exclusively positive, indicating that this scenario will always avert adverse events; however the scatter around costs is more evenly distributed around zero. This suggests the strategy can be either more or less costly.

Figure 3.3: Probabilistic Sensitivity Analysis Scatterplot for Adverse Events Averted High UM Scenario



A CEAC was also plotted for this scenario. Figure 3.4 displays the proportion of time each of the strategies was cost effective at a various WTP thresholds among a population that had a high UM prevalence.

Figure 3.4: Cost-Effectiveness Acceptability Curve for Adverse Event Outcome in a High UM Population



The second scenario as described in the methods was the case of a caesarean section target population. In this scenario the probability of codeine use was increased to 0.93, with a range of 0.78 to 1.00 (East et al. 2007, Greene et al. 1999). The probability of an adverse event for a nonUM patient was increased to 0.22, with a range of 0.02 to 0.67. The decision analysis of this scenario revealed a cost for the screening strategy of $575.80 and for the no screening strategy of $244.28, with an incremental cost of $331.52. The ICER was $6777.01 per adverse event averted (Table 3.17)

Table 3.17: Cost-Consequence Analysis of Adverse Events Averted for Caesarean Section Group

Strategy	Cost per Case	Adverse Events per Case	Cost-Effectiveness Ratio
Screen	$575.80	0.187	
No Screen	$244.28	0.236	
Incremental	$331.52	- 0.0489	**$6777.01**

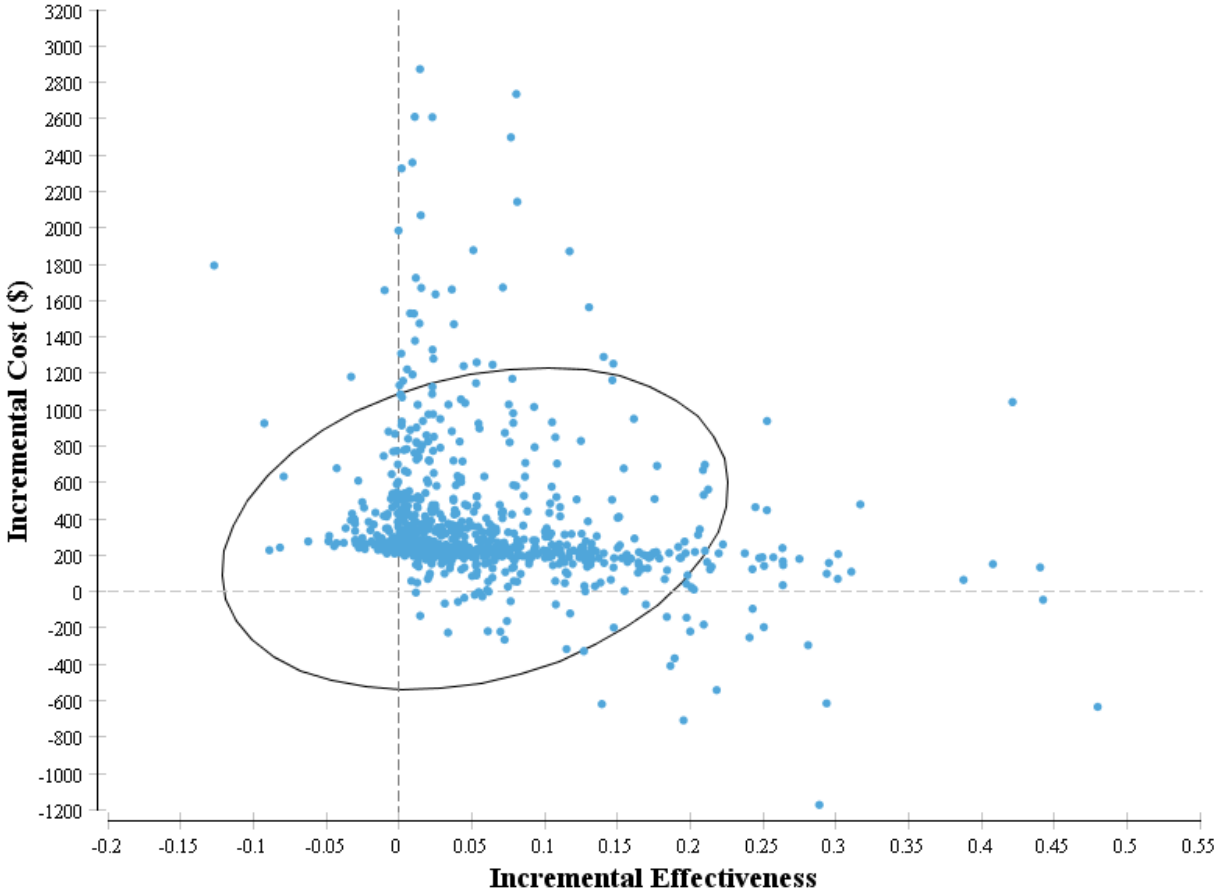
A PSA was run for this second scenario. Results of the mean values for costs and adverse events for each strategy are shown in Table 3.18.

Table 3.18: Results of Probabilistic Sensitivity Analysis for Caesarean Section Deliveries Only Scenario

Strategy	Mean Cost per Case (95% CI)	Mean Adverse Events per Case (95% CI)	Cost-Effectiveness Ratio
Screen	$613.57 ($234.70, $2268.88)	0.1885 (0.0152, 0.5371)	
No Screen	$267.73 ($8.19, $1610.98)	0.2407 (0.0283, 0.5982)	
Incremental	$345.82 (-$95.27, $1329.49)	- 0.0522 (-0.0266, 0.2494)	$6,626.50

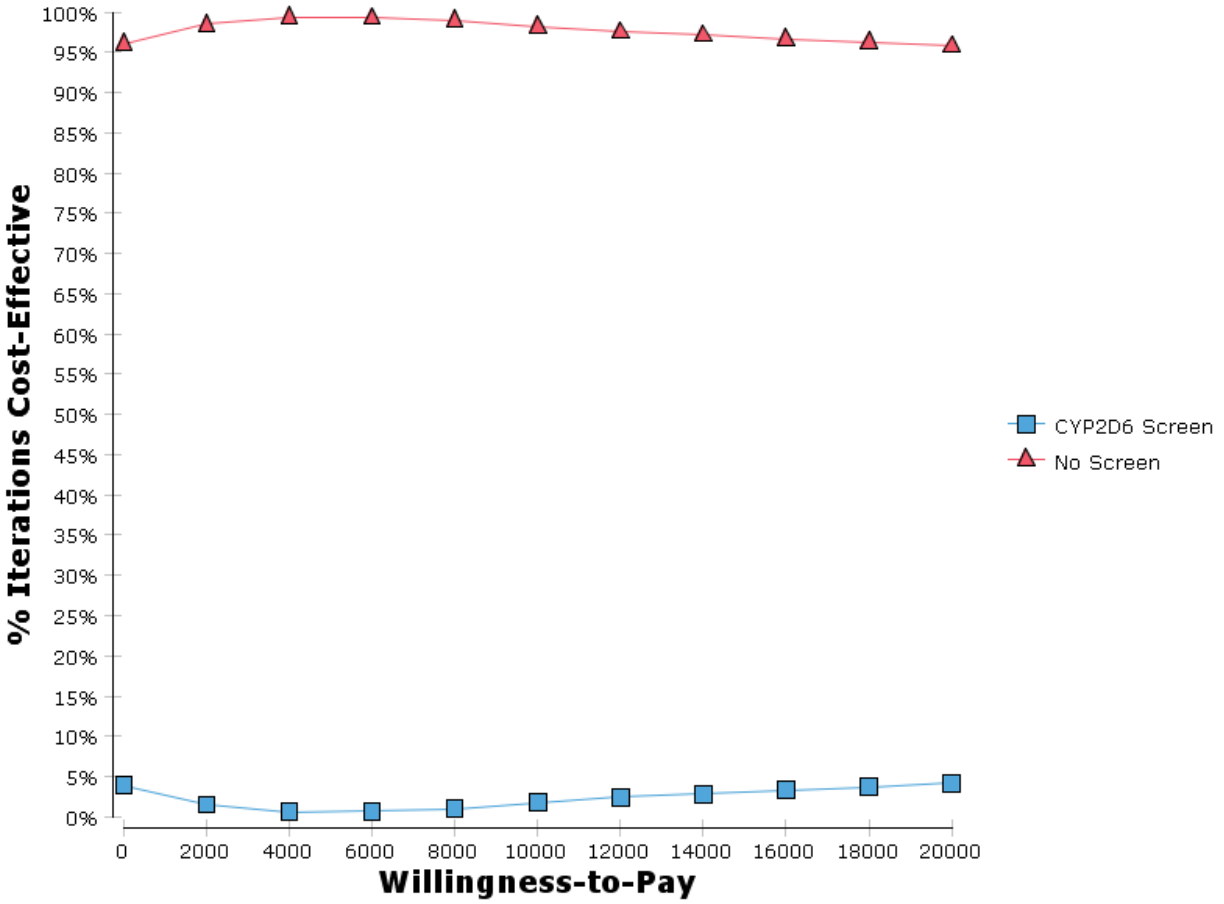
The PSA scatter plot (Figure 3.5), indicates scatter largely confined to the upper right quadrant, more costly and more effective.

