Barriers to Personalized Medicine in Pediatrics: The Implementation of A Novel Pharmacogenomic Test for Pediatric Neuroblastoma

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June 2015

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Family Medicine.

Table of Contents

ABSTRACT – ENGLISH

Background: Primary brain tumours, specifically high-grade astrocytoma (HGA), are one of the leading causes of death from cancer in children under the age of 20. A novel laboratory derived pharmacogenomic (PGx) test has been developed and is well placed for use as a standard of care. The test is able diagnostically stratify the disease, it can readily identify whether or not a child is a carrier of a genetic mutation causing resistance to all available curative treatments. Knowledge of this mutation will move pediatric patients directly into palliative care; doing so will prevent the child from receiving harsh, ineffective treatments. Personalized medicine in pediatrics is often met with controversy; the practical and ethical barriers associated with this test must be explored prior to implementation.

Objective: The purpose of the investigation was to evaluate relevant barriers associated with the use of the novel PGx test as a standard of care in clinical pediatric oncology. Methods*:* A mixed methods embedded design was used to explore the barriers perceived by the end users of the novel pharmacogenomic test; end users included healthcare professionals working in either pediatric palliative care or pediatric oncology. Deliberative stakeholder consultations were used to explore barriers associated with the test. Stakeholder deliberations are unique in that they promote a space for open discussion, with a goal of generating meaningful exchange and rich dialogue with informed stakeholders. The deliberations were followed by quantitative assessment using a tool aimed at evaluating the occurrence of deliberation and to measure the deliberation success. Consultations were recorded and a thematic analysis was conducted. Setting: The study took place at Montreal Children's Hospital in Montreal, Quebec.

Participants: End users of the test, including: pediatric oncologists, pediatric palliative care physicians, pediatric palliative care nurses, pediatric oncology nurses, bioethicists and a social worker, were recruited as stakeholders to participate in the deliberations. Results: A better understanding of the barriers surrounding the use of this novel PGx test was attained. Relevant barriers to implementation identified by stakeholders included: the role of palliative care in patient management, communication, the impact of the test on care and the existence of conflicting cultures of care between pediatric oncology and palliative care. Several minor themes were also identified, including: the need for training to prevent the patient's experience of abandonment, difficulties with maintaining hope, providing inter-professional support and media as barrier. Results from the self-administered quantitative survey corroborated qualitative results showing that deliberation occurred; deliberative output was generated and it was concluded that a joint pre-clinic weekly meeting between pediatric oncology and pediatric palliative care would facilitate the introduction of this test as a standard of care.

Conclusions: The study identified barriers that exist when implementing a pharmacogenomic test, capable of delivering a terminal diagnosis, as a standard of care in clinical pediatric oncology. It is hoped that this framework for exploring the implementation of a PGx test in clinical care can be generalized and used for other tests.

RÉSUMÉ – FRANÇIAS

Contexte: Les tumeurs cérébrales primaires, en particulier d' haute qualité astrocytome (HQA), sont l'une des principales causes de décès par cancer pour les enfants sous l'âge de 20. Une nouvelle analyse pharmacogénomique a été mis au point lorsque les enfants peuvent stratifier la diagnostique avec l'HQA pédiatrique. Ce nouveau analyse est bien placé d'être utilisé comme une norme de soins, on peut facilement identifier si oui ou non un enfant avec HQA est porteuse d'une mutation génétique qui est responsable de la résistance à tous les traitements disponibles. La connaissance de cette mutation va déplacer les patients pédiatriques directement dans les soins palliatifs; cela lui permet de les empêcher de recevoir les traitments severe et inutile. La médecine personnalisée en pédiatrie est souvent imbu en controverse; les obstacles pratiques et éthiques associés à ce test doivent être explorées avant la mise en œuvre.

Objectif: Le but de cette enquête était d'évaluer les obstacles pertinents associés à l'utilisation de ce nouvelle PGx pharmacogénomique comme une norme de soins en oncologie pédiatrique clinique.

Méthodes: Un design de méthodes mixtes intégré a été utilisé pour évaluer les obstacles anticipés perçus par les utilisateurs finaux de l'essai pharmacogénomique, incluant les professionnels de la santé travaillant dans les deux soins palliatifs pédiatriques ou l'oncologie pédiatrique. Consultations des parties prenantes délibératifs ont été utilisés pour étudier les obstacles associés à ce test pharmacogénomique, les intervenants ont été invités à diffuser l'utilisation de ce nouvelle analyse pharmacogénomique comme une norme de soins. Délibérations de qualité sont uniques en ce qu'ils favorisent un espace de discussion ouvert, avec un objectif de générer des échanges et un dialogue riche avec les

parties prenantes informées. Les délibérations ont été suivis par une évaluation quantitative en utilisant un outil destiné à évaluer la survenance de la délibération et de mesurer le succès de la délibération. Des consultations ont été enregistrées et transcrites, analyse thématique a été menée et la sortie délibérative généré a été évaluée.

Cadre: L'étude a eu lieu à l'Hôpital de Montréal pour enfants à Montréal, Québec.

Participants: Les participants recrutés pour délibération incluant utilisateurs finaux de l'essai, y compris les oncologues pédiatriques et pédiatriques médecins en soins palliatifs pédiatriques.

Résultats: Une meilleure compréhension des obstacles liés à l'utilisation de ce nouvelle analyse pharmacogénomique a été atteint. Les obstacles à la mise en œuvre pertinents identifiés par les intervenants: le rôle des soins palliatifs dans la gestion des patients, la communication, l'impact du test sur les soins et l'existence de cultures conflictuelles des soins entre l'oncologie pédiatrique et les soins palliatifs. Plusieurs thèmes mineurs ont également été identifiés, notamment: la nécessité d'une formation pour éviter l'expérience de l'abandon du patient, difficultés pour maintenir l'espoir, fournissant un soutien inter-professionnelle et les médias comme barrière. Les résultats de l'enquête quantitative auto-administré corroborées résultats qualitatifs et ont montré que la délibération a eu lieu. Sortie délibérante a également été généré et il a été conclu qu'une réunion hebdomadaire pré-clinique conjointe entre l'oncologie pédiatrique et les soins palliatifs pédiatriques faciliterait l'introduction de ce analyse comme une norme de soins en oncologie pédiatrique pour les patients atteints HQA.

Conclusions: L'étude identifie des nouvelles barrières qui existent lorsque la mise en œuvre avec ce ne nouveau analyse pharmacogénomique, capable de fournir un diagnostic

terminal, comme une norme de soins en oncologie pédiatrique clinique. Il est à espérer que ce cadre pour l'exploration de l'utilisation d'un analyse pharmacogénomique PGx dans les soins cliniques peut être généralisé et utilisé pour d'autres tests.

ACKNOWLEDGEMENTS

This thesis was completed with the assistance, encouragement and advice from many individuals. Financial support for this project was provided by Genome Canada, partnered with the Canadian Institutes of Health Research, as a part of a the 2012 Large-Scale Applied Research Project Competition in Genomics and Personalized Health, "Biomarkers for Pediatric Glioblastoma through Genomics and Epigenetics", spearheaded by Dr. Nada Jabado at the McGill University Health Centre, with Dr. Gillian Bartlett being scientific lead for the GE3LS portion of the project. Financial aid was also provided in the form of a multi-disciplinary and translational genetics fellowship from the Réseau de médecine génétique appliquée (RMGA) also in conjunction with the Canadian Institutes of Health Research.

Further financial support was awarded by the Department of Family Medicine at McGill University in the form of an Entrance Scholarship and a Travel Award. The Faculty of Medicine at McGill University also provided funding through the International Travel Fund award. The Department of Experimental Medicine at McGill University offered support in the form of the Graduate Excellence Award and the Graduate Excellence Award for Productivity in Research. The Canadian Institute for Health Research provided further support in the form of the Institute Community Support and Travel Award. These awards supported graduate coursework, the completion of this Master's thesis and the presentation of relevant findings at various conferences.

Dr. Gillian Bartlett provided unwavering advisory support and invaluable advice during

the completion of this Master's thesis. Dr. Bartlett aided in the core development of this project, including the cultivation of the methodological framework and provided considerable constructive feedback and editorial help. Dr. Peter Nugus, a member of the thesis committee, was also a source of editorial support and provided valuable critiques of the qualitative analysis conducted within the following study. The final member of the thesis committee, Dr. Nada Jabado, provided feedback regarding the scientific background and clinical context of the investigation and actively facilitated the feasible development of the investigation.

PREFACE

This thesis was completed in accordance with guidelines outlined by McGill University for the submission of Master's level thesis. The foundation of this research project was a based on a collaborative effort between the author, Laura Crimi, and thesis supervisor, Dr. Gillian Bartlett. This thesis is an original piece of work constructed and completed by Laura Crimi. The candidate independently performed the literature review, data transcription, data analysis and interpretation. The deliberative stakeholder consultations were facilitated Dr. Gillian Bartlett with the assistance of Laura Crimi.

The study described in this thesis is an unpublished piece of work. The author has presented portions of this study at the North American Primary Care Research Conference, New York, New York in November 2014, Canadian GE^{3}LS and Health vices and Policy Research Conference in Vancouver, British Columbia in April 2015, and the Inaugural McGill Department of Family Medicine Research Day, Montreal, Quebec in February 2015.

I. INTRODUCTION

Cancer is the second most common cause of death in children; it is only outnumbered by accidental deaths (Canadian Cancer Society, 2014). In Canada, between 2005 and 2009, 60% of childhood cancer deaths were attributed to central nervous system and brain cancer, and leukemia (Canada Cancer Society, 2014). In recent years, much progress has been made in field of pediatric oncology (McGregor et al, 2007). With modern technological advancements and the development of increasingly targeted treatments, the prognosis for all childhood cancers remains overwhelmingly positive, with an overall observed survival five years after diagnosis of 83% (Canadian Cancer Society 2014).

The delivery of a cancer diagnosis to a pediatric patient is a unique phenomena, it is an exceptionally burdensome disease. Not only is it difficult for the child, it can be exceptionally taxing on both caregivers and the patient's immediate family (Salvador et al, 2014). Parents' of children diagnosed with a severe illness can often present with increased anxiety, increased stress, or posttraumatic stress disorder (Bruce 2006; Rosenberg et al, 2014). Siblings of children with cancer are also psychologically at risk group (Alderfer et al 2010). Younger siblings are often neglected and are at risk of exhibiting distress or developing increased anxiety, depression or posttraumatic stress disorder (Massimo & Wiley, 2006; Rosenberg et al 2014).

Advancement in the field of biomedical research has given rise to exceptional improvement in the cure rate of childhood malignancies; yet, some cancers remain resistant to available treatment (Paugh et al, 2011). Though there has been much progress

in the scientific understanding of the manifestation of pediatric cancer, much of which has been driven by advancements in genomic technology and drug development, some pediatric cancers still carry an exceptionally poor prognosis (Canada Cancer Society 2014). Despite varied treatment strategies and novel approaches, high-grade astrocytoma (HGA), a type of pediatric brain cancer, has a grim prognosis, with the majority of children succumbing to the disease (Broniscer & Gajjar, 2004; Finlay & Zacharoulis, 2005; Broniscer & Gajjar 2004; Cohen et al 2011). Current treatment options for pediatric patients with HGA include invasive brain resection and radiation. In Canada, 200 – 300 Canadian children and young adults are diagnosed with pediatric HGA every year, 90% of those afflicted die within the first three years of diagnosis (Canadian Cancer Society 2014). Despite the poor prognosis of pediatric HGA, patients and their families often grasp onto the small chance at survival. Pediatric patients are often subjected to harsh blanket therapies, which have high morbidity and can be detrimental to a patient's quality of life. This treatment strategy falls in line with the maxim of modern day medicine, having a primary focus on curative medicine.

A novel pharmacogenomic test is currently well placed for clinical implementation as a standard of care for pediatric patients with HGA. The stratification and identification of genetic subgroups of a disease is generally able to increase patient survival, improve quality of life and minimize the burden associated with a cancer diagnosis (Pui et al, 2011). A pharmacogenomic test developed at Montreal Children's Hospital is able to stratify pediatric HGA patients into two genetic subgroups based on specific genetic mutations affecting histone 3 variant 3 (H3.3), lysine (K) 27 and 36. This new laboratory

derived pharmacogenomic test is able to classify patients into subgroups, those that are responsive to treatment, with K36, and those that are not, with the K27 mutation. Pediatric HGA patients with the K27 residue do not benefit from current "blanket" therapies, they present with distinct molecular changes in chromatin structure and methylation that renders current medical interventions unsuccessful (Fontebasso et al, 2013; Gerges et al, 2013). Thus, subsets of patients who are non-responsive to current treatment are currently being 'over-treated' and would benefit from palliative care.

The integration of personalized medical treatment into clinical care often presents with many barriers (Hamburg & Collins, 2010; Ginsburg & Willard, 2009; Najafzadeh et al, 2012). These barriers must be fully explored prior to implementation, especially when used in the context of a vulnerable population, such as pediatric oncology patients. The specific test in question will be able to streamline patients with the terminal K27 mutation, which constitutes up to 20% of pediatric patients diagnosed with glioblastoma, into palliation because any prescribed curative therapy would significantly increase the burden of suffering for these patients without any curative effect. It has been shown that early integration of palliative care in patients presenting with a poor prognosis, and the avoidance of aggressive care at the end of life, can lead to longer survival (Temel et al 2010). Though the integration of palliative care at the point of diagnosis in pediatric patient's with HGA could increase a patient's quality of life, it is currently unknown as to how accepting a patient, and their family, would be of the palliative treatment.

This thesis explores the obstacles associated with implementing a new PGx test into

clinical pediatric oncology, taking special consideration to address all barriers perceived by stakeholders and end-users of the test. This study is part of a greater initiative at Montreal Children's Hospital aimed at developing the novel test and implementing it as a standard of care. This thesis comprises a portion of the qualitative arm of the larger project. This particular study assesses the attitudes of end-users of the PGx test and the relevant barriers associated with implementation. The results will be used in the next phase of the larger initiative, which will involve other end-users of the test, including patients with HGA and their families.

Conducting deliberative stakeholder consultations is an effective strategy for addressing complex health interventions (Avard et al, 2009; O'Doherty & Burgess, 2009). Employing the use of deliberative stakeholder consultations is appropriate for this study, because it promotes citizen engagement and provides a democratic public arena fit for addressing problems in the health-care sector (Abelson et al, 2003). This study employed the use of deliberative stakeholder consultations to explore the impact of integrating the novel PGx test into clinical practice. Conducting deliberative consultations with end-users of the pharmacogenomic test allowed for successful public debate and the identification of both points of agreement and disagreement regarding the clinical impact of the test. This methodology is based in "rationalization through conversational exchange" with a diverse stakeholder group and the minimization of researcher bias through participant led discussion (O'Doherty & Burgess, 2009). The results will be used to inform and support future guidelines for clinical practice surrounding the use of this novel test in pediatric oncology. The objective of this thesis is to address prevalent

barriers associated integrating novel technology within the framework of modern medicine. The project aims to contribute in developing a feasible solution to a case study, based in pediatric oncology, through providing recommendations to facilitate the implementation of technology in practice.

II. LITERATURE REVIEW

Considerable advancement in the successful treatment of human health has been a byproduct of the implementation of technology into clinical care. Large strides were made in the first half-century of modern medicine; medicine precipitated an increased life expectancy, decreased mortality and increased quality of life (Bunker 2001). Genomic medicine is well placed to generate even greater change within the landscape of medicine; many are optimistic about the benefits patients will incur as a product of the incorporation of their genomic information into clinical care (Manolio et al 2013). Genomic medicine is projected to play a promising role in the development of personalized medicine, specifically within oncology; the identification and validation of causative genomic variants will allow for faster and accurate cancer diagnosis and better, more personalized care (Gordon et al, 2015). However, the implementation of genomic medicine is not straightforward, exploring the history of medicine can facilitate a better understanding of genomic technology and current healthcare culture.

A. Evolution of Medicine: Impact of Genomics in Modernity

Perception of disease causation has varied throughout history. Beginning with antiquity, disease manifestation was first attributed to both supernatural and naturalistic forces (Bury 1998). Disease was previously viewed as a means of punishment via supernatural forces; disease was also seen as being a product of the disruption of the natural balance between an individual and the environment (Fox 1998). A heavy Greco-Roman influence existed during these ages, but this was quickly overshadowed by the popularization of Hippocrates' theory of humoralism (Bynum 1994). This new system of medicine focused on how the inner workings of the human body were directly influenced by four bodily fluids, including: blood, yellow bile, phlegm and black bile (Bos 2009). This period also fuelled the development of a set of ethical standards for physicians in the 5th Century BCE, called the Hippocratic Oath, which is still used in a modified form in present day (Smith 1996). Humoarlistic ideology was readily supported both physicians and other philosophers (Bynum, 1997). This theory co-existed with broader concepts such as Ayurveda, based in India, which had premises similar to that of naturalistic theory, and Vitalism, which had Chinese origins and gave credence to the role of energy flow in disease causation (Joshi, Ghodke & Shintre, 2010). Following humoralism, the Miasma Theory developed during the Middle Ages; these beliefs were framed by the assumption that manifestation of disease was directly correlated with filth and polluted air (Bynum, 1997). For example, dead bodies were known to produce foul, polluted vapors and were removed more readily than in previous periods. Though this doctrine was well founded, with some interventions providing an effective means of improving the general health of the population, it gave way to an inflection point in the history of medicine. This turning

point fuelled the establishment of modernity and the beginnings of an ideals shift that effectively gave rise to modern day western medicine. (Bynum 1997)

The age of modernity in medicine has been characterized by the rapid advancement of scientific knowledge (Lawrence 1995). The acquisition of new knowledge was a prominent force in the formation of the medical profession, which brought about the objective evaluation of disease and further recognition of specific disease causation (Lawrence 1995). Progression into post-modernity led to the creation of health-based infrastructure, including the specialization of medical professionals and the construction of hospitals (Bury 1998). The establishment of health infrastructure elicited change in how medical treatment was delivered; from the administration of medical care to people in home or bedside, medicine was institutionalized and the primary focus shifted from personalized care to case-based analysis of patients (Jacyna 2004). This new-found clinical lens is still maintained current practice and present-day medical discourse, which gives less credence to patient experience, or lay perspective, and places more weight on the 'expert opinion' of the medical professional (Bury 1998). Historically, the teaching of medicine was based in apprenticeship, but, following the establishment of modernity, the medical community moved toward evidence-based practice (Claridge & Fabian, 2005). The dogma of post-modern evidence-based medicine is focused on attaining the best possible clinical outcome through the application of evidence based in rigorous and reproducible research (Goldenberg 2006). A product of post-modernity is the placement of less weight on subjective physician opinion, because of the bias evident at the level of individual practice, and greater reliance on critical appraisal of a patient information and

the application of research, with stringent methodology, into practice.

The push for increased medical research also resulted in the legitimization various diseases and the medicalization of numerous conditions, including: childbirth, pregnancy and death (Clark 2002; Johanson, Newburn & MacFarlane, 2002). The medicalization of both birth and life has been extensively documented, especially in present-day with the application of novel gene technology, including genome sequencing at birth and the amniocentesis of a fetus (Bury 2007; Lucke et al, 2010).

A primary focus of the age of medical modernity is to incorporate more scientific evidence into practice (Goldenberg 2006). This has not only assigned power and authority to physicians over other healthcare professionals, but it has also fuelled the development of medicine as an institution and provoked the emergence of a "bourgeois approach" to novel technology (Bury 1998). The medical community has welcomed the implementation of new knowledge and techniques into practice; this can be "crudely" described the establishment of an increasingly personalized method of medicine (Kumar 2007). The certainty of novel technology often acts as the driving force behind personalized diagnosis and the implementation of curative interventions and the avoidance of risk (Knoppers et al 2014). Physicians are increasingly welcome to incorporating new scientific knowledge into their practice, whereas patient acceptance of novel technology, such as genetic testing, has been shown to be heavily influenced by psychosocial factors, including: a supportive attitude towards the test, perceiving the test as reliable and the ability to attain relevant scientific information about the test (Pivetti et

al, 2013). A prevalent example of the personalization of medicine can be found in genetics; we will evaluate the evolution of genetic testing through a clinical pediatric lens. One wonders whether the progression of medicine has had substantive impact on active practice in clinical pediatrics.

B. Genomic Medicine in Pediatrics: A Modern Approach

Since its emergence, more than 50 years ago, the application of genetic testing in pediatric practice has had long standing public support (Haga & Terry, 2009). The 1960s saw the use of a genetic test for phenylketonuria (PKU) in the US, and was quickly followed by prenatal testing for trisomy 21 in the 1970s. Though some view the implementation of newborn screening at this time was premature, the use of predictive genetic tests in pediatric medicine continued to flourish in the coming years (Elger 2010; Markel 1992; Wilfond & Thomson, 2003). Early cases of newborn screening first brought attention to the ethical considerations that accompany the use of genetic testing in medicine, including: the medical beneficence of such a test, the impact of genetic results on both a child and their family, and the true clinical utility of genetic testing in pediatrics (Wade, Tarini & Wilfond 2013). The historic use of genetic screening of newborns substantially differs from the information generated from genomic sequencing today.

Modern day medicine and post-modern medical ideology is progressing into an era in which genomic testing is well placed to become a standard of care in pediatrics. Though genetic information can be overwhelming for patients, it can be used to project

substantiated lifetime risk of a child for various conditions and allow a patient and their family to make more informed decisions throughout all subsequent care (Wade, Wilfond & McBride, 2010; McBride et al, 2010).

The cost of genomic sequencing and subsequent data analysis has drastically decreased; this has become one of the primary forces behind the development of clinical applications of genomic technology (Townsend et al, 2012; Matros et al, 2004). Genomic technology can guide patient management and facilitate diagnosis (Dancey 2012). Genomic sequencing is currently used in a limited capacity in the pediatric environment; it generally functions as a tool for targeting children with undiagnosed health conditions (Krepischi-Santos et al, 2006). Pediatricians will only prescribe genomic testing when a child presents with an unknown condition that may have a genetic origin, or when genetic information would help guide treatment for a child with a complex diagnosis (Conolly & Hakonarson, 2012). The scientific community is striving to fill gaps in genetic knowledge and has made significant strides in incorporation of genetic information into clinical decision-making (Butts et al, 2013).

Today, the development of low-cost and high throughput genomic technology has fuelled pediatric research targeting childhood-onset genetic disease (Conolly & Hakonarson, 2012). The ability of genomic sequencing to accurately diagnose disease is entirely dependent on the clinical validity of the variant in question (Knoppers et al 2014). Though genetic research, a practical form of evidence-based medicine, holds great promise, further investigation is required to facilitate the integration of genetic health

data into clinical pediatric care. Medical practice is moving towards becoming increasingly evidence-based, and there is an established transition towards the promotion of patient centred care (Goldenburg 2006). In light of this, special attention must be given to how to convey novel genetic results in pediatrics, being especially conscious of the well being of the child, and their family, to prevent unnecessary anxiety and undue strain on current health infrastructure (Abdul-Karim et al, 2013).

There has been a recent shift in the age of modern medicine with respect to pediatrics; greater focus has been placed on the well being and quality of life of the child. The conclusions drawn at the 1989 'Convention on the Rights of the Child' (United Nations 1989) was the initial turning point in the medical community's recognition of the rights of the pediatric population. The best interest and autonomy of the child has since been on of the predominant guiding ideals in the development of subsequent pediatric research and clinical care. The age of modern medicine has become increasingly evidence-based and exhibits an emphasis on patient centred care (Bensing 2000). The application of genomic testing is still a relatively novel technique in a clinical environment and substantial barriers exist that cause the dissemination and integration of genetic information into practice, decision-making difficult (Dunnenberger et al, 2015). Implementing genomic testing as a form of standard of care in pediatrics has been a topic of debate between policy makers, bioethicists and clinicians; there is overwhelming commitment to providing patient centred care, preserving the autonomy of the patient and promoting non-malfeasance in pediatrics (Friedman Ross et al, 2013). Genomic sequencing has potential to become a common standard of care in pediatric medicine, for

it adheres the ideals of medicine in the post-modern era. There is much to gain from integrating genomic information into the clinical decision making process, yet there are countless ethical and practical concerns surrounding the integration of genomic testing specifically at the level of pediatric oncology.