Figure 3.5: Probabilistic Sensitivity Analysis for Adverse Events Averted Caesarean Section Scenario



Once again a CEAC curve was generated from the results of this PSA to show the proportion of time each strategy would be cost effective. This plot is shown below in Figure 3.6.

Figure 3.6: Cost-Effectiveness Acceptability Curve for Adverse Event Outcome Caesarean Section Scenario



3.3.6 Summary of Decision Model

The cost effectiveness analysis of CYP2D6 screening to guide pharmacotherapy for post-partum pain was not found to be cost-saving when compared to standard care. For each outcome, adverse events and symptom days, the model revealed an incremental positive cost for the treatment strategy. However, this was also accompanied by an incremental decrease in adverse events or symptom days. Hence, the model was able to predict an incremental cost per adverse event averted in the amount of $10,432.73 and an incremental cost per symptom day averted in the amount of $2,173.35. The model was robust in that it was not sensitive to most variables in one-way sensitivity analyses and the PSA revealed that this would hold true most of the time.

Altering the base case to evaluate alternative clinical scenarios continued to indicate that the model was not cost savings but that the ICER was substantially lower in both scenarios suggesting that more adverse events and/or symptom days would be averted, thereby costing less per case.

4 Discussion

As genetic testing strategies improve and the demand for these services increases it has become increasingly critical to evaluate their clinical merit and cost-effectiveness for allocation decision-making under constrained budgets.

This first part of the work described here evaluated the rate of analgesic use in a postnatal ward. In this study cohort just under 50% of patient medical records documented the use of opioids to treat postnatal pain. This rate is similar to rates reported in other industrialized nations and still represents a large proportion of exposed patients. In fact, there are very few studies that have reported utilization rates of analgesics postnatally and most were published several decades ago. A survey in Norway, at five university hospitals (Matheson 1989) found between 65-95% of women used analgesics postpartum and another, from Ireland, found that 45% of new mothers used analgesics containing codeine (Treacy and MacDonald 1981). The most recent work documenting the utilization rates comes from Norway (Nordeng et al. 2010) where 48.4% of women with vaginal deliveries used analgesics postnatally. They did not include caesarean delivery in this cohort and did not provide enough detail to specify which types of analgesics were used. Our results also showed that the use of opioids varied by type of delivery. It is clear that mode of delivery is a significant factor in the type of analgesic used as the utilization survey described here found close to 80% of caesarean sections used an opioid after delivery while only 16% of vaginal deliveries used an opioid. This is not surprising, as any surgical intervention is more likely to cause pain and inflammation and patients would be more likely to request pharmacotherapy to alleviate their symptoms.

Though our findings are similar to the available literature it is important to note that this may be an under representation of all analgesia exposure because patients at St. Michael's hospital were also able to self-administer over-the-counter products such as ibuprofen and acetaminophen. Patient self-administration is often not well recorded in the medical record.

The single arm standard care cohort study sought to evaluate the infant outcomes following maternal use of codeine during breastfeeding in an observational manner. Overall, there were 5 adverse events reported by mothers among the exposed infants, a rate of 2%, well below the event rate observed in previously published cohorts (East et al. 2007, Madadi et al. 2008, Ito et al. 1993) and this may be reflective of subtle changes in practice and administration of codeine

since the Health Canada warning. This lower adverse event rate was in an urban academic setting and whether this rate or practice changes translate to other hospitals or other parts of the province or country are not yet known.

Part of the clinical study included surveys of HRQoL in subjects, administered before and after their use of codeine while breastfeeding. Among the subjects who completed both SF-36v2 surveys, the overall physical component scores improved at follow up ($p=0.0008$) while their mental component scores decreased somewhat between the survey times ($p=0.017$). Upon comparison of the subscores it was found that these differences were largely accounted for by increases in the physical functioning ($p=0.0002$) and bodily pain ($p=0.024$) component scores. These findings likely reflect the fact that as recruitment was on the first day after delivery subjects would have been in some pain and therefore their scores in these domains were low. Since the second survey was completed after patients were home, had begun to recover from delivery and had completed their pharmacotherapy it is expected that their physical status would begin to approach that of their non-pregnant state and therefore not unexpectedly their scores began to increase. The global quality of life scores were similar to those observed in other populations of normal vaginal or caesarean deliveries and similar to women in their childbearing years in general (Borders 2006, Emmanuel and Sun 2014, Torkan et al. 2009). However, as most of the prior surveys used earlier versions of the survey instruments which had different scoring algorithms, a direct comparison of scores cannot be made. Studies comparing repeated quality of life surveys at delivery, and then seven days later suggest that physical ability and pain were the most affected (Baghirzada et al. 2013) and that these scores improved over time.

While the mental component score did show a small decrease between the two time points (<1/2 a standard deviation), there were no observed changes in any of the related subscores such as vitality, social function, role emotional or mental health. While it is not known whether maternal pharmacotherapy had any impact on these scores across time, it is more likely that the slight decrease was simply a measure of patient mental well-being as they return home having the increased workload and sometimes overwhelming task of having to now care for a newborn. In other populations of mothers without mental health issues, mental health scores were shown to remain similar across several interview time points around the perinatal period (Symon et al. 2002).

When quality of life scores were converted to SF-6D utility scores a small increase in scores between the initial interview and follow-up interview was noted, though this did not reach statistical significance (p=0.052). The increase in utility would suggest that patients experienced improvement in health status upon follow up. This would concur with the changes noted in the SF-36v2 scores which indicated that the physical component, physical functioning and bodily pain scores all improved and would be reasonable to expect once patients began to feel better after delivery. The mean utility scores before and after treatment (0.57 and 0.62 respectively) were lower than utility scores reported by Petrou et al. (Petrou et al. 2009), who surveyed all women who had just had a normal live birth and reported a mean utility of 0.861. As the population in our cohort was women who were receiving codeine for pain relief, most of whom had delivered their child by caesarean section, they may not be reflective of the general postnatal patients studied by Petrou et al.