C. Ethical & Practical Considerations of Genomic Tests in Pediatrics

Evidence has shown that the use of genomic testing in a pediatric setting has the potential to drastically improve clinical practice through facilitating diagnosis, providing improved, patient-centred care (Saunderset al, 2012), revealing pharmacogenomic information (Daly 2010), and detecting more conditions than conventional testing, especially those that are heritable (Lewis et al, 2011). Despite the clear benefits, it is not sufficient to justify the use of genomic testing as a standard of care without thorough evaluation (Hall, Finnegan & Alberg 2014). Debate amongst clinicians, ethicists, and policy makers exists as to whether or not genomic sequencing is appropriate in clinical practice. There are a unique set of concerns that arise specifically surrounding genomic testing in pediatrics as ethical apprehensions are exacerbated due to the fact that children are considered an especially vulnerable population. A multitude of issues that surface when discussing the practical and ethical ramifications of implementing genomic testing in clinical pediatrics, which are explored in the following sections.

i. Incidental Findings

Currently, predictive genetic testing in minors is only recommended when results are clinically valid and can be paired with effective medical treatment (Dondorp & Wert, 2013). Generally, genetic testing in pediatrics is confined to disease with onset in childhood. Thus, the reporting of any incidental finding for an adult onset disease or carrier status is frowned upon for it creates considerable tension surrounding the use of genomic data, especially in a privacy context between the capacity of minors and the rights of their parents (Burke et al, 2011) (Knoppers et al, 2014). Incidental findings concerning adult-onset disease can often be beneficial for both a child and their family. Despite this, the reporting of incidental findings inherently revokes a child's autonomy as they cannot 'unlearn' his or her disease/carrier status and have effectively lost both their 'right to an open future' and ability to exercise their decision-making capacity as a result (Wade, Tarini & Wilfond, 2013).

ii. Communication

Communication between a pediatrician and their patient, and their patient's family, is a main concern associated with employing the use of genome sequencing as the standard of care in pediatrics. Though there are a multitude of highly penetrant mutations that can be identified from genetic testing, which can be used to inform a clinician's decision-making process, it can also reveal a plethora of vague results related to a child's potential risk factors for disease. There have been noted psychological impacts of predictive testing; the resultant responsibility to inform biological relatives is a common concern surrounding the use of genomic testing in clinical care (Cornel et al, 2014). The relaying

of genetic information to patients and parents is a known source of anxiety (Hewlett 2006). Thus, adequate communication between a pediatrician and their patient is extremely critical in negating anxiety stemming from the results of genomic test.

Communication is also integral to treating children, especially within the context of palliative care. There are six known domains in which children and families have deemed as influential on the quality of care received and adequate communication, these include: relationship building, demonstration of effort and competence, information exchange, availability and appropriate level of child and parent involvement (Meyer et al, 2006)

The public is seemingly enthusiastic about the use of genetic screening in care; they have a tendency to 'buy into' the hype surround genomic testing (Caulfield & Condit 2012). Yet, a recent study has shown that parents are generally less willing to employ of the use of broad whole genome sequencing in children compared to current new born screening panels, which are noted as being able to identify known conditions (Bombard et al, 2014). This exhibition of 'healthy skepticism' may be a product of the public acknowledgement about the harms of genetic screening, including the potential for genetic discrimination in the workplace or within the context of insurance (Bombard et al, 2014). The burden falls upon the pediatrician to appropriately explain the reasoning behind the use of genomic testing and to negate the public's expectation of benefit, which is likely a product of the media sensationalizing science.

iii. Impact on Health Systems

The costs associated with genomic testing guides much of the discussion surrounding its implementation, as a standard of care, in pediatrics. The expected benefit of implementing a test into care also comes with a number of concerns, specifically surrounding health systems and infrastructure. But as the newborn screening panel widens to include more variant, so increases the potential for false positives (Burke et al, 2011) (Howard et al, 2015). Though a goal of genomic sequencing is to avoid the "diagnostic odyssey", integration without proper healthcare infrastructure would be extremely burdensome on the system (Howard et al, 2015).

iv. Education

A auxiliary burden of integrating genomic testing into pediatric clinical care includes the need for education for health care professionals and other allied healthcare workers on how to best translate the information to the patient and communicate the results (Knoppers et al, 2014). The education of patients, families, and healthcare professionals has proven to be a significant obstacle when implementing genetic tests in clinical pediatrics (Andermann & Blancquaert, 2010; Scheuner, Sieverding Sheklelle, 2008). Caroll et al (2003) conducted a study with physicians and qualitatively evaluated their experiences with genetic susceptibility to cancer. The verdict of the study concluded that a lack of education was inhibiting the success of the practice; developing educational guidelines for improving genetic information communication is crucial. Battista et al, 2012, proposed a practical solution to this problem with new paradigm for using genetic services assessing cancer predisposition that addresses these barriers. It involved the use

of a multidisciplinary team which would include genetic counselors, primary care, nurses and relevant specialists to all be play a role in delivering diagnosis. Though the idea of having a team of health professionals would be ideal, it is noted that such a group would come with its own set of inter-professional and inter-organizational barriers (Battista et al, 2012).

A further study conducted by Kirk et al, 2008 addressed the implementation of genomics in healthcare from the perspective of a nurse identified many relevant barriers. It was found that obstacles that impeded the implementation of novel genomic tests in healthcare include a nurse's lack of awareness of genetics and failure to understand its relevance to practice. Many nurses cited a relevant 'fear' of genetic information and felt that the use of genomic tests had low priority in relation to other duties. In general, resources presenting genetic information to healthcare professionals generally target specialists, but within the context of a healthcare team it is important to make genetic information accessible for the entire team (Hetteberg et al, 1999; Bramwell & Carter 2001; Peterson et al, 2001; Alexander et al, 2002; Burke & Kirk 2006; Edwards 2006 et al). There is an overwhelming need to demonstrate the relevance of genomics in practice to nurses, educators and clinicians (Kirk, Lea & Skirton, 2008).

v. Cost

There is also high cost associated with the communication of genomic results over time (Boyd et al, 2014). As science advances, and the variant databases mature, more genetic variants will be associated with the expression of disease. This then falls upon the

pediatrician, specialists and allied health professionals to report new results and follow-up, thus putting further burden upon on the health system.

As the information revolution continues to take hold of healthcare infrastructure, the future use of genomic sequencing in pediatrics looms near and a pressing need exists for the development of practice recommendations, institutional policy, province-wide or federal policy to address the practical and ethical ramifications of employing genomic testing as a standard of care for children. Genomic sequencing technology is advancing at a remarkably fast rate. The speed at which disease-causing variants are being discovered is out-pacing the ability of policy makers and clinicians to address all of the practical and ethical concerns that arise from the integration of new genomic technology into clinical care (Milner et al, 2015). Special attention must also be given to those genomic tests that are capable of revealing an especially severe disease or illness with a grim prognosis, for any perceived barriers will be exacerbated in a vulnerable population.

D. Life and Death in the Modern Age

In addition to the issues related to the broad use of genomic testing, any genomic test that reveals a poor prognosis will have be of particular challenge for our death-averse modern medicine culture. Along with the pursuit of knowledge and improved medical treatment, the age of modernity gave rise to the medicalization of 'natural' conditions, such as birth and death. It has become apparent that both the natural phenomena in which humans enter and leave this world are now perceived as warranting medical attention. The social construct of death framed within post-modern medicine can be juxtaposed with the

attitude towards death exhibited during the Middle Ages (Ariès 1975). Death, once a historically ubiquitous and often familiar experience, has transformed into exceptionally shameful event by the exceedingly death averse society of present day (Ariès 1975).

Western medicine has traditionally been equated as having a death-averse culture and often presents controversy surrounding the cessation of treatment, hospice care as being controversial, and the avoidance palliative treatment in lieu of futile curative efforts. Despite the well-established death aversion, there has been a push in recent years towards the incorporation of palliative and hospice care philosophy to be a more prominent component of modern day medical practice (Zimmerman & Wennberg, 2006). This push has been hindered by the overwhelming emphasis on providing life sustaining treatment during physician training, the negative connotation associated with palliative care and the lack of formal physician education on how to converse with patients surrounding death and dying (Moon 2008).

Mortality salience, a product of the terror management theory, is the revelation that one's death is inevitable (Greenberg et al, 1990). A distinct facet of mortality salience is the distinct fear or anxiety of developing cancer, which for many is synonymous with death (Penson et al, 2005). The fear of death by cancer, in combination with the over-medicalized culture of modern day medicine, has propelled the public to seek answers and satiate their fear of death through the acquisition of genetic information. This is exhibited in individuals who worry more about cancer and those who have been found to present with greater intention to seek genetic testing than their less worried counterparts

(Kelly et al, 2007).

Media, especially framed in western culture, plays an extremely influential role on the public's perception of genetic information and the heredity of disease; the media actively promotes an overly fatalistic view of the role genes play in the manifestation cancer. The media more frequently reports on the success of aggressive cancer treatments and survival, and rarely commentates on treatment failure, adverse events, end-of-life care or death from cancer (Fishman, Have & Casarett, 2010). This works to substantiate the established cure-centric and death averse mentality of modern day medicine, which effectively presents the public with an overly optimistic role of genetics in both the development and treatment of cancer. This unfounded optimism perpetuates anxiety in those exhibiting mortality salience surrounding cancer and cause them to seek genetic testing, especially those who actively seek cancer information (Agurs-Collins et al, 2015).

Mortality salience surrounding cancer is warranted simply based on the high prevalence of the disease. Cancer is exceptionally pervasive on a global scale. The International Agency for Research on Cancer (IARC) reported the Global Cancer Statistics in 2012 and showed that cancer is the leading cause of death in both more developed and less developed countries worldwide (Torre et al, 2015). In 2012, there were an estimated 14.1 million new cancer diagnoses and 8.2 million deaths worldwide. Globally, lung cancer and breast cancer are the most prevalent forms of cancer, but prostate and lung being the most prevalent in men and women, respectively (Torre et al, 2015). Though the cancer

death rate peaked in 1991, cancer is currently the second leading cause of death in the United States, but it is projected to become the primary source of death, overcoming heart disease, over the next few years (Siegal, Miller & Jemal, 2015). There will be an estimated 1.7 million new cases of cancer diagnosed in the US in 2015, with 589,430 deaths projected to be attributable to cancer (Siegel, Miller & Jemal, 2015). Similar statistics exist for Canada, where cancer is the leading cause of death. It is projected that 2 in 5 Canadians will develop cancer over the course of their lifetime, and an estimated 1 in 4 Canadians will succumb to the disease (Canadian Cancer Society 2014). Overall, the survival ratio 5 years after a cancer diagnosis, in Canada, is 63%; though this is positive, individual cancers are highly variable, with many - including pancreatic esophageal cancers - carrying a much lower rate of survival (Canadian Cancer Society 2014). Presently, there is much known about the causation and manifestation of cancer, how it develops and how to best treat it (Canadian Cancer Society 2014). This, in part, can be attributed to the rapid advancement of genomic technology increasing the early detection of cancer (Kumar 2007; Gordon et al, 2015). This thesis will maintain the pediatric lens used in the previous example, and demonstrate the realized impact of modernity through the integration of pharmacogenomic medicine into clinical practice.

i. Clinical Pediatric Oncology & Pharmacogenomics

The field of pediatric oncology is exceptionally challenging, not only do pediatric tumours grow faster, they are also more likely to metastasize to other areas of the body (Canadian Cancer Society, 2014). In Canada, the most prevalent forms of pediatric cancer, between the years of 2005 and 2009, were leukemia and cancers of the central

nervous system and brain, together this made up 60% of all childhood cancer deaths in children age 0-14 (Canadian Cancer Society, 2014). Though the overall survival rate of children diagnosed with cancer has drastically increased since 1970 (National Cancer Institute), there has been limited advancement in childhood cancer survival in recent years (Canadian Cancer Society, 2014). It is currently accepted that the majority of pediatric cancer, similar to adults, is attributable to genetic mutation results in uncontrolled cell growth; an estimated 5 percent of all pediatric cancer can be attributed to heritable genes (National Cancer Institute). This marks an extremely apparent and distinct need to pursue new research, specifically the development of genomic testing, aimed at identifying more targeted and effective treatment to reduce childhood cancer mortality (National Cancer Institute).

The application of pharmacogenomics in oncology holds great promise, it is traditionally defined as a type of genomic test that uses sequencing technology to specifically evaluate the influence that an individual's genetic makeup has on their physical ability to metabolize various drugs (Kumar 2007). The use of a pharmacogenomic test in pediatric oncology has the potential to improve treatment strategies; by tailoring treatments to an individual, and developing personalized treatments based in concrete evidence, the occurrence of positive outcomes is projected to increase. This type of information can be used to stratify a disease using genetics and aid a pediatrician during decision-making by informing them of clinically relevant mutations that may impact a patient's drug response (Ely 2009; Lomberk 2008).

Advancements in clinical oncology have stemmed from the use of pharmacogenomics in the context of personalized medical treatments in care. Today, a personalized treatment or drug therapy plan can be created for cancer patients using the results of a pharmacogenomic test. The scientific community's improved understanding of genetic composition has helped develop more effective care, tailored to meet individual needs (Yeatman et al, 2008; Phan et al, 2009;Marko-Varga et al, 2007). Conventional methods of diagnosis, typically involving the prediction of disease manifestation and the effectiveness of drug therapies, are not always accurate in predicting treatment outcome (Crivellari et al, 2003; Eifel et al, 2001; Jiang 2010.). Pharmacogenomic tests in clinical oncology, however, are more effective in typing the cancer than traditional methods and can prevent the prescription of ineffective or toxic drugs to individual patients (Lomberk 2008).