In a paired analysis, there were no changes between the two measurement time points for either the State scores (p=0.27) or Trait Scores (p=0.70). Overall STAI scores were 34.81 before and 32.74 after, which was similar to he published literature. Paul et al. (Paul et al. 2013) found mean state scores of 31.0 immediately after delivery and scores of 25.9 two months after delivery in a cohort of over 1000 postnatal women. This decrease of several points resembles the decrease observed in this work, suggesting the changes over time after delivery are likely related to maternal well-being in general and probably not associated significantly with acute analgesic exposure around the time of delivery.

The primary component of the thesis research was a cost-effective analysis using a decision model comparing pharmacogenetic screening to guide pharmacotherapy for post-partum analgesia to standard care, which does not include pharmacogenetic testing. The base-case analysis showed that pharmacogenetic testing had an ICER of $9,997.43 per adverse event averted or $2,173.35 per symptom day averted from a societal perspective. Although the screening strategy did not save money it was not completely dominated by the standard care strategy. That is, it cost more but it also produced, on average, a more favorable outcome, a reduction in adverse events in infants.

The model was not sensitive to most changes in any of the variables with the exception of cost of a hospital admission for an adverse event. When hospital admission costs were extremely high

(>$100,000) the standard care strategy became dominated by the screening strategy, at which time the screening strategy would have a favorable ICER, less costly and more effective. This price for a hospital stay is rather unlikely as it would mean that the infant was admitted for a lengthy amount of time and would have had extensive procedures or interventions. Though the parameter estimate had a range that included this value the mean costs of hospitalization was significantly lower, at $5000. The second variable of note in the one-way sensitivity analysis was the probability of codeine use in the population. When codeine use was less than 53% the screening strategy became dominated by the standard care strategy, meaning that the incremental costs were higher and the incremental effects were negative, that is, it did not show a decrease in adverse events. This value is relevant as the probability of codeine use could approach this value in a number of populations. The retrospective medical record review at St. Michael's hospital did show a prevalence of opioid use below this value, suggesting that screening in this population would not be cost-effective. However, other populations (Nordeng et al. 2010) had considerably higher prevalence of opioid use, 73% in their patient population and therefore screening may be viable in some jurisdictions.

PSA was also used to evaluate uncertainty in many variables simultaneously. The PSA of the base case evaluation revealed an ICER of $10,432.73, similar to the value obtained from the deterministic analysis. The scatter plots indicate that 70% of iterations were in the upper right quadrant (i.e. more costly but more effective) and 27% were in the lower right quadrant (less costly and more effective). In an ideal setting a new intervention would be more effective and less costly; however this is not often the case. Most commonly decision makers are faced with the challenge of an intervention which is more effective but also more costly and the choice of implementing a strategy must be balanced against other interventions competing for the same resources.

The analysis further attempted to evaluate the robustness of the model and evaluate cost-effectiveness in special populations to determine if there were differences in the decisions or the preferred strategy. When evaluating a selected screening strategy of only a particular ethnic group, i.e. those who are known to have a higher prevalence of UM status, thereby making them at a higher risk for adverse events and greater health care costs the model continued to show that screening was more effective but also more costly to avert an adverse event. A hypothetical population with an UM rate of 40% was considered; this would represent a population from

North Africa. In this case the ICER was markedly lower than the base case evaluation at $1,182.82 per adverse event averted. Since screening a population with such a high UM rate would identify many more susceptible mother-infant pairs, such a strategy would avoid a larger number of adverse events by altering the choice of analgesics in those patients. The greater reduction in AEs results in a more favorable ICER as shown. This significant reduction in the ICER may make such an intervention appropriate in this ethnic group as the dollar value is less than a single emergency room visit when one considers hospital costs, ambulance costs and the mother's lost productivity costs. There are several populations with higher UM rates including those residing in the Middle East, Oceania as well as the North Africans. Provided these populations could be identified prior to delivery as part of prenatal care, they may be a potential target population that would benefit from screening based pharmacotherapy. However, in Canada only 0.8% of the population identifies their ethnic origins as North African. With such a small proportion of the population eligible for this targeted screening, the overall impact on costs or AEs averted can be expected to be negligible.

When evaluating a hypothetical population of patients having caesarean sections, who are more likely to require codeine therapy, the model continued to show that the screening strategy was more costly but more effective in averting AEs. The incremental cost per adverse event averted was also lower at $6,626.50 per adverse event averted. This may represent better value and may make the implementation viable in some settings. This amount would be less than a single hospital stay. The challenge in this type of scenario is that since screening needs to be completed before delivery it could only be implemented in those patients for whom caesarean section is scheduled and therefore tissue sampling can occur in advance of delivery. For patients who need emergency caesarean sections the screening could not be done until genotyping procedures become available at the bedside. The current platforms used commercially in research labs generally have turnaround time of several days; however this is a rapidly evolving field. It is anticipated that in coming years the analysis timeframe will be reduced to hours, and the ability to test a patient when she presents in labour may become a viable option.

Overall, our CEA found that screening reduced adverse events but was more costly than standard care. This reduction in adverse events was not large, as the overall rate of susceptible cases resulting from UM status is relatively small in our base case population, representing a patient population from Ontario. However, the costs to avert an adverse event were not remarkable and

are certainly lower than the costs of some hospital stays. Despite this, there may be other strategies to avert adverse events that would have little to no costs associated with them and these strategies may present an alternative to testing in this particular setting, that is, a postnatal ward at an academic hospital. As shown by Kelly et al. (2013), fewer adverse events were observed when a more judicious and cautious approach to dosing and a more careful adherence to a follow-up protocol were used. Alternatively, other analgesics may be administered that could offer equivalent pain relief and fewer risks for the breastfed infant. Direct administration of morphine may be an alternative as it confers pain relief mediated by the opioid receptors but is not complicated by genetic differences in the metabolic conversion to active agent. The use of other categories of analgesics such as non-steroidal anti-inflammatory agents may completely control pain in some patients or could be used as adjunctive therapy. Unfortunately, as these are relatively old agents, there is limited evidence on their comparative effectiveness and little data exists on opioids compared to NSAIDs for the treatment of perinatal pain.

This decision model was limited by the availability of published data. As noted throughout this text, research around mother-infant pairs in this context is sparse and there were limited studies from which parameter estimates could be derived. In some areas, such as rates of hospital admission following an adverse event, expert opinion was used. In addition, when only a single estimate was available in the literature, expert opinion was required to estimate plausible ranges. For this reason, relatively wide ranges were used in the sensitivity analyses and this accommodated for this uncertainty as the model findings remained consistent throughout. Also, as the overall numbers of adverse events in the literature were few, no assessment of severity could be incorporated into distinct branches of the model and the duration of adverse events was assumed to be constant. Had a variety of estimates of adverse event durations been available, this outcome variable could have been included in the model as a continuous measure, accounting, in part, for AE severity. On the other hand, the model did account for infants who went to emergency rooms and those who did not, as well as infants who were admitted and those who were not. While not an absolute measure of severity, this certainly would capture the fact that the more severe an event, the more likely the child will present at the hospital and be admitted. Once again, large ranges around these estimates in sensitivity analysis showed that the model decision was not changed and therefore it is not expected that more severe or less severe events would have altered the findings appreciably. The model also did not capture any long

term sequelae in the child resulting from an adverse event. To date, no long term effects have been reported among infants experiencing the adverse events and therefore parameter estimates, consequences and costs for a longer time horizon could not be accounted for in this model. Furthermore, as the focus of the model was the serious nature of the adverse events in the child, maternal adverse events were not addressed. Again, data on maternal outcomes were lacking and appropriate estimates for adverse events and costs for maternal events could not be established. This cost effectiveness model evaluated only the clinical outcomes of adverse events in the infant and symptoms days. Since published patient utilities were not available for the population described in the model, the QALY could not be used as an effect measure for the decision model. The evaluation of QALYs as an outcome would have been beneficial to decision makers who need to choose among interventions across different clinical settings.