The results of a pharmacogenomic test are inherently more difficult to communicate than other forms of medical information; this is especially magnified when dealing with a vulnerable population, such as children with cancer (Lanie et al, 2004). In a study conducted by Johnson et al (2005) it was found that pediatric oncology residents did not understand the genetic information being reported and increased confusion for the patient and their families (Kegley 2003; Johnson et al, 2005). Not only do barriers exist because of the complexity of genetic results, but health care professionals, including practicing pediatric physicians, often do not thoroughly understand the genetic information well enough prior to delivering test results to patients and their families (Kegley 2003; Stratakis et al, 1995). The advent of treatment based in new age pharmacogenomic

medicine has become an effective means of delivering improved, personalized, patient-centred care, but substantial barriers exist that hinder effective implementation (Ely 2009; Ashley et al, 2010; Nickola et al, 2011).

E. Looking into Modern Medicine: Personalization

Since the 18th century, medical practice has evolved, and developed ideology and framework entrenched in the pursuit of new scientific knowledge, attributing greater worth to specialized medical expertise, a focus on preventative and curative measures, and the perception of death as a negative outcome. Power is a fundamental part of every relationship, even in medicine; physicians inherently need to maintain a position of power to preserve their professional integrity (Goodyear-Smith & Buetow 2001). The power now wielded by medical professionals was not always evident, specialized doctors have established a cultural authority, which is a product of the emergence of scientific medicine that has proved to "undermine lay confidence in self-help" (Daniels 1984). Though medicine has historically been viewed as a patriarchal enterprise, there has been a concerted effort to shift from paternalism to a patient-centred model of care (McKinstry 1992). Not only has modernity established a new found focus on the personalization of medicine and the power of intervention, but also further social phenomena evidences the ultimate and unfading trust in the efficacy of western medicine by society as a whole (Daniels 1984).

A subsequent facet that characterizes modern day medical practice is medical heroism. This is where a physician employs a heroic course of treatment that poses a high risk for

causing further harm to a patient as a last resort, where any other form of treatment would result in failure, this is in part to due modern medicine's cure-centric bias towards over treatment (Staffen 1994). The perception that anything other than achieving cure is considered failure falls in line with death-averse culture and substantiates the growing stigma associated with shifting from traditional curative care to palliation. The advent of personalized medicine is projected to promote patient-centred care, which will place an increased value on the patient experience, their quality of life, and work to minimize harm and reduce harmful acts of aggressive medical heroism near the end of life. There are acknowledged barriers associated with the implementation of personalized medicine, here we will once again discuss the facets of modern medicine within the context of pediatric oncology.

F. Facilitators Associated with Personalized Medicine:

The merging of pure of genetic research with clinical infrastructure, in the form of personalized medicine, has many known benefits and barriers in clinical use. Benefits include more targeted treatments, earlier detection of disease and a more accurate diagnosis (Andermann & Blancquaert, 2010; Kirk, Lea & Skirton 2008). The practical barriers of implementing personalized medicine are of great concern. Najafzadeh et al (2013) undertook a qualitative study using practicing physicians in British Columbia, Canada, investigating the barriers of integrating personalized medicine into clinical practice. The end results presented three relevant issues impeding smooth implementation of personalized medicine into care, including: uncertainty in validity, equity and implementation. These findings presented several key themes surrounding the barriers

associated with the implementation of genomic tests in medicine, which were in concordance with other similar studies in the field (Najafzadeh et al, 2013). The results showed that health professionals were concerned about several aspects of using genomics in care, including: a lack of guidelines for the use of genetic tests in practice, uncertainty about appropriate use of genomic information, privacy issues and the potential harm incurred due to learning about genetic disease predisposition (Crivellari et al, 2003).

Finally, a systematic literature review conducted by Rosas-Blum et al (2007) found several communicative barriers exemplified by pediatricians when presenting the results of a genetic test to patients. Four skills were identified that were perceived as being required by physicians to promote clear patient-physician communication: i) understanding, ii) simplifying, iii) explaining and iv) discrimination of the complexity, content and nature of information being delivered. Patient communication is an established barrier to personalized medicine. A service evaluation of pediatric cancer patients has shown that individualized treatment summaries may be valuable to patients and their families (Firth, Davies & Skinner, 2013). It is also stipulated that language barriers and individual needs must be met in developing treatment summaries (Firth, Davies & Skinner, 2013).

Genomic sequencing technology is advancing at a remarkably fast rate; the speed at which disease-causing variants are being discovered is out-pacing the ability of policy makers and clinicians to address the practical and ethical concerns. As the information revolution continues to take hold of healthcare infrastructure, the future use of genomic

technology in pediatrics looms near. There is a pressing need for the development creation of policy to specifically address the practical, and ethical, ramifications of employing personalized medicine, specifically within the context of a pediatric population.

It is evident that medical doctrine has undergone significant changes since its inception in the 5th century BCE. The advancement has been firmly rooted in the generation of new knowledge and the development of novel technology. New technology, such as genomic sequencing, has increased survival rates and has been shown to be of benefit for current medical practice. Yet there is an obvious need to evaluate and assess barriers associated with delivering genetic results to patients and the integration of genomic testing as a standard of care. The implementation and evaluation of complex health interventions, such as the application of personalized medicine into practice, is intricate and must be addressed in a transparent manner. Employing deliberative stakeholder consultations is an appropriate method of appraising a complex health problem by creating an arena where stakeholders can openly engage with one another in value-based discussion to find consensus (Abelson et al, 2003). A method that engages stakeholders is critical in assessing dominant barriers of the implementation of new medical technologies, especially in highly vulnerable population such as pediatric oncology.

G. Conceptual Framework: Deliberative Democratic Theory

Health Canada has committed to involving the public in formal discussions about health policy issues as Canadians feel health care is their 'right'. In fact, to increase the

democratic legitimacy and transparency of the research process, it is recommended that health research projects incorporate the participation of relevant stakeholders or end-user groups to discuss controversial scientific developments in a public forum (Caron-Flinterman, Broerse & Bunders 2007; Tenbensel 2010). There are moral, instrumental, and political rationales to support public participation in health research and decision-making. As far as moral justifications are concerned, it is a citizen's right to participate in policy decisions that may eventually impact their health care (Caron-Flinterman, Broerse & Bunders 2007). Instrumental reasons for stakeholder engagement include: i) enrich the interpretation of research findings through the integration of various stakeholder perspectives, ii) increase the potential for wider dissemination and translation of research results, iii) promote capacity building and empowerment of stakeholders, iv) improve existing or create new services, practices, and policies, and v) increase the probability of successful policy and/or guideline adoption since the research will consider the needs of end-users (Caron-Flinterman, Broerse & Bunders 2007; Cargo & Mercer 2008). The democratization of research and decision-making processes will give a voice to "the people" and is considered to be a 'public good' (Caron-Flinterman, Broerse & Bunders 2007). The deliberative turn in democratic theory, referred to as deliberative democracy, has allowed for the development of novel public engagement approaches with potential to resolve complex ethical and policy related issues arising from research and will be used as the conceptual framework for this mixed methods research study (Chambers 2003).

The use of Fishkin's deliberative democratic theory as a methodological conceptual framework will guide the recruitment and sampling strategy, the deliberative process

itself, and the analysis of research results. It is known that deliberative democracy can be achieved if two fundamental values, namely political equality and deliberation, are fulfilled. While political equality aims at providing citizens with the equal opportunity to voice their perspectives on the policy issue at hand, deliberation is the communicative process by which these diverging opinions are exchanged and discussed in a mutually respectful environment. In simpler terms, deliberative democracy ensures that the public's perspectives – in this thesis the public is healthcare professionals -- on a given policy issue are considered and counted equally under conditions where participants are effectively motivated to engage in an informative and mutually respectful debate while remaining reflective, open-minded and understanding about contrasting arguments or opinions (Fishkin 2009; Walmsley 2007). It follows that if democratic deliberation occurs, participants are more likely to change their initial positions or preferences following the discussions and to arrive at considered judgments, i.e. participants will have the ability and the desire to reach a correct decision and/or solution for the common good of the people (Fishkin 2009; Dryzek 1990; Gutmann &Thompson 1996).

The basis of knowledge and underlying framework at the root of the above methodology and theory is naturalistic inquiry. Framing this research within the bounds of naturalistic inquiry allowed for the construction of reality, through observation, as perceived by relevant stakeholders. Overall, naturalistic inquiry provides a guiding structure for observing real-world complexities in their natural state without a pre-selection of variables or a priori assumptions (Lincoln & Guba, 1985). This will be critical for vulnerable populations where much of the research findings and assumptions based on

the literature may not be applicable.

Below is a case study that will be used in this thesis that clearly establishes the difficulties associated with implementing evidence-based medicine rooted in genomic testing and delivering patient centred care. This case study also works to address barriers associated with modern day medical practice, including: the cure centric focus of modern day medicine, the exertion of power by medical professionals and the overtly death-averse culture.

H. Clinical Case: Pharmacogenomic Test in Pediatric Oncology & Palliative Care

Increased emphasis has been placed on the importance of pediatric palliative care through promoting a child's quality of life and the minimization of suffering during treatment (Friebert 2014). Here, we define pediatric palliative care as having a primary focus on the relief of suffering, slowing the progression of a disease and improving the quality of life of a child (Klick & Hauer, 2010). Parents of children in pediatric palliation have identified honesty and receiving uncensored information from healthcare staff as being important to the quality of care their child receives (Davies & Connaughty, 2002; James & Johnson, 1997; Meyer et al, 2005). A child's direct communication with their healthcare provider is known to be an important during pediatric palliative care (Mack et al, 2005).

In light of recent genomic advancements, pediatric palliative care should be considered

the standard of care for patients presenting with the K27 mutation for pediatric HGA. Pediatric HGA is one of the leading causes of death in children under the age of 20 (Canadian Cancer Society 2014). An HGA diagnosis carries a grim prognosis; yet patients undergo aggressive treatment, including brain resection and full brain radiation therapy, both of which are linked to a low quality of life and a high morbidity (Hui-Qi 2010). Though pediatric HGA is currently incurable (Valera et al 2009), revolutionary work has been done in progressing the scientific understanding of it in pediatric populations. A new pharmacogenomic laboratory developed test has been developed, which can be used for diagnostic stratification of the disease. This test shows that pediatric HGA is a highly heterogeneous disease, meaning there are several different genetic mutations that can contribute to the expression of HGA (Fontebasso et al, 2013). Harsh, debilitating "blanket" treatments have been found to be ineffective in a subset of patients with a specific genetic variation. This novel pharmacogenomic test can easily identify whether or not a child is a carrier of the specific genetic mutation, making them resistant to all current HGA treatment; this population amounts to ~20% of all pediatric HGA patients. The introduction of this test into clinical care would show that all current treatment is not effective for this subgroup (Fontebasso et al, 2013). This is the first test of its kind; there are no other tests that identify a specific mutation as being the root cause of an individual's resistance to all know curative therapy currently used for treating patients presenting with HGA. It is unknown to what extent parents of children with brain tumours would accept palliative therapy, in exchange for a chance at increased quality of life for their child.

Contention exists between pediatric palliative care and pediatric oncology. Though

recommendations advise physicians to integrate palliative care into the treatment of all pediatric oncology patients, it is not always carried out in practice (Johnston & Vadeboncoeur, 2010). A recent survey has shown that some pediatricians will only recommend palliation, or refer a patient to the palliative care team, once all curative treatment has been exhausted (Thompson et al 2002).

A specific concern regarding the delivery of the terminal diagnosis surrounds potential for unclear communication. Unclear communication at the point of diagnosis, that fails to adequately convey the positives, such as an increased quality of life for a child, could promote parents to take their children to another treatment centre that does not utilize this newly developed laboratory derived test. This would cause a child to be unnecessarily subjected to highly toxic and futile treatment, which contradicts one of the core moral principles of medical ethics – practicing non-maleficence.

There is also a concern that a positive result of this test, and the subsequent change in type of care provided, may induce a loss of hope in a child, which has been shown to impact their quality of life, possibly negating the effects of removal of toxic therapies. This new laboratory developed test will be able to provide a better standard of care through stratifying disease based on genetic variation, which will accurately predict an individual's response to treatment and streamline those resistant to all known therapy into palliative care. A further barrier of this novel pharmacogenomic test is potential conflict amongst healthcare providers concerning immediate streamlining into palliative care.

A unique aspect of diagnosing a patient with a terminal illness encompasses ethical

concerns associated with communicating a terminal diagnosis and the removal of a patient's hope for recovery. Possessing hope is an important, and often an underestimated, component of healthcare; it has been proven that sustaining hope can increase quality of life of a patient (Garrard & Wrigley, 2009). An ethical tension exists in palliative care where physicians recognize the benefits of deceiving a patient and fostering a sense of 'false hope', yet they acknowledge the harm caused by not respecting patient autonomy by withholding the truth (Garrard & Wrigley, 2009). Hope, as defined in nursing literature, has been documented to improve a patient's quality of life (Chu-Hui-Lin 2007). Thus, working to maintain hope for a high quality of life is critical when delivering a terminal diagnosis.