The pharmacogenetic screen evaluated here, would reveal information not only to a patient about her metabolism of codeine to its active metabolite morphine, but would also provide information about the patient's metabolic capacity for a number of other medications currently in use. A limitation of this model then, is that the benefits of knowledge of metabolizer status on any future exposure to opioids or exposure to other drugs metabolized by the same enzyme system could not be measured and was not incorporated into the model. It is very likely that this knowledge that would remain with the patient, would impact her use of drugs well into the future and clinicians may be able to tailor their prescribing to better suit the patient. This would be expected to translate into better clinical effectiveness and safety profile for the patient, resulting in cost savings well into the future.

5 Conclusions

As we are beginning to learn more about the role of genetics in the susceptibility to both beneficial and harmful effects of medications, genetic testing will become more critical as a valuable clinical resource to guide patient care. While many other CEAs have evaluated the benefits of pharmacogenetic testing to guide treatment and improve outcomes in patients in a number of therapeutic areas, to date, there have been no other studies evaluating the cost-effectiveness of pharmacogenetic testing to guide pharmacotherapy in lactating patients. Nor have there been evaluations that look at treatments in one patient, the mother, avoid outcomes in

another patient, her infant. However, as analgesia among the most common treatments used by lactating women, particularly in the perinatal period, this type of evaluation is very relevant to the vast majority of patients. This study found that pharmacogenetic screening to guide postnatal analgesic treatment was not costs savings, and was associated with a cost of $9,997 to avert one adverse event. The work also showed that the utilization of opioids in the postnatal ward in a Toronto hospital was comparable to rates previously published in the literature and that these patients were also similar in terms of HRQoL and anxiety levels to postnatal patients elsewhere. These similarities suggest that this CEA may be relevant to a wider audience across Canada and beyond.

For the decision maker, this provides a valuable step towards understanding the value of novel interventions, which hold promise but may not quite be appropriate for wide-scale implementation. New technologies are emerging at a rapid pace but the benefits to the patient, and to society at large need to be evaluated systematically. The choices they must make are difficult and challenging because healthcare resources are finite and certainly constrained around the world. The choices about the best treatment strategies that present the best value for the healthcare dollar are critical to improving the health of a population.

References

Guidelines for the economic evaluation of health technologies: Canada. 3rd ed. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.

QualityMetric Health Outcomes Scoring Software (Version 4) [Computer Software] Lincoln,RI: QualityMetric Incorporated; 2010.

Ontario Case Costing Initiative. (2014) from http://www.occp.com/

Adedinsewo DA, Fleming AS, Steiner M, Meaney MJ, Girard AW. Maternal anxiety and breastfeeding: findings from the MAVAN (Maternal Adversity, Vulnerability and Neurodevelopment) Study. *J Hum Lact* 2014;30:102-109.

Akehurst R, Anderson P, Brazier J et al. Decision analytic modelling in the economic evaluation of health technologies - A consensus statement. *Pharmacoeconomics* 2000;17:443-444.

Almoguera B, Riveiro-Alvarez R, Gomez-Dominguez B et al. Evaluating a newly developed pharmacogenetic array: screening in a Spanish population. *Pharmacogenomics* 2010;11:1619-1625.

American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics* 2001;108:776-789.

Anderson PO, Pochop SL, Manoguerra AS. Adverse drug reactions in breastfed infants: less than imagined. *Clin Pediatr (Phila)* 2003;42:325-340.

Baghirzada L, Downey KN, Macarthur AJ. Assessment of quality of life indicators in the postpartum period. *Int J Obstet Anesth* 2013;22:209-216.

Bai YK, Middlestadt SE, Joanne Peng CY, Fly AD. Psychosocial factors underlying the mother's decision to continue exclusive breastfeeding for 6 months: an elicitation study. *J Hum Nutr Diet* 2009;22:134-140.

Barclay AR, Russell RK, Wilson ML, Gilmour WH, Satsangi J, Wilson DC. Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. *J Pediatr* 2009;155:421-426.

Beaulieu M, de DS, Lachaine J. Systematic review of pharmacoeconomic studies of pharmacogenomic tests. *Pharmacogenomics* 2010;11:1573-1590.

Beeson D, Golbus MS. Anxiety engendered by amniocentesis. *Birth Defects Orig Artic Ser* 1979;15:191-197.

Beitelshees AL, Veenstra DL. Evolving research and stakeholder perspectives on pharmacogenomics. *JAMA* 2011;306:1252-1253.

Berger MB, Xu X, Williams JA, Van de Ven CJ, Mozurkewich EL. Early hospital discharge of infants born to group B streptococci-positive mothers: a decision analysis. *BJOG* 2012;119:439-448.

Berger ML, International Society for Pharmacoeconomics and Outcomes Research. *Health care cost, quality, and outcomes: ISPOR book of terms*. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research; 2003.

Berwick DM, Weinstein MC. What do patients value? Willingness to pay for ultrasound in normal pregnancy. *Med Care* 1985;23:881-893.

Birch S, Donaldson C. Valuing the benefits and costs of health care programmes: where's the 'extra' in extra-welfarism? *Soc Sci Med* 2003;56:1121-1133.

Bjune K, Stubhaug A, Dodgson MS, Breivik H. Additive analgesic effect of codeine and paracetamol can be detected in strong, but not moderate, pain after Caesarean section. Baseline pain-intensity is a determinant of assay-sensitivity in a postoperative analgesic trial. *Acta Anaesthesiol Scand* 1996;40:399-407.

Blomquist JL, McDermott K, Handa VL. Pelvic pain and mode of delivery. *Am J Obstet Gynecol* 2014;210:423-426.

Bloomfield SS, Barden TP, Mitchell J. Naproxen, aspirin, and codeine in postpartum uterine pain. *Clin Pharmacol Ther* 1977;21:414-421.

Borders N. After the afterbirth: a critical review of postpartum health relative to method of delivery. *J Midwifery Womens Health* 2006;51:242-248.

Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care* 2004;42:851-859.

Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000;17:479-500.

Briggs AH, Claxton K, Sculpher MJ. *Decision modelling for health economic evaluation*. Oxford: Oxford University Press; 2006 *Handbooks in health economic evaluation series*.

Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53-72.

Cascorbi I. Pharmacogenetics of cytochrome p4502D6: genetic background and clinical implication. *Eur J Clin Invest* 2003;33 Suppl 2:17-22.

Chan YM, Sahota DS, Leung TY, Choy KW, Chan OK, Lau TK. Chinese women's preferences for prenatal diagnostic procedure and their willingness to trade between procedures. *Prenat Diagn* 2009;29:1270-1276.

Chen A, Rogan WJ. Breastfeeding and the risk of postneonatal death in the United States. *Pediatrics* 2004;113:e435-e439.

Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* 2002;360:187-195.

Cooper PJ, Murray L, Stein A. Psychosocial factors associated with the early termination of breast-feeding. *J Psychosom Res* 1993;37:171-176.

Crews KR, Gaedigk A, Dunnenberger HM et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther* 2014;95:376-382.

Critch JN. Nutrition for healthy term infants, birth to six months: An overview. *Paediatr Child Health* 2013;18:206-209.

Davis JM, Bhutani VK. Neonatal Apnea and Maternal Codeine Use [abstract]. *Ped Res* 1985;19.

de los Santos AR, Marti MI, Espinosa D, Di GG, Vinacur JC, Casadei A. Lysine clonixinate vs. paracetamol/codeine in postepisiotomy pain. *Acta Physiol Pharmacol Ther Latinoam* 1998;48:52-58.

Declercq E, Cunningham DK, Johnson C, Sakala C. Mothers' reports of postpartum pain associated with vaginal and cesarean deliveries: results of a national survey. *Birth* 2008;35:16-24.

Der G, Batty GD, Deary IJ. Effect of breast feeding on intelligence in children: prospective study, sibling pairs analysis, and meta-analysis. *BMJ* 2006;333:945.

Dewey KG, Heinig MJ, Nommsen LA. Maternal weight-loss patterns during prolonged lactation. *Am J Clin Nutr* 1993;58:162-166.

Ding Y, Zangwill KM, Hay JW, Allred NJ, Yeh SH. Cost-benefit analysis of in-hospital influenza vaccination of postpartum women. *Obstet Gynecol* 2012;119:306-314.

Dosiou C, Barnes J, Schwartz A, Negro R, Crapo L, Stagnaro-Green A. Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. *J Clin Endocrinol Metab* 2012;97:1536-1546.

Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. *Med Decis Making* 1985;5:157-177.

Drane DL, Logemann JA. A critical evaluation of the evidence on the association between type of infant feeding and cognitive development. *Paediatr Perinat Epidemiol* 2000;14:349-356.

Drummond MF, Sculpher MJ, Gorrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford: Oxford University Press; 2005 *Oxford medical publications*.

Duijts L, Jaddoe VW, Hofman A, Moll HA. Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. *Pediatrics* 2010;126:e18-e25.

East N, Dube J, Perreault EL. Postpartum pain relief: a randomized comparison of self-administered medication and standard administration. *J Obstet Gynaecol Can* 2007;29:975-981.

Eichelbaum M, Ingelman-Sundberg M, Evans WE. Pharmacogenomics and individualized drug therapy. *Annu Rev Med* 2006;57:119-137.

Emmanuel EN, Sun J. Health related quality of life across the perinatal period among Australian women. *J Clin Nurs* 2014;23:1611-1619.

European Medicines Agency. *Assessment report for codeine-containing medicinal products indicated in the management of pain in children*. London: 2013. EMA/441891/2013.

Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science* 1999;286:487-491.

Feeny D, Furlong W, Torrance GW et al. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. *Med Care* 2002a;40:113-128.

Feeny D, Townsend M, Furlong W et al. Health-related quality-of-life assessment of prenatal diagnosis: chorionic villi sampling and amniocentesis. *Genet Test* 2002b;6:39-46.

Findlay JW, DeAngelis RL, Kearney MF, Welch RM, Findlay JM. Analgesic drugs in breast milk and plasma. *Clin Pharmacol Ther* 1981;29:625-633.

Fleeman N, Dundar Y, Dickson R et al. Cytochrome P450 testing for prescribing antipsychotics in adults with schizophrenia: systematic review and meta-analyses. *Pharmacogenomics J* 2011;11:1-14.

Fleeman N, McLeod C, Bagust A et al. The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: a systematic review and economic evaluation. *Health Technol Assess* 2010;14:1-157, iii.

Furlong WJ, Feeny DH, Torrance GW, Barr RD. The Health Utilities Index (HUI) system for assessing health-related quality of life in clinical studies. *Ann Med* 2001;33:375-384.

Gaedigk A. Complexities of CYP2D6 gene analysis and interpretation. *Int Rev Psychiatry* 2013;25:534-553.

Gold MR, Siegel JJ, Russell LB, Weinstein MC. *Cost-effectiveness in health and medicine*. New York: Oxford University Press; 1996.

Green JM, Hewison J, Bekker HL, Bryant LD, Cuckle HS. Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review. *Health Technol Assess* 2004;8:iii, ix-iii,109.

Greene JF, Kuiper O, Morosky M, Wightman S, Curry SL. A postpartum self-medication program: effect on narcotic use. *J Womens Health Gend Based Med* 1999;8:1073-1076.

Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;121:183-191.

Haga SB, Kawamoto K, Agans R, Ginsburg GS. Consideration of patient preferences and challenges in storage and access of pharmacogenetic test results. *Genet Med* 2011;13:887-890.

Haga SB, O'Daniel JM, Tindall GM, Lipkus IR, Agans R. Survey of US public attitudes toward pharmacogenetic testing. *Pharmacogenomics J* 2012a;12:197-204.

Haga SB, Tindall G, O'Daniel JM. Public perspectives about pharmacogenetic testing and managing ancillary findings. *Genet Test Mol Biomarkers* 2012b;16:193-197.

Hancock RL, Ungar WJ, Einarson A, Goodstadt M, Koren G. Providing information regarding exposures in pregnancy: a survey of North American Teratology Information Services. *Reprod Toxicol* 2008;25:381-387.

Harris RA, Washington AE, Feeny D, Kuppermann M. Decision analysis of prenatal testing for chromosomal disorders: what do the preferences of pregnant women tell us? *Genet Test* 2001;5:23-32.

Hauck FR, Thompson JM, Tanabe KO, Moon RY, Vennemann MM. Breastfeeding and reduced risk of sudden infant death syndrome: a meta-analysis. *Pediatrics* 2011;128:103-110.

Haynes RB, Sackett DL, Taylor DW, Gibson ES, Johnson AL. Increased absenteeism from work after detection and labeling of hypertensive patients. *N Engl J Med* 1978;299:741-744.

Health Canada. Use of Codeine Products by Nursing Mothers. (2014) from http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_164-eng.php

Health Canada Marketed Health Products Directorate. Important Safety Information on Tylenol with Codeine in Nursing Mothers and Ultra-Rapid Metabolizers of Codeine. (2008) Accessed June 1,2014, from http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2008/13255a-eng.php

Henderson JJ, Evans SF, Straton JA, Priest SR, Hagan R. Impact of postnatal depression on breastfeeding duration. *Birth* 2003;30:175-180.

Hewison J, Nixon J, Fountain J et al. A randomised trial of two methods of issuing prenatal test results: the ARIA (Amniocentesis Results: Investigation of Anxiety) trial. *BJOG* 2007;114:462-468.

Horta BL, Bahl R, Martinés JC, Victora CG, World Health Organization. *Evidence on the long-term effects of breastfeeding: Systematic reviews and meta-analyses*. Geneva: World Health Organization; 2007.

Ingelman-Sundberg M. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. *Trends Pharmacol Sci* 2004;25:193-200.

Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J* 2005;5:6-13.

Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. *Pharmacol Ther* 2007;116:496-526.

Ip S, Chung M, Raman G et al. Breastfeeding and maternal and infant health outcomes in developed countries. *Evid Rep Technol Assess (Full Rep)* 2007;1-186.

Ito S, Blajchman A, Stephenson M, Eliopoulos C, Koren G. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. *Am J Obstet Gynecol* 1993;168:1393-1399.

Ito S, Moretti M, Liau M, Koren G. Initiation and duration of breast-feeding in women receiving antiepileptics. *Am J Obstet Gynecol* 1995;172:881-886.

Jain A, Concato J, Leventhal JM. How good is the evidence linking breastfeeding and intelligence? *Pediatrics* 2002;109:1044-1053.