Finally, there are anticipated practical barriers of implementing a novel pharmacogenomic test into clinical pediatric oncology. The test in question will inherently be a vehicle for delivering a terminal diagnosis, not only will there be a subsequent change in treatment strategy, but the adequate integration of the palliative care team must be considered. Many barriers are known to arise surrounding the often-burdensome integration of high functioning interdisciplinary teams, including: within group conflict, power discrepancy, undeveloped team skills resulting in patient mismanagement, waste of resources and medical error (Mitchell et al 2012).

Despite the large body of scientific literature evaluating the integration of genomic medicine and personalized treatment plans in healthcare, there is little that addresses the barriers that exist in modern day medicine that are associated with using a

pharmacogenomic tests as a means of delivering a terminal diagnosis within the context of a vulnerable pediatric population. As stated above, this study aims to clarify the obstacles associated with progressive modern medicine as perceived by relevant stakeholders, specifically surrounding the use of a novel pharmacogenomic test as a standard of care in pediatric oncology and construct a feasible solution for a specific case study. This thesis will address the following research question:

1. Based on deliberative stakeholder consultations with relevant stakeholders, what are the points of agreement and disagreement regarding optimal implementation strategies associated with the use of this laboratory derived pharmacogenomic test as a standard of care for patients in pediatric oncology?

II METHODS & METHODOLOGY

A. STUDY DESIGN

The study was an embedded mixed methods design, where both quantitative and qualitative components of the investigation were sequentially aligned. Qualitative deliberative stakeholder consultations were held with the projected end-users of the novel pharmacogenomic test in question, and were paired with the administration of a validated tool aimed at quantitatively evaluating the success of each deliberative session. Both qualitative and quantitative research methods were employed in order to ascertain different, but complementary data on the deliberative process. A deliberative stakeholder forum was chosen as a medium because it promotes a higher level of insight into barriers

associated with the implementation of the novel pharmacogenomic test into pediatric oncology, as perceived by participating stakeholders (O'Doherty & Burgess, 2009). Analysis of the qualitative and quantitative data occurred independently; the point of interface of results occurred at the conclusion of analysis (Creswell & Plano-Clark, 2011). The mixing of and merging of data allowed for full contextualization of the deliberations, quantitative results illustrate the success of the deliberation and thereby elicited a more complete understanding of the phenomenon being evaluated.

i. Setting

The design of this thesis is a mixed methods project. This project is a piece of a larger study that began in 2012 at Montreal Children's Hospital, which is affiliated with the McGill University Health Network. The investigation spearheaded the development of a pharmacogenomic test evaluating genomic biomarkers in pediatric glioblastoma. The research team was responsible for initiating the ICHANGE consortium; the consortium provides a means of grouping available samples and scientific expertise; this promoted the transformation of the global understanding of pediatric HGA in children. The greater project aimed at providing healthcare practitioners with tools to better stratify the disease based on specific genetic mutations that provide aid during therapeutic decision making, which promotes the streamlining of children into the best treatment strategy. As stated above, 20% of the children with pediatric HGA have been shown to be non-responsive to all current treatment. This thesis is situated within the qualitative arm of the greater project that assesses the attitudes of health care professionals who are end-users of this novel PGx test and the relevant barriers associated with implementation. The results of

this thesis will be used in the next phase of the greater project that will engage families of patients with pediatric HGA and finally with the patients themselves. Eventually, policy recommendations will be presented as to how to best implement this test in practice. It is hoped that this framework can be adopted as a generalizable means of engaging relevant stakeholders and evaluating barriers surrounding novel genomic tests.

ii. Deliberative Stakeholder Consultations

The qualitative portion of the study employed the use of deliberative stakeholder consultations, traditionally used within the context of policy development and based in political theory, this qualitative method can also be used as a means of solving complex issues in healthcare. Individuals bring different base-line values and perspectives to the discussion. In order to adequately evaluate and differentiate between participant statements during a deliberative consultation, the analysis must differentiate between the deliberative and analytical output (O'Doherty & Burgess, 2009). O'Doherty & Burgess (2009) define deliberative output as "explicit collective statements of participants that outline a particular position on an issue or a particular policy preference", it is simply a comprehensive overview of the results of participants' deliberations that surround the issue presented. An important aspect of this method is the ratification of the deliberative outputs from each deliberation by every participants involved. A thematic analysis of substantive perspectives and opinions explored during the consultation will also be used to evaluate the deliberation (O'Doherty, 2013). The analysis of analytical output is a discursive process that allows for the creation of further insight into the phenomenon though the incorporation of field notes and ethnographic analysis (O'Doherty & Burgess,

2009).

There has been increasing interest in the application of deliberative stakeholder consultations to address contentious issues that are specific to the health arena. Quality consultations are unique in that it promotes a space that "sincerely weighs the merits of competing arguments in discussions together" (Chambers 2003). Deliberative consultations not only require participants to be well informed about the topic at hand, but it also that there must be a representation of diverse perspectives in addition to a substantive balance in the exchange of contrasting views. The goal of using this method is to create a meaningful exchange and generate an in-depth and rich dialogue with informed stakeholders (Fishkin 2009; Walmsley 2007). The process of a deliberation promotes a structured output, where stakeholders present their ideas, and potentially revise their positions in an iterative fashion (O'Doherty & Burgess, 2009).

ii. Structure

Two small group deliberative consultations, one with each stakeholder group (pediatric oncology and pediatric palliative care), were conducted. Each began with a brief 20-minute presentation given by an expert who has research experience in this field. The overview outlined the novel pharmacogenomic test targeting pediatric HGA and its potential for use as a standard of care. Once the presentation was complete, an open forum question period took place. At the close of the question period the facilitator removed herself from the discussion and stakeholders were presented with an informational pamphlet and a set of questions (Appendix I) that were to be addressed

during the deliberation, discussion lasted for one hour. Deliberation stakeholder consultations took place in a non-clinical, private setting. Two note takers were present during each deliberation and took substantive notes throughout. A trained expert, who maintained neutrality, was also present and was responsible for facilitating the sessions. Facilitators and note takers did not participate in deliberations in any way, as their role was to observe. Effectively removing research bias is a distinct strength of deliberative consultations. All sessions were audio recorded and transcribed.

A deliberative stakeholder consultation steering committee ensured that the information provided to participants prior to the deliberation was an accurate representation of diverse perspectives and current issues. An augmented version of a questionnaire validated by De Vries et al (2010) aimed at evaluating the presence of deliberation, was administered at the close of each consultation; a copy of the questionnaire can be found in Appendix II. Questions that were not pertinent to the research setting were removed. The questionnaire aimed at evaluating whether or not deliberation occurred on an individual level during the sessions and participant experience on the day of the consultation. The survey included 7 questions answered on a 10-point scale (1=Not at all, 10= Very much).

After each deliberation, a summary document was generated and participating stakeholders were asked to ratify a set of statements summarizing the positions stated during deliberation. This final step of the deliberative process was crucial, as it allowed for the participants to revisit the points addressed during the consultation and permitted further clarification or validation of their position. This also ensured all stakeholder

viewpoints were considered in the formulation of the collective statements.

After both small group deliberations were conducted, a final large deliberation was held. The final deliberation followed the same format as previous deliberation, with the exception that the facilitator highlighted relevant themes and points of agreement and disagreement elicited from the previous two small group deliberations. A copy of this summary document and questions that were addressed during the mixed deliberation can be found in Appendix I. The goal of the final large group deliberation was to mix both stakeholder groups and work towards actively towards addressing pertinent barriers they perceived as relevant to the implementation of this test. A copy of the DeVries questionnaire as also administered at the end of the final large-group deliberation. The questionnaire administered after each deliberation was a validated tool that tests whether or not deliberation took place during the consultations. The tool, validated by DeVries et al (2010), has undergone stringent reliability testing. It was used to evaluate the quality of the deliberative stakeholder consultation sessions and provided a measure of the degree to which stakeholders were willing to adopt a societal perspective or changed their views during the deliberative process (which is a product of a successful deliberation). We included seven relevant questions that were answered on a ten-point scale, a copy of the survey can be found in Appendix I. Appendix IV illustrates the conceptual framework and sequence of both the deliberative stakeholder consultations and administration of questionnaires.

The outcome of the deliberations was informed using principles from deliberative

democracy. The results, deliberative outputs, focus on the conclusions and consensus reached at the close of the deliberations (O'Doherty & Burgess, 2009). Participants were asked to ratify the output of each consultation. Participants were presented with a summary document and were encouraged to provide input, as they felt fit. The summary document was then adjusted to represent all participant perspectives. The results of the deliberations and quantitative questionnaires study were combined at the end of analysis.

This study is part of a comprehensive GE^{3}Ls project funded by Genome Canada. The McGill Research Ethics Board (REB) at the McGill University Health Network (MUHC) and the Institutional Review Board at Montreal Children's Hospital have approved all activities. Relevant documents, such as consent and ethics approval, can be found in Appendix III.

B. RECRUITMENT

Individuals recruited for the deliberative consultations were targeted as end users of the novel PGx test at Montreal Children's Hospital, which fell within two stakeholder groups, pediatric oncology and palliative care. End-users were recruited as their practice stands to be the most impacted if the novel pharmacogenomic test is implemented as a standard of care. Deliberative stakeholder consultations allowed the end-users to collaborate and engage in productive discussion surrounding the feasibility of the laboratory derived PGx test, this elicited valuable data and facilitated the implementation of the test. Recruitment included pediatric oncologists, pediatric oncology residents, pediatric palliative care physicians, pediatric palliative care residents, residents, ethicists,

registered nurses, clinical nurse specialists and social workers. To be considered for inclusion the study participants had to be associated with Montreal Children's Hospital and an active member of either the pediatric oncology floor or palliative care unit. All eligible healthcare professionals fitting into the above criteria were invited to participate via email.

The first deliberative consultation included members of the palliative care team at Montreal Children's Hospital, four health care professionals participated in this deliberation including: two pediatric palliative care physicians, one clinical nurse specialist and a palliative care nurse. The second deliberation targeted members of the oncology ward at Montreal Children's Hospital; there were 12 members present during the deliberation. Participants included: pediatric hematologists-oncologists, a pediatric clinical ethicist, an oncology social worker, oncology nurses, medical students and medical residents. The final, large group deliberation consisted of a mix stakeholders coming from both groups, including healthcare professionals from the pediatric oncology ward and the palliative care team at Montreal Children's Hospital. The heterogeneous group of nine participants included seven professionals who work in palliative care and two with positions based in pediatric oncology.

C. Information Provided to Participants

An informational pamphlet was provided to every participant at the start of each deliberation. The informational document provided two questions for discussion and an overview of key issues pertaining to the application of the novel pharmacogenomic test in

clinical practice (Appendix I). The same pamphlet was provided to stakeholders in both the first and second small group deliberation. Based on the literature review and consultation with the research committee, questions were developed based on the gaps in current literature and specifically addressed the optimal implementation of the novel pharmacogenomic test and its perceived clinical impact. An exact copy of the questions given to participants can be found in Appendix I.

The participants of the third deliberation received an informational pamphlet with two questions for discussion, and a summary the points of an agreement and disagreement between the stakeholder groups that were elicited during the previous small group deliberations. All relevant documents can be found in Appendix I.

D. ANALYSIS

As previously described, two small group discussions were first conducted to evaluate the social, ethical and practical issues, as perceived by stakeholders, surrounding the implementation of the pharmacogenomic test in pediatric oncological care. The deliberative process concluded with a final large group joint discussion that included both stakeholder groups. The final large deliberation promoted the exploration of various practice recommendations and solutions to perceived barriers that would come with the implementation of the novel test pharmacogenomic into current practice as a standard of care.

Current literature fails to present an explicit consensus on the definition of deliberation, especially within the context of evaluating complex health interventions. Political theorists offer varying definitions of deliberation as it has been applied to many scenarios or conditions (Gally 2007), often it can refer to either the analysis of casual political conversations or analyzing group consensus. We aim to be conceptually clear, so for the purposes of this investigation deliberation is defined as: the discussion of a common problem and reaching a consensus on how to solve that problem.

Evidence that establishes the occurrence of deliberation have been presented by Niemeyer and Dryzek (2007) as a including meta-consensus, the agreement about the nature of the issue at hand and not necessarily the outcome, and intersubjective rationality, which includes individuals who agree on preferences also concur on the relevant reasons and vice versa for disagreement. We quantitatively evaluated the occurrence of deliberation using the DeVries tool. We sought to analyze the content of deliberation primarily through the deliberative output and the thematic evaluation of substantive themes addressed during the consultation.