Jentink J, Boersma C, de Jong-van den Berg LT, Postma MJ. Economic evaluation of anti-epileptic drug therapies with specific focus on teratogenic outcomes. *J Med Econ* 2012;15:862-868.

Jentink J, van de Vrie-Hoekstra NW, de Jong-van den Berg LT, Postma MJ. Economic evaluation of folic acid food fortification in The Netherlands. *Eur J Public Health* 2008;18:270-274.

Jernstrom H, Lubinski J, Lynch HT et al. Breast-feeding and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst* 2004;96:1094-1098.

Johnson M, Landers S, Noble L, Szucs K, Viehmann L, The American Academy of Pediatrics. Breastfeeding and the use of human milk. *Pediatrics* 2012;129:e827-e841.

Kelly LE, Chaudhry SA, Rieder MJ et al. A clinical tool for reducing central nervous system depression among neonates exposed to codeine through breast milk. *PLoS One* 2013;8:e70073.

Kharroubi SA, Brazier JE, Roberts J, O'Hagan A. Modelling SF-6D health state preference data using a nonparametric Bayesian method. *J Health Econ* 2007;26:597-612.

Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998;316:736-741.

Kirchheiner J, Schmidt H, Tzvetkov M et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J* 2007;7:257-265.

Kirchheiner J, Seeringer A. Clinical implications of pharmacogenetics of cytochrome P450 drug metabolizing enzymes. *Biochim Biophys Acta* 2007;1770:489-494.

Knight RG, Waal-Manning HJ, Spears GF. Some norms and reliability data for the State--Trait Anxiety Inventory and the Zung Self-Rating Depression scale. *Br J Clin Psychol* 1983;22 (Pt 4):245-249.

Kohlrausch FB, Gama CS, Lobato MI et al. Molecular diversity at the CYP2D6 locus in healthy and schizophrenic southern Brazilians. *Pharmacogenomics* 2009;10:1457-1466.

Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006;368:704.

Kramer MS, Aboud F, Mironova E et al. Breastfeeding and child cognitive development: new evidence from a large randomized trial. *Arch Gen Psychiatry* 2008;65:578-584.

Krause KM, Lovelady CA, Peterson BL, Chowdhury N, Ostbye T. Effect of breast-feeding on weight retention at 3 and 6 months postpartum: data from the North Carolina WIC Programme. *Public Health Nutr* 2010;13:2019-2026.

Kuppermann M, Feeny D, Gates E, Posner SF, Blumberg B, Washington AE. Preferences of women facing a prenatal diagnostic choice: long-term outcomes matter most. *Prenat Diagn* 1999;19:711-716.

Kuppermann M, Nease Jr RF, Gates E et al. How do women of diverse backgrounds value prenatal testing outcomes? *Prenat Diagn* 2004;24:424-429.

Kuppermann M, Nease RF, Learman LA, Gates E, Blumberg B, Washington AE. Procedure-related miscarriages and Down syndrome-affected births: implications for prenatal testing based on women's preferences. *Obstet Gynecol* 2000;96:511-516.

Kuppermann M, Shiboski S, Feeny D, Elkin EP, Washington AE. Can preference scores for discrete states be used to derive preference scores for an entire path of events? An application to prenatal diagnosis. *Med Decis Making* 1997;17:42-55.

Lam J, Kelly L, Ciszkowski C et al. Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. *J Pediatr* 2012;160:33-37.

Laska EM, Sunshine A. Fenoprofen and codeine analgesia. *Clin Pharmacol Ther* 1981;29:606-616.

Ledford H. All about Craig: the first 'full' genome sequence. *Nature* 2007;449:6-7.

Lee A, Moretti ME, Collantes A et al. Choice of breastfeeding and physicians' advice: a cohort study of women receiving propylthiouracil. *Pediatrics* 2000;106:27-30.

León-Cava N, Lutter C, Ross J, Martin L. *Quantifying the benefits of bresatfeeding: A summary of the evidence*. Washington, D.C.: The Food and Nutrition Program (HPN) Pan American Health Organization (PAHO); 2002.

Levin HM, Bare WW, Berry FN, Miller JM. Acetaminophen with codeine for the relief of severe pain in postpartum patients. *Curr Ther Res Clin Exp* 1974;16:921-927.

Levitt C, Hanvey L, Bartholomew S et al. Use of routine interventions in labour and birth in Canadian hospitals: comparing results of the 1993 and 2007 Canadian hospital maternity policies and practices surveys. *J Obstet Gynaecol Can* 2011;33:1208-1217.

Levy S, Sutton G, Ng PC et al. The diploid genome sequence of an individual human. *PLoS Biol* 2007;5:e254.

Llerena A, Dorado P, Penas-Lledo EM. Pharmacogenetics of debrisoquine and its use as a marker for CYP2D6 hydroxylation capacity. *Pharmacogenomics* 2009;10:17-28.

Lotsch J, Skarke C, Liefhold J, Geisslinger G. Genetic predictors of the clinical response to opioid analgesics: clinical utility and future perspectives. *Clin Pharmacokinet* 2004;43:983-1013.

Lugner AK, Mollema L, Ruijs WL, Hahne SJ. A cost-utility analysis of antenatal screening to prevent congenital rubella syndrome. *Epidemiol Infect* 2010;138:1172-1184.

Macarthur AJ, MacArthur C. Incidence, severity, and determinants of perineal pain after vaginal delivery: a prospective cohort study. *Am J Obstet Gynecol* 2004;191:1199-1204.

Macbeth AH, Luine VN. Changes in anxiety and cognition due to reproductive experience: a review of data from rodent and human mothers. *Neurosci Biobehav Rev* 2010;34:452-467.

Madadi P, Moretti M, Djokanovic N et al. Guidelines for maternal codeine use during breastfeeding. *Can Fam Physician* 2009a;55:1077-1078.

Madadi P, Ross CJ, Hayden MR et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther* 2009b;85:31-35.

Madadi P, Shirazi F, Walter FG, Koren G. Establishing causality of CNS depression in breastfed infants following maternal codeine use. *Paediatric Drugs* 2008;10:399-404.

Matheson I. Drugs to mother and infant in the maternity wart a survey at 5 university hospitals in Norway. *Tidsskrift for den Norske Laegeforening* 1989;109:2128-2122.

McCabe C, Brazier J, Gilks P et al. Using rank data to estimate health state utility models. *J Health Econ* 2006;25:418-431.

McRorie TI, Lynn AM, Nespeca MK, Opheim KE, Slattery JT. The maturation of morphine clearance and metabolism. *Am J Dis Child* 1992;146:972-976.

Meny RG, Naumburg EG, Alger LS, Brill-Miller JL, Brown S. Codeine and the breastfed neonate. *J Hum Lact* 1993;9:237-240.

Ministry of Health and Long Term Care. *Schedule of Benefits - Physician Services Under te Health Insurance Act*. 2013.

Ministry of Health and Long Term Care HDBDSU. *Ontario Case Costing Guide Version 7.0*. 2009.

Moretti ME, Lee A, Ito S. Which drugs are contraindicated during breastfeeding? Practice guidelines. *Can Fam Physician* 2000;46:1753-1757.

Murray TH. Assessing genetic technologies. Two ethical issues. *Int J Technol Assess Health Care* 1994;10:573-582.

National Library of Medicine. LactMed: A TOXNET database. (2014) from http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACTMED

Naumburg EG, Meny RG. Breast milk opioids and neonatal apnea. *Am J Dis Child* 1988;142:11-12.

Newcomb PA, Storer BE, Longnecker MP et al. Lactation and a reduced risk of premenopausal breast cancer. *N Engl J Med* 1994;330:81-87.