All deliberative stakeholder consultations were recorded and transcribed verbatim. Participant names were replaced by a code to ensure confidentiality and anonymity was maintained. Transcripts were then imported into qualitative analysis software, NVivo Version 10.2.0 and coded. Transcripts were coded into categories and in concordance with naturalistic inquiry; we allowed these codes to emerge directly from the data. These categories were then grouped into recurrent and common themes and provided a means

of presenting the key viewpoints of participants. Thematic analysis was a recurrent process whereby transcripts and notes provided by note-takers during deliberation were analyzed, coded and categorized into themes. The most prevalent and recurrent topics of discussion were categorized as major themes; other significant points of discussion were categorized as minor themes. The analysis began with initial exploration of emergent issues brought forward by stakeholders during deliberation; subsequent analysis included constant contrasting, comparison of linkages and evaluation of similarities and differences amongst stakeholders. The typical analysis of deliberative stakeholder consultations is focused on the points of convergence and divergence established by participants (O'Doherty & Burgess, 2009; Coradetti & Bartlett, 2015). The creation of specific thematic categories allowed for further contextualization of stakeholder opinion (Thorne, 2000). In addition to providing explanation behind the conclusions reached in the deliberate output, these overarching themes also shed light on the substantive basis of both points of agreement and disagreement found amongst and within stakeholders groups.

This framework was fit for the analysis of these deliberative consultations for the setting mimics a naturalistic setting in the healthcare arena, provided by the minimization of researcher bias. Naturalistic inquiry facilitated the understanding of portrayed social action between stakeholders and provided key insight into perspectives presented by each participant (Schwandt 2007). This context acknowledged that professional relationships are both complex and interactive (Daniels 1984; Guba 1990).

This method was chosen over other qualitative methods, such as focus groups or semi-structured interviews, because it allows for stakeholders to drive the discussion and detail their concerns. This avoids researcher bias that can occur when a research sets all of the questions being asked and probes for answers to these predetermined questions (Coradetti & Bartlett, 2015). Focus groups seek to get more information on a subject that has previously been established by the researcher whereas the deliberative stakeholder consultations allows the stakeholders to both determine the issues addressed and prioritize them based on their own perspectives (Coradetti & Bartlett, 2015)

IV. RESULTS

QUALITATIVE RESULTS TRANSCRIPT ANALYSIS

A. MAJOR THEMES

The deliberative output of the final large-group deliberation was generated through a substantive analysis of transcripts. Doing so, established group consensus regarding how to best address the anticipated barriers of integrating the novel pharmacogenomic test into clinical care. The deliberative output involved the creation of a joint pre-clinic with members from both the oncology team and the pediatric palliative care team at Montreal Children's Hospital. Stakeholders viewed the pre-clinic as a means of addressing barriers that may arise as a result of implementing the novel pharmacogenomic test as a standard in pediatric oncology. Further functional analysis of the deliberative democratic forum provides greater insight into the development of this solution and the prevalent barriers that it addressed.

All three sessions addressed the potential use of the novel pharmacogenomic test in pediatric oncology as a standard of care. The test would be able to accurately diagnosis children with pediatric HGA as being non-responsive to all available treatment and streamline them directly into palliative care. Below is a summary of the emergent themes generated the transcripts of both the small-group and large-group deliberative stakeholder consultations. Instead of accrediting individuals, quotes were attributed to stakeholder groups. The palliative care and oncology community at Montreal Children's Hospital is small and providing more information could jeopardize participant anonymity.

i. Role of Palliative Care and Patient Management

The role of palliative care, and its integration into patient treatment, was extremely prevalent point of discussion throughout the deliberative process. It was acknowledged by the palliative care team that many families experience difficulties accepting a terminal diagnosis. It was evident that families often reject the idea of palliative care, and instead grasp onto the low odds that their child will beat a disease with an extremely poor prognosis. Members of the oncology team also ratified this during the deliberation.

> *"You would never say a zero outcome. You'd say 10 -20%, families would grasp on to that 20% and say "well my child is going to be in that 20%, I can't give up on them, of course we'll have treatment." There are very few families that would opt to palliate up front, because there is something, you can try to chemotherapy"*

The palliative care team felt they are often be perceived as the "dentists of medicine", implying that patients do not want to see them. Not only did the oncology team corroborate this, it was also evident that medical professionals working in the field of oncology felt that within the context of their practice it was apparent that the word palliation carried a negative connotation. This inhibited a pediatric oncologist's ability to involve palliative care in patient treatment. It was proposed that there might be benefit to renaming it something more positive, such as, "Pain and Symptom Management".

While the members of the palliative care team viewed their work as playing a vital role in a patient's overall care, it was unanimously agreed amongst themselves that their work

often goes appreciated by other members of the healthcare team. Though these experiential feelings of those working in palliation hold merit, it was also recognized during the second deliberative forum with members of the oncology team that

"[*Palliation is] a skill, and when it's done well, it's magic to watch*".

There was overall consensus in that to be a good doctor is doing everything that one can to help a patient and their families without doing any harm. Despite this, the palliative care team is often met with resistance from both patients and other healthcare professionals, even when it is clear that there is no curative treatment available. During the deliberative forum, stakeholders working in oncology felt that the integration of the new pharmacogenomic test in care will improve the decision making process because it will provide certainty on whether or not treating a child with high grade astrocytoma will be helpful or harmful.

It was also found that there is some hesitation from the oncology team to readily involve palliative care in patient management because of the underlying negative connotation that comes with the de-escalation of care, "*doing nothing*". Currently, if a patient meets with the palliative care team while there is still a sliver of hope for survival it can be perceived as "*the team giving up*".

> *"That said, the other disadvantage is how comfortable you, as a care giver are, to doing nothing. Not suggesting that that's true, that you do nothing, but how comfortable you are, with that perception that you're doing nothing."*

It was reported that when faced with a terminal diagnosis families routinely sought out therapies that were not regulated or based in science. This behaviour was supported by

members of oncology team, as there is always the possibility of trying a different treatment to maintain that '*sliver of hope*' for a cure. It was also noted by pediatric oncologists that they often find it difficult to move a patient into palliative care; the shift in moving from a cure centric goal to goals focused on symptom management and providing a '*gentle death'* was paired with the underlying perception that the team was giving up or now '*doing nothing'*. All participating stakeholders were in agreement that this is not actually the case, and palliation does not imply '*doing nothing*', patients and families often present with a deep-rooted perception that palliative care is analogous to giving up.

Both stakeholder groups felt that the earlier that palliative care is involved, the better; there was a general consent that ideally, palliative care should be involved in symptom management at the start. If the standard of care began with meeting all members of the healthcare team, including social workers, psychologists and members of the palliative care team, it could prevent manifestation of feelings of isolation in both the patient and families with a terminal diagnosis.

> *"I just wonder if the palliative care team was integrated as part of the HEME-ONC team, it might not feel so isolating for these parents if they also saw, you know, they saw members of the palliative care team, but do did others who are participating in it… you know there may be a way there of kind of opening a door, where family's are expected to do well could have help with some of the symptom control expertise that they happen to have and the ones who don't have the opportunity for cure, the could be integrated and they're a part of the team and all the kids are seeing them and it might not be quite so scary to think that we're also seeing palliative care, like everyone is seeing palliative care"*

> *"So, when you catch them at the right time, or when you're listening and trying to hear the doubts and the questions … time plays a big factor as well. When it's too fast they just don't have time to adjust. In my experience… at the beginning, they don't want to hear anything, but slowly progress over enough time"*

This consensus was a driving factor in the development of the deliberative output. Addressing the timing of the involvement of palliative care team spearheaded the proposed solution of early integration.

ii. Communication

There was a general consensus between all participating stakeholders that families are not likely to be accepting of being streamlined into palliation based solely on the results of a pharmacogenomic test. It was agreed that there much importance surrounding communication what a physician '*can do*' and less on what you '*can't do'*.

> "*[The family is] going to go on the web and they're going to find somebody that is going to say to them they have a proposed therapy, by the way. [Physician's] say there is [no treatment available] now, [but the family is] going to find something that somebody is doing. It could be waving a chicken over their head, it could be starting steroid at high doses, and it doesn't really matter. There will be something to do. Those parents, they will grab onto that. It doesn't matter how out there [it is]. It's not that they don't believe us, or we haven't given them good information, or talked to them, they just can't… it's a huge psychological barrier. The communication tool that you're talking about, is basically what I think I'm trying to do, I'm not speaking for my colleagues, every single day, figuring out how to connect with people who don't want to hear what's actually happening.*"

It was stressed by all deliberants that communication will play a vital role in delivering diagnosis and how to navigate subsequent care for these rare cases of pediatric HGA that are non-responsive to all current therapy. It was also communally recognized that a lot of training and experience is required to have conversations relaying a terminal diagnosis as a product of a pharmacogenomic test and appropriately discussing the reframing treatment goals.

The development of a clinical tool to facilitate communication was proposed as a means of aiding in the use of this new pharmacogenomic test in clinical care. Though this was found to have has some merits, the palliative team felt it could not completely replace the role of a palliative care healthcare professional. Palliative care physicians felt that their clinical wisdom could not be "boiled down" to a clinical communication tool.

> *"[A communication tool does] not actually address the underlying issues of the conversations and the discussions needed with families in practices. Creating a tool…. there's so much more to [it than] the use of that tool."*

All stakeholders felt that a one page protocol or informed decision tool could be helpful in delivering a terminal diagnosis because it could provide a cognitive framework or act as a teaching tool. Both members of oncology and palliative care expressed that there is a distinct need to for an increased level of training for physicians working in oncology on how to best communicate have the necessary, often difficult, conversations with the rare subset of terminally ill patients with pediatric HGA and their families. It was also established amongst all stakeholders that maintaining hope while communicating a shift

in treatment goals, from cure centric to maintaining quality of life and symptom management, was a critical element of delivering the terminal diagnosis.

iii. The Impact of the Novel Pharmacogenomic Test

Oncology team members believed that having certainty with this pharmacogenomic test would be beneficial and facilitate the decision making process. Though the survival rates for pediatric HGA are extremely poor, prior to the existence of this definitive pharmacogenomic test, oncologists would rarely tell families that there is a zero percent for their child. Implementing this test as a standard of care would definitely change current practice.

> *"So, one of the weaknesses would be my confidence in the reliability of the test. That would sway my presentation. So, if I could say categorically that your child has a very bad disease, and the information that I have now says its fatal, anything that we try will not change your child's out come*"

Pediatric oncologists deemed that they would feel more comfortable involving palliative care if they had evidence from a well validated pharmacogenomic test that administering any kind of treatment would negatively impact their patient and cause harm. During the deliberation, pediatric oncologists admitted that having a valid test would provide them with more confidence in diagnosis and give a greater sense of credence in the cessation of treatment and streamlining patients with the mutation placing them in the subset of patients with terminal pediatric HGA into palliative care. Contrary to this, palliative care physicians and nurses felt that this novel pharmacogenomic test stratifying pediatric

HGA patients into terminally ill and not terminally ill subsets would not affect their current practice in any way.

iv. Conflicting Cultures of Care

The palliative care team believed that their colleagues often fail to understand what palliative care is and the role they can play in a patient's treatment. There was a distinct consensus that many physicians outside of palliative care viewed palliation an absolute last resort and generally possess a *"black and white mentality*" when it comes to integrating palliation. Often times, the palliative care team felt that they are called in too late and are forced to 'pick up the pieces'. This is perceived as being both physically and psychologically detrimental to the patient and their families. The palliative care team is aware of the 'cure complex' that exists in modern medicine – many continue to administer futile treatment for they are "not ready to stop yet" and are inclined to believe that the oncology team fails to send their patients to palliative care because they refuse to allow the patient and their parents to lose hope.

> *"[An] attitude change is needed to stop seeing palliative care as the absolute end of the line when there is absolutely nothing else they could possibly throw at that child.*"

The oncologists and other allied health professionals on the oncology team also recognized and reflected upon the fact that their medical training was extremely cure-centered. They expressed that they found it difficult to tell a family that treatment is futile and their child should be moved into palliative care.

"[When] the oncology team gets to the realization that it's time to call palliative care they're very happy to include you, but some of the conversations that go on [during rounds]…. people are raising palliative care months and months before the team gets to the place where they think it's appropriate to call you. I just wonder if there's some missed opportunity"

"*Several staff people, say "Oh no, I'm not calling palliative care because we still have other stuff to do".*

"So… it's not, now speaking as a physician, [dealing with terminally ill patient] is not a skill that is addressed, not in your training, because as you're training it's cure, cure, cure."

The palliative care team also made it evident that when other colleagues disclose that '*there is no more hope [for a cure]*' it can be detrimental to their practice. Instead of being the '*last resort'* for most oncologists, palliative care physicians saw the potential benefit in meeting with patients and their families early on in a patient's treatment, in the same capacity as meeting with the psychologist or social worker.

B. MINOR THEMES

The four major themes listed above were elicited from the transcriptions of all three deliberative consultations. Over the course of the three deliberative democratic forums, there were also many concerns presented surrounding the existence of practical obstacles that must be addressed prior to implementation of the novel pharmacogenomic test in pediatric oncology. Below is a brief summary of specific barriers that were perceived to be particularly relevant to incorporating this novel test as a standard of care.

i. Preventing Abandonment: Need for Training

Feelings of abandonment experienced by both terminally ill oncology patients, and their families, was seen by some members of the oncology team as one of the primary barriers to providing adequate care for patients receiving terminal diagnosis. These oncologists recognized that terminally ill children and their families experiencing abandonment could impact the patient's quality of life. Diagnosing a child positive for the K27 mutation would be especially difficult because it would immediately funnel them into palliative treatment, there was persistent agreement amongst the oncologists that further training would be required to have these conversations.

> *"I think there are advantages, but there are disadvantages if you don't know how to have those conversations, in terms the harms that you can do also in having those conversations. So, I think the point that you made in having the support or the training continuously, I mean over the years you get some, but I think it's something that you need on a continuous basis because it's not easy to have those conversations, you don't have them all the time."*

Factors that were seen as contributing to feelings of abandonment in terminal patients and their families include: a terminally ill patient being seen last because their conversation will be longer, members of the health care team feeling that they must be more present for the children receiving the aggressive treatment (because of allergic reactions or they're getting sick) and families often not knowing who they will be seeing or who they should direct questions to when they come for appointments in the hospital. Pediatric oncologists and nurses generally acknowledged that terminally ill patients "*slip through*

the cracks" as a product of not necessarily being "*attached to a team*".

> *"I also find that these families are, because the follow-ups and the treatments and all that, being cared with kids that are getting cured actively, they kind of feel abandoned."*

Other allied members of the pediatric oncology team agreed and found that the perceptions of feelings of abandonment in patients were founded and generally based in a lack of patient ownership and failure to provide adequate support or integrate palliative care.

> *"And the parents do feel [abandoned], they come into clinic and they're expecting to see one and they're not sure who is going to come today and it also depends, you know is it the question for neurosurgery and they get all mixed up and... They don't know who to call. "*

A proposed means of overcoming was to make these terminally ill patients being streamlined into palliative care feel less different (more similar) to children and families who are receiving treatment. It would also be of benefit to involve the palliative care team at the start of care of all patients to act as a resource for support and to help with symptom control. This will prevent the isolation of families with terminally ill children.

ii. Maintaining Hope

Maintaining hope in a patient with a terminal diagnosis, as opposed to 'giving up', was

seen as a prominent psychological barrier for patients and their families that could impede on the smooth implementation of the pharmacogenomic test as a standard of care. Maintaining hope was seen as a crucial means of preventing the terminally ill patient and their families from experiencing feelings of abandonment and working towards maintaining an optimal and realistic quality of life for the patient in palliative care.

It was found by both palliative care professionals and members of the oncology team that despite the fact that curative therapies are no longer a viable treatment option for these patients, working towards maintain a sense of hope, through communicating that the child would still receive the very best care, was critical.

iii. Providing Support for other Healthcare Professionals

The palliative care team recognizes that at times it can be difficult for their colleagues to see value in palliative care because they are hesitant to 'give up', this was attributed to the cure-centric culture of pediatric oncology.

> *"As a general rule, then you can argue with me, when any child presents to [pediatric oncology], your goal is cure. Which is slightly different for adults, with physicians who care for adults the goal might be prolongation of life, but no expectation of cure"*

Palliative care physicians and nurses came to a general consensus that an important aspect of their role in palliative care was providing adequate communication, as well as support, for their colleagues in other disciplines when with difficult, often terminal,

situations.

iv. Media as a Barrier

The media portrays that there is always a cure and often this conflicts with information from healthcare professionals, especially when relaying a terminal diagnosis.

> *"The television suggests we've got cures for everything, [patients] have gone on to the internet that says get into that solar box, and you'll be fine. You know, there's a lot of conflicting information, some of which is unadulterated nonsense, but still... When you're faced with no chance, or the internet says there is a chance, how can you not go with that."*

Adequate communication of a terminal diagnosis as a product of this pharmacogenomic test is exceptionally important, being able to relay the certainty of the test to a patient and their family was communally agreed as being extremely crucial to its applicability in clinical care. Healthcare professionals all agreed that these conversations must be developed in a way that clearly establishes the lack of curative treatment and prevents families from taking their child elsewhere to receive harmful, futile treatment with high morbidity from another institution.

C. Deliberants Conclusions on PGx Implementation

A further objective of employing the use of deliberative stakeholder consultations to address barriers, as perceived by stakeholders, surrounding the implementation of this

pharmacogenomic test in care is to identify both points of agreement and persistent disagreement amongst participants.

i. Major Points of Convergence

Products of the deliberative forum included two major points of consensus amongst the palliative care team and medical professionals working in pediatric oncology regarding the implementation of this novel pharmacogenomic test in clinical practice as a standard of care. The first aspect of overall agreement amongst all stakeholders was the importance of communication with the patients testing positive for the K27 mutation and their families when delivering the terminal diagnosis. It was deemed by all stakeholders that the difficult conversations and must be conducted carefully, in a way that both a patient and their family could work to grasp the validity of the diagnosis and accept palliation. There was also unanimous agreement that patient's and their families would not be generally accepting of the diagnosis initially, but overtime come to terms with it if the conversation held appropriately.

The second point of agreement surrounded changing the involvement of the palliative care team; unanimous consensus amongst stakeholders elicited the conclusion that the point of integration of palliative care should be much earlier than is current practice. Early integration of the pediatric palliative care team was seen as being crucial facet of facilitating the transition of a newly diagnosed patient with a terminal illness into palliation without receiving any form of curative treatment.

ii. Major Points of Disagreement

One of the most evident points of disagreement between the two stakeholder groups was the culture of care that existed within each practice. It was clearly evident that members of pediatric oncology held a very 'cure-centric' approach to medicine, whereas medical processionals working in palliative care assumed a much less imposing position. Pediatric oncologists acknowledged that their medical training had given them a focus centred on curing patients. In comparison to this, members of the pediatric palliative care team agreed that oncology should be cure focused but constantly reiterated pediatric oncologists often fail to be cognizant of the harm incurred by patients during 'last ditch' curative efforts.

A further point of contention that arose during the deliberative process was the potential for the pharmacogenomic test to impact practice. Palliative care physicians universally agreed that the implementation of this test as a standard of care would not change their work in any way; the fact that a terminal diagnosis was delivered as a product of a pharmacogenomic test was not an issue for them.

This was opposed to the unanimous view held by all members of the oncology team that the test would drastically impact their medical practice. Pediatric oncologists deemed that they would be exponentially more comfortable forgoing 'curative' treatments if there was validated evidence that administering such therapy was harmful.

iii. Deliberative Output

The existence of distinct points of consensus and the acknowledgement of barriers to implementation, regarding the use of the novel pharmacogenomic test in clinical care promoted the development of a feasible intervention that would address relevant stakeholder concerns. The development of this intervention was considered the *deliberative output* and was reached during the third deliberative stakeholder forum; this included the development of recommendations defining how the intervention should be carried out.

The question addressed in the final large group deliberation was as follows: "How can palliative care and oncology be better integrated into the care of all families with HGA so that the result of the pharmacogenomic test informs optimal active, albeit not curative, care?" The collective group, comprised of 9 members of the palliative care team and 2 from pediatric oncology, reached a conclusion that both teams must work together more cohesively to deliver better care for patients who will receive a terminal diagnosis as a product of the pharmacogenomic test. Both stakeholder groups agreed that communication regarding patient clinical care and treatment strategies was an extremely important facet of delivering a high standard of care.

The group mutually agreed that it would be best practice for these terminally ill pediatric patients with HGA be streamlined into palliation. There was also recognition from both

those in pediatric palliative care and members of the oncology team that these patients often feel abandoned and framed their treatment as "a little bit of a black hole" for they are not active patients in oncology. It was also established that these terminally ill patients are often unknown to the oncologists because they are not in active treatment, and can frequently be glossed over or forgotten during clinic. This was viewed as an active contributor to the patient's experience of abandonment. To fill this clear void, and prevent further feelings of abandonment, it was specifically decided that the palliative care team would be integrated at an earlier stage and the treatment of these terminally patients would be followed more closely by both teams.

> *"One of things that we've been trying to advocate for, is to have it earlier introduction and involvement with families and it would be best at the time of diagnosis to be considered, not offered to the families, this is part of our care team, this is part of the care we offer and it's considered standard, is to have palliative care there, along with social worker, psychology and child life, nothing to be ... but from the very get go*"

> *"In the end, the families may want to talk to the oncologists again, who knows. So we want to be embedded in a clinic, where they wouldn't feel as outsiders.*"

Deliberants discussed the means in which the early integration of palliation could occur and how these patients could be more closely followed. A solution was found, it was agreed that a representative from palliative care would attend a weekly pre-clinic with the oncology team. This representative of the palliative team would be responsible for attending the oncology pre-clinics every week, to both represent the team palliation expert and act as a constant resource for both the palliative care team and the medical professionals working in oncology. It was also decided that the representative would be

responsible for flagging the charts of the most relevant patients for that week, and present them for review during pre-clinic. Participants acknowledged that pediatric oncologists, along with those working on the oncology floor, are often quite busy. Having an individual representing palliative care at each weekly the pre-clinic meeting will prevent the palliative care team from placing undue burden on the oncologists, as their representative at the pre-clinic will act as their initial point of contact. This is projected to optimistically facilitate the streamlining of patients testing positive for the K27 mutation using the novel pharmacogenomic test from oncology into palliative care.

The heterogeneous pre-clinic team, comprised of palliative care and oncology team members, would together decide the subsequent care pathway for the patient and determine which members of the healthcare team the patient and their family would see that week. This would promote the early integration of palliation and allow the palliative team to then prioritize these patients and give them the "time, energy, the motivation" that they deserve. The presence of the palliative care representative in the oncology pre-clinic was seen by all deliberants as a feasible solution to the acknowledged gap in care and would ensure optimal palliative care is delivered to these terminally ill patients with pediatric HGA.

D. Quantitative Results

i. Assessment of Questionnaire

The first three survey questions demonstrate that the opinions of all stakeholders during

each deliberation were respected during all deliberations (9.7, SD:0.75, Table 1), the facilitator actively listened to participants during the deliberation (9.8, SD:0.42, Table 1) and the process of reaching a group consensus was fair (9.7, SD:0.68, Table 1); thus consolidating the qualitative findings that deliberation was evident during the consultations. There was consensus by all participants that their opinions were respected by others in the group and the underlying process of reaching a group consensus on how to address the implementation of this novel pharmacogenomic test in to clinical care was fair. The summary of all survey results can be found in Table 1.

The results from the DeVries tool also corroborated the qualitative results that deliberation occurred. All stakeholders participating in the deliberative process completed this self-reported evaluation, it provided distinct evidence that productive discussion amongst all stakeholders occurred and provided quantitative evidence of deliberation during all three consultations.

ii. Summary Table

Table 1. Evaluation of the Democratic Deliberation Session (1= Not at all, 10=Very much; N=19

Question	Session 1(N=4) Mean (SD)	Session 2(N=6) Mean (SD)	Session 3 (N=9) Mean (SD)	Total (N=19) Mean (SD)
1. Do you feel that your opinions were respected by your group?	10(0)	9(1.1)	10(0)	9.7(0.7)
2. Do you feel you were listened to by your facilitator?	10(0)	9.3(0.5)	10(0)	9.8(0.4)
3. Do you feel that the process that led to your group's discussion was fair?	10(0)	8.8(0.7)	10(0)	9.7(0.7)
4. How willing are you to abide by the group's final position, even if you personally have a different view?	9.5(1)	8.2(1.9)	9.1(1.4)	9.0(1.4)
5. How helpful did you find each of the following? a. Question and answer interaction with the experts? b. The formal presentations given by the experts? c. Discussing the issues with other participants?	 9.5(0.6) 10(0) 10(0)	 7.4(0.9) 7.3(0.6) 7.5(2.3)	 9.1(0.9) 8.8(1.9) 9.6(0.7)	 8.8(1.6) 9.1(1.7) 9.1(1.7)
6. How much did attending the session change your *understanding* about the use of this new pharmacogenomic test in pediatric oncology?	1.75(1.5)	6.8(1.1)	7(2)	5.3(2.8)
7. How much did attending the session change your opinion about the use of this new pharmacogenomic test in pediatric oncology?	3.0(2.3)	5.4(2.2)	7.1(2.1)	5.4(2.7)

V. DISCUSSION

We found four major themes related to the implementation of a novel pharmacogenomic test into pediatric oncology as a standard of care, these include: the role of palliative care, communication, the perceived impact of the test and the existence of conflicting cultures of care. Further themes that emerged as potential barriers to the implementation of this test included: potential for abandonment, maintaining hope, providing inter-professional support and the media. Points of agreement and disagreement that were a product of the deliberation were also identified; areas of convergence between stakeholder groups included earlier integration of palliative care and the inordinate need for adequate communication of results. At the end of the final group deliberative consultation there were still points of divergence between stakeholder groups, these included differing approaches to administering medicine and dissimilar views on how the test would impact clinical practice. Based on the established difficulty of delivering a terminal diagnosis, it was surprising to find that some of the more prominent barriers of implementing this test surrounded the perceived clinical impact of this test and the varying "cultures of care" evident amongst healthcare professionals and not necessarily the established barrier of communication found in the literature (Meyer et al, 2006).