Nordeng H, Eskild A, Nesheim BI. Post natal use of analgesics: comparisons between conventional postnatal wards and a maternity hotel. *Pharm World Sci* 2010;32:206-211.

Norman SL, Jeavons BI, O'Brien PM et al. A double-blind comparison of a new ibuprofen-codeine phosphate combination, codeine phosphate, and placebo in the relief of postepisiotomy pain. *Clin Ther* 1985;7:549-554.

Ontario Ministry of Health and Long-Term Care. Ambulance Services Billing. (2012) from http://www.health.gov.on.ca/en/public/publications/ohip/amb.aspx

Ontario Ministry of Health and Long-Term Care. *Ontario drug benefit formulary/comparative drug index - Edition 42*. 2010-01361 ed. Toronto: Ministry of Health and Long-Term Care; 2014 *Microlog*.

Paul IM, Downs DS, Schaefer EW, Beiler JS, Weisman CS. Postpartum anxiety and maternal-infant health outcomes. *Pediatrics* 2013;131:e1218-e1224.

Peter EA, Janssen PA, Grange CS, Douglas MJ. Ibuprofen versus acetaminophen with codeine for the relief of perineal pain after childbirth: a randomized controlled trial. *CMAJ* 2001;165:1203-1209.

Petrou S, Morrell J, Spiby H. Assessing the empirical validity of alternative multi-attribute utility measures in the maternity context. *Health Qual Life Outcomes* 2009;7:40.

Perinatal health indicators for Canada 2013: a Report of the Canadian Perinatal Surveillance System. 2013.

Quiding H, Olsson GL, Boreus LO, Bondesson U. Infants and young children metabolise codeine to morphine. A study after single and repeated rectal administration. *Br J Clin Pharmacol* 1992;33:45-49.

Quigley MA, Hockley C, Carson C, Kelly Y, Renfrew MJ, Sacker A. Breastfeeding is associated with improved child cognitive development: a population-based cohort study. *J Pediatr* 2012;160:25-32.

R Core Team *R: A language and environment for statistical computing* Vianna, Austria: R Foundation for Statistical Computing; 2014.

Rabin R, de CF. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33:337-343.

Razurel C, Kaiser B, Sellenet C, Epiney M. Relation between perceived stress, social support, and coping strategies and maternal well-being: a review of the literature. *Women Health* 2013;53:74-99.

Rosenbauer J, Herzig P, Giani G. Early infant feeding and risk of type 1 diabetes mellitus-a nationwide population-based case-control study in pre-school children. *Diabetes Metab Res Rev* 2008;24:211-222.

Rosenblatt KA, Thomas DB. Lactation and the risk of epithelial ovarian cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Epidemiol* 1993;22:192-197.

Sachs HC, Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics* 2013;132:e796-e809.

Sanfilipo G. Contributo sperimentale all'ipotesi della smetilazione della codeina. *Boll Soc Ital Biol Sper* 1948;24:723-726.

Sistonen J, Sajantila A, Lao O, Corander J, Barbujani G, Fuselli S. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. *Pharmacogenet Genomics* 2007;17:93-101.

State-Strait Anxiety Inventry for Adults. Mind Garden, Inc.; 1977.

Spielberger CD, Gorssuch RL, Lushene PR, Vagg PR, Jacobs GA. *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press, Inc.; 1983.

Statistics Canada. Table 282-0069 - Labour force survey estimates (LFS), wages of employees by type of work, National Occupational Classification for Statistics, sex and age group, unadjsuted for seasonality, monthly, CANSIM. (2014a) Accessed June 1,2014a, from http://www5.statcan.gc.ca/cansim/a26?lang=eng&retrLang=eng&id=2820069&paSer=&pattern=&stByVal=1&p1=1&p2=37&tabMode=dataTable&csid=

Statistics Canada. Table 282-0073 - Labour force survey estimates (LFS), wages of employees by job permanence, union coverage, sex and age group, unadjusted for seasonality, monthly, CANSIM. (2014b) Accessed June 1,2014b, from http://www5.statcan.gc.ca/cansim/a26?lang=eng&retrLang=eng&id=2820073&paSer=&pattern=&stByVal=1&p1=1&p2=37&tabMode=dataTable&csid

Statistics Canada. Table 326-0021 - Consumer Price Index, health and personal care, by province (Canada). (2014c) from http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ161a-eng.htm

Stone DH, Stewart S. Screening and the new genetics; a public health perspective on the ethical debate. *J Public Health Med* 1996;18:3-5.

Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, Michels KB. Duration of lactation and incidence of type 2 diabetes. *JAMA* 2005;294:2601-2610.

Swain J, Dahlen HG. Putting evidence into practice: a quality activity of proactive pain relief for postpartum perineal pain. *Women Birth* 2013;26:65-70.

Symon A, MacDonald A, Ruta D. Postnatal quality of life assessment: introducing the mother-generated index. *Birth* 2002;29:40-46.

Teh LK, Bertilsson L. Pharmacogenomics of CYP2D6: molecular genetics, interethnic differences and clinical importance. *Drug Metab Pharmacokinet* 2012;27:55-67.

Thompson AJ, Newman WG, Elliott RA, Roberts SA, Tricker K, Payne K. The cost-effectiveness of a pharmacogenetic test: a trial-based evaluation of TPMT genotyping for azathioprine. *Value Health* 2014;17:22-33.

Thorn CF, Klein TE, Altman RB. Codeine and morphine pathway. *Pharmacogenetics and genomics.* 2009; http://www.pharmgkb.org/pathway/PA146123006.

Torkan B, Parsay S, Lamyian M, Kazemnejad A, Montazeri A. Postnatal quality of life in women after normal vaginal delivery and caesarean section. *BMC Pregnancy Childbirth* 2009;9:4.

Torrance GW. Social preferences for health states: An empirical evaluation of three measurement techniques. *Socio-Economic Planning Sciences* 1976;10:129-136.

Tracy TS, Venkataramanan R, Glover DD, Caritis SN. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. *Am J Obstet Gynecol* 2005;192:633-639.

Treacy V, MacDonald D. Drug utilisation in antenatal and postnatal wards. *Ir Med J* 1981;74:159-160.

Tu MT, Lupien SJ, Walker CD. Measuring stress responses in postpartum mothers: perspectives from studies in human and animal populations. *Stress* 2005;8:19-34.

Unal ER, Lazenby GB, Lintzenich AE, Simpson KN, Newman R, Goetzl L. Cost-effectiveness of maternal treatment to prevent perinatal hepatitis B virus transmission. *Obstet Gynecol* 2011;118:655-662.

Ungar WJ. *Economic evaluation in child health*. Oxford: Oxford University Press; 2010.

US Food and Drug Administration. Use of Codeine By Some Breastfeeding Mothers May Lead To Life-Threatening Side Effects In Nursing Babies. (2007) Accessed June 1,2014, from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm054717.htm

Vegter S, Boersma C, Rozenbaum M, Wilffert B, Navis G, Postma MJ. Pharmacoeconomic evaluations of pharmacogenetic and genomic screening programmes: a systematic review on content and adherence to guidelines. *Pharmacoeconomics* 2008;26:569-587.

von Neumann J, Morgenstern O. *Theory of games and economic behaviour*. Princeton, New Jersey: Princeton University Press; 1944.

Wadelius M, Darj E, Frenne G, Rane A. Induction of CYP2D6 in pregnancy. *Clin Pharmacol Ther* 1997;62:400-407.

Ware J, Jr. *The SF-36 Health Survey*. 1996.

Ware JE, Jr., Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. *SF-36v2® Health Survey: Administration guide for clinical trial investigators*. Lincoln,RI: QualityMetric Incorporated; 2008.

Warner R, Appleby L, Whitton A, Faragher B. Demographic and obstetric risk factors for postnatal psychiatric morbidity. *Br J Psychiatry* 1996;168:607-611.

Williams DG, Hatch DJ, Howard RF. Codeine phosphate in paediatric medicine. *Br J Anaesth* 2001;86:413-421.

Wong WB, Carlson JJ, Thariani R, Veenstra DL. Cost effectiveness of pharmacogenomics: a critical and systematic review. *Pharmacoeconomics* 2010;28:1001-1013.

Report of the Expert Consultation on the Optimal Duration of Exclusive Breastfeeding. Geneva: Department of Nutrition for Health and Development and Department of Child and Adolescent Health and Development; 2001.

Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther* 2013;138:103-141.

Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: Part I. *Clin Pharmacokinet* 2009a;48:689-723.

Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part II. *Clin Pharmacokinet* 2009b;48:761-804.

APPENDICES

Appendix A: Formulas for Specific Cost Items

Cost Item	Variable Name	Cost Components	Formula
Screening Procedure	cScreen	cTesting cTestPrep cShipping cCounselling	cTesting + cCounselling+cTestPrep+cShipping
Codeine Exposure	cCodeineExp	cCodeineUnit qCodeineUnit cAddAnalgesic qAddAnalgesic cDispense qDispense	(cCodeineUnit*qCodeineUnit)+(cAddAnalgesic*qAddAnalgesic)+(cDispense*qDispense)
Non-Codeine Exposure	cNonCodeineExp	cOtherAnalgesic qOtherAnalgesic cDispense qDispense	(cOtherAnalgesic*qOtherAnalgesic)+(cDispense*qDispense)
Infant Adverse Event Costs	cAE	cPatientOutofPocket cHelpCall cPhysicianVisit qPhysicianVisit cLabTest qLabTest	PatientOutofPocket+(cPhysicianVisit*qPhysicianVisit)+(cLabTest*qLabTest)+cHelpCall
Emergency Visit Costs	cEmergency	cAmbulance cERVisit cER_Physician cLostProdDay	cAmbulance+cERVisit+cER_Physician+cER_LostProdDay
Hospital Admission Costs	cAdmit	cHospAdmit qAdmitDays cAdmit_PhysDay1 cAdmit_PhysSubs cLostProdDay	cHospAdmit+cAdmit_PhysDay1+(cAdmit_PhysSubs*(ceiling(qAdmitDays)-1))+ (cAdmit_LostProdDay*qAdmitDays)

Appendix B: Model Pathway Cost Formulas for Terminal Nodes

Path	Path Details	Cost Formula
1	Screen, UM/Test+, Codeine, AE, Emerg, Admit, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency+cAdmit
2	Screen, UM/Test+, Codeine, AE, Emerg, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency
3	Screen, UM/Test+, Codeine, AE, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE
4	Screen, UM/Test+, Codeine, Well	cScreen+cCodeineExp+cNonCodeineExp
5	Screen, UM/Test+, Non-Codeine, AE, Emerg, Admit, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency+cAdmit
6	Screen, UM/Test+, Non-Codeine, AE, Emerg, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency
7	Screen, UM/Test+, Non-Codeine, AE, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE
8	Screen, UM/Test+, Non-Codeine, Well	cScreen+cCodeineExp+cNonCodeineExp
9	Screen, UM/Test-, Codeine, AE, Emerg, Admit, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency+cAdmit
10	Screen, UM/Test-, Codeine, AE, Emerg, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency
11	Screen, UM/Test-, Codeine, AE, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE
12	Screen, UM/Test-, Codeine, Well	cScreen+cCodeineExp+cNonCodeineExp+cNonCodeineExp
13	Screen, UM/Test-, Non-Codeine, AE, Emerg, Admit, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency+cAdmit
14	Screen, UM/Test-, Non-Codeine, AE, Emerg, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency
15	Screen, UM/Test-, Non-Codeine, AE, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE
16	Screen, UM/Test-, Non-Codeine, Well	cScreen+cCodeineExp+cNonCodeineExp
17	Screen, nonUM/Test+, Codeine, AE, Emerg, Admit, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency+cAdmit
18	Screen, nonUM/Test+, Codeine, AE, Emerg, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency
19	Screen, nonUM/Test+, Codeine, AE, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE
20	Screen, nonUM/Test+, Codeine, Well	cScreen+cCodeineExp+cNonCodeineExp+cNonCodeineExp
21	Screen, nonUM/Test+, Non-Codeine, AE, Emerg, Admit, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency+cAdmit
22	Screen, nonUM/Test+, Non-Codeine, AE, Emerg, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency
23	Screen, nonUM/Test+, Non-Codeine, AE, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE
24	Screen, nonUM/Test+, Non-Codeine, Well	cScreen+cCodeineExp+cNonCodeineExp
25	Screen, nonUM/Test-, Codeine, AE, Emerg, Admit, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency+cAdmit

26	Screen, nonUM/Test-, Codeine, AE, Emerg, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency
27	Screen, nonUM/Test-, Codeine, AE, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE
28	Screen, nonUM/Test-, Codeine, Well	cScreen+cCodeineExp+cNonCodeineExp+cNonCodeineExp
29	Screen, nonUM/Test-, Non-Codeine, AE, Emerg, Admit, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency+cAdmit
30	Screen, nonUM/Test-, Non-Codeine, AE, Emerg, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency
31	Screen, nonUM/Test-, Non-Codeine, AE, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE
32	Screen, nonUM/Test-, Non-Codeine, Well	cScreen+cCodeineExp+cNonCodeineExp
33	NoScreen, UM/unknown, Codeine, AE, Emerg, Admit, Well	cNoScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency+cAdmit
34	NoScreen, UM/unknown, Codeine, AE, Emerg, Well	cNoScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency
35	NoScreen, UM/unknown, Codeine, AE, Well	cNoScreen+cCodeineExp+cNonCodeineExp+cAE
36	NoScreen, UM/unknown, Codeine, Well	cNoScreen+cCodeineExp+cNonCodeineExp+cNonCodeineExp
37	NoScreen, UM/unknown, Non-Codeine, AE, Emerg, Admit, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency+cAdmit
38	NoScreen, UM/unknown, Non-Codeine, AE, Emerg, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency
39	NoScreen, UM/unknown, Non-Codeine, AE, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE
40	NoScreen, UM/unknown, Non-Codeine, Well	cScreen+cCodeineExp+cNonCodeineExp
41	NoScreen, nonUM/unknown, Codeine, AE, Emerg, Admit, Well	cNoScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency+cAdmit
42	NoScreen, nonUM/unknown, Codeine, AE, Emerg, Well	cNoScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency
43	NoScreen, nonUM/unknown, Codeine, AE, Well	cNoScreen+cCodeineExp+cNonCodeineExp+cAE
44	NoScreen, nonUM/unknown, Codeine, Well	cNoScreen+cCodeineExp+cNonCodeineExp+cNonCodeineExp
45	NoScreen, nonUM/unknown, Non-Codeine, AE, Emerg, Admit, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency+cAdmit
46	NoScreen, nonUM/unknown, Non-Codeine, AE, Emerg, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE+cEmergency
47	NoScreen, nonUM/unknown, Non-Codeine, AE, Well	cScreen+cCodeineExp+cNonCodeineExp+cAE
48	NoScreen, nonUM/unknown, Non-Codeine, Well	cScreen+cCodeineExp+cNonCodeineExp