The progression of medicine, from the age of naturalism to the modern day, has primarily been fuelled by the acquisition of knowledge. Present day medical practice is based in the development of evidence-based medicine and the deliverance of personalized, patient-centered care. A realized effect of the modern medical landscape is the rapid advancement of genomic medicine; the implementation of novel genomic tests into

clinical care, founded on validated research, must be fully evaluated prior to integration into practice (Kumar 2007). The novel pharmacogenomic test addressed in this study posed unique barriers because it applies to an extremely vulnerable pediatric population and involves the collaboration of two medical disciplines. This thesis brings to light varying issues that result from delivering a terminal diagnosis via a pharmacogenomic test in a pediatric population.

The test is designed to identify pediatric oncology patients with HGA who will not be responsive to available therapy, thus they should be streamlined into palliative care. It was evident that there were pre-existing points of contention between the palliative care team and those that work in pediatric oncology, this made the proposed integration of a personalized medical test as a standard of care more complicated than anticipated. The deliberative process elicited great insight into the professional relationship between the pediatric oncology and the palliative care teams at Montreal Children's Hospital. It was found that communication or coordination between the stakeholders groups is often an obstacle; this may be a product of differing "cultures of care". Here, we define a "culture of care" as a distinguishing set of beliefs and behaviour that works to inform practice specific to the intention of medical treatment being administered to patients. We found that the "culture of care" varied amongst the two medical specialties of palliative care and oncology. The existence of unique "cultures of care" likely promotes the development of better technical care in each respective medical discipline; however, the integration of the two specialties needs to be carefully mitigated to ensure that optimal patient management.

The deliberative process elicited that the "culture of care" associated with pediatric oncology is generally cure-centric, whereas the culture of care of palliation surrounds optimizing a patient's quality of life and pain management. Though both disciplines seek to provide optimal patient care, it is evident that pediatric oncology exhibits medical heroism that is characteristic of medical modernity, in that pediatric oncologists often grasp on to the "sliver of hope" through prescribing harsh intensive treatment for children with pediatric HGA (Staffen 1994). In the light of medical modernity, this can be seen as a product of modern day death-averse culture and medical heroism. Death has been increasingly medicalized (Clark, 2002), medical professionals often implicitly perceive death as a 'failure' – this may be a prominent force driving pediatric oncologists to administer intensive therapies for pediatric HGA patients who have a poor prognosis. The novel pharmacogenomic test has validated that administering current blanket treatments actually invoke harm upon 20% of HGA patients, thus attempt at administering curative treatment would, in fact, cause more harm than good. It was recognized by both palliative care physicians and pediatric oncologists, that in light of this new information and the potential use of this test as a standard of care, the best course of action for these patients would be to streamline them into palliation at the point of diagnosis.

In addition to the established barrier of communication of genetic results, through the deliberative process it was made evident that conflicting cultures of care were a root aspect of the perceived obstacles associated with the implementation of this novel pharmacogenomic test in pediatric oncology. A multitude of barriers surrounding the

implementation of this novel pharmacogenomic test were acknowledged by both stakeholders from pediatric oncology and those in palliative care, yet it appears that the cure-centric attitudes found in pediatric oncology was the primary factor inhibiting the development of treatment strategies for a terminally ill patient. Discussion during the deliberative forum elicited that the cure-centric goals of pediatric oncology often promote the incorrect prolongation of curative therapy and prevent the integration of palliative care at an appropriate time during treatment. It was inferred that the improper prolongation of curative treatment could often be a decision of the lead pediatric oncologist. This could, in part, be a product of the negative connotation of "giving up" associated with the introduction of palliative care and the perceived notion that the move towards palliation was viewed as physician failure. The act of involving palliative care was nuanced during deliberation; all stakeholders viewed the improper prolongation of harsh therapies as a prominent problem and acknowledged that the introduction of palliation often holds a negative connation within the medical community. This is consistent with current death averse culture and curative focus of medicine present in modern day (Billings & Block 1997; Ferrell et al, 2000; Moon 2008; Ariès 1975). Personalized medicine cannot be adequately implemented until stakeholders from both disciplines can develop common objectives, to ensure optimal patient management. We propose that cultivating a singular culture of care between two disciplines, for example, by defining a common goal such as explicitly providing optimal treatment strategies while being conscious of potential harm of aggressive end of life treatment. If conflicting cultures exist between pediatric oncology and pediatric palliative care persists, it is unlikely that the novel pharmacogenomic test will be used to its full potential.

A further finding regarding the integration of this pharmacogenomic test into clinical care was the professed impact it would have on practice, as perceived by individual stakeholders. It was apparent that pediatric oncology felt that this test would definitely change their practice, as it would prevent their apparent hesitation in moving a pediatric patient into palliative care, and would provide definitive evidence that any attempt at curative treatment would cause more harm than good. Contrary to pediatric oncologists, palliative care physician felt that this test would not change their practice. This can be seen as a product of clashing "cultures of care". This test will effectively shift the curative focus of pediatric oncology to be in favour of palliation, which would work to optimize a child's quality of life. Employing validated evidence-based medicine, such as this pharmacogenomic test, works to promote patient experience during personalized treatment (Kumar 2007).

The deliberative process promoted the identification of barriers that would specifically inhibit the implementation of this novel pharmacogenomic test as a means of delivering a terminal diagnosis, these included: the development feelings of abandonment in patients, established difficulties associated with maintaining hope and the lack of adequate training for medical professionals working in oncology in delivering this type of terminal diagnosis. Another facet of integrating this test into care elicited during deliberation was the effective power dynamic evidence between the two stakeholder groups. Pediatric oncologists effectively hold some magnitude of power over those in palliative care because they ultimately decide at what point palliative care is first brought in to consult

with a patient and their family. Power differential is a known barrier to integrating new technology into clinical care (Goodyear-Smith & Buetow 2001). Though stakeholders may not have been entirely self-aware of this aspect of their professional relationship, the deliberative output innately addressed this problem. The suggested solution of the presence of a palliative care representative during the weekly pediatric oncology pre-clinic meetings will work to mitigate the evident power differential and work to integrate their professional opinion as to when palliation should be initiated for each patient.

Pediatric oncologists also readily recognized the media as a prominent impediment to integrating this novel pharmacogenomic test as a standard of care. Stakeholders observed that the Internet and television often suggest that there is a cure for everything, the media is known as being responsible for societal optimism towards finding successful curative treatment (Fishman 2010). This is an obvious projection of the death-averse culture evident in modern medicine. Communication is an established barrier that exists when implementing novel genomic medicine into clinical practice (Meyer et al, 2006). Healthcare professionals noted communication as being a means of addressing this barrier; adequately communicating the results of this novel test was seen as being able to negate the acquisition of misinformation via the media.

A. PRACTICE IMPLICATIONS

A productive solution was reached during the deliberation that will have tangible implications in practice if implemented. There was general consensus amongst stakeholders that a conducting joint pre-clinic rounds will work to develop a communal

culture of care and help provide optimal treatment for pediatric patient's testing positive for the terminal K27 mutation. This joint clinic will emphasize the early integration of palliative care and the adequate communication of the terminal diagnosis to both the patient and their family. Though this solution appears to be viable in practice, an evaluation of relevant policy is required to contextualize the realistic feasibility of integrating a novel pharmacogenomic test into clinical pediatric oncology.

B. Policy Implications

Here we present an overview of current policy related to the application of genomic testing in clinical pediatrics. The Canadian College of Medical Geneticists (CCMG) and the Canadian Pediatric Society (CPS) last issued conjoined guidelines that regulate the use of genetic testing in children in 2003. Recently, a proposal presented by Zawati et al (2014) was approved by the CCMG; they recommended using a principlism-based approach to guide the application of genome sequencing in a clinical pediatric setting. The recommendations conveyed that the use of genomic in children should be driven by the best interest of the child and that the child's views must be solicited and given adequate weight based on the child's maturity. It was also recommended that clinically significant conditions, which are actionable in childhood, must be reported to the child's parents, they cannot refuse this information. Finally, genetic information regarding adult-onset conditions should not be communicated to the parents, unless it could prevent serious harm to their health or that of their family member, parents have a right to refuse this type of information.

National policy from the US, presented by the American College of Medical Genetics (ACMG) in 2013, addresses the use of genomic in pediatric care. The ACMG states that 56 known pathogenic variants, that are associated with medically actionable conditions, should be actively tested for and reported back to the patient, no matter what age (Green et al. 2013). The guidelines of the ACMG drastically differ from the American Academy of Pediatrics, an opposing organization that discourages predictive genetic testing of children for adult onset diseases (Clatyon 2014, Szego 2014). Once again, both statements claim that their mandate is driven by the best interest of the child, yet the two guidelines have extremely different outcomes. In 2013, the European Society of Human Genetics also published recommendations on the clinical use of genome sequencing. Though they refrained from establishing differences in the return of incidental findings in children and adults, they posited that the provider should balance the autonomy and best interest of the child, and paternal rights, along with the best interest of the family as a whole.

In Canada, newborn genetic screening currently takes place in all territories and provinces. It is considered a standard of care, and consent to such tests is implied rather than explicit. Currently, the number of disorders tested widely varies from province to province, from 5 to 38 different disorders included on the panel depending on the jurisdiction (Bombard 2014, Morrison & Dowlerl 2011). This is similar to the United States where a primary and secondary genetic panel, for 31 and 25 conditions respectively, must be conducted as they have been justified as a compulsory of protecting

a child's welfare (Goldenberg 2012).

The application of genomic testing in clinical oncology clearly holds great promise. Validated molecular tests, including DNA mutation detection, epigenetic profiling, DNA copy number variation, gene expression profiling, detection of splicing RNA forms and functional proteomics, can all work to assess various tumours and have been used to guide therapeutic decision making (Gonzalez-Agulo 2010). The caveat that comes with integrating a genomic test into clinical pediatric oncology in Canada is provincial regulation. Personalized medicine in oncology in Canadian healthcare is monitored at the provincial level, which allows provinces to develop individualized programs and policy targeting cancer control (Butts 2013). Thus, the processes that are used to evaluate the clinical validity, applicability and economic feasibility of a genomic test in each province have resulted in highly inconsistent regulation; some even provinces lack established mechanisms to review the implementation of a new genomic test (Butts 2013). Hospitals are currently under high pressure from physicians, patients and researchers to make decisions regarding the implementation of new genetic tests; there has been a substantial push for the development of independent in-house review processes at the institutional level. There is a clear lack in Canadian policy in this area, and associations including the Canadian Standards Association and the National Standards Committee of the Canadian Association of Pathologists, need to work together to develop a pan-Canadian framework and create an overarching process that standardizes the regulation process of genomic tests in pediatrics (Butts 2013). Due to the clear lack in policy surrounding personalized medicine in pediatric oncology, any push to implement novel genomic or

pharmacogenomic tests into clinical pediatric care must be thoroughly investigated and nuanced. This project reveals that not only is it important to address communication barriers when implementing a novel technology in to clinical practice, but it distinctly shows the implementation of technology that will impact multiple medical disciplines with differing "cultures of care" must be carefully evaluated.

C. Strengths & Limitations

The strength of employing deliberative stakeholder consultations to evaluate the prospective barriers to implementing this novel pharmacogenomic test, as a standard of care in pediatric oncology, is that it provides an equitable arena that promotes the identification and resolution to perceived barriers through productive discussion amongst relevant stakeholders. This methodology is appropriate to address translational science for it promotes the documentation of barriers that may not be evident in the literature and minimizes researcher bias.

One of the major limitations of using deliberative stakeholder consultations is that the findings are not necessarily generalizable. Though the results of this study may not be generalizable to other populations, it is hoped that the framework developed can be used to address barriers associated with the integration of future genomic tests into clinical care.

VI. CONCLUSION

There are clear benefits of implementing this laboratory derived pharmacogenomic test as a standard of care in pediatric oncology, as it will reduce the occurrence of children being subjected to harmful and ineffective therapies. Despite the lack of relevant policy in Canada that addresses the medical communities movement towards personalized genomic medicine, it is essential that all relevant barriers regarding the use of this test be addressed prior to implementation to ensure optimal therapeutic benefit. This set of deliberative stakeholder consultations can been seen as successful, for it facilitated the development of a practical solution that will work to promote inter-professional collaboration between pediatric oncology and palliative care. Not only did this research generate a feasible solution to a complex health problem, but allowed for the identification of varying "cultures of care", which is a novel finding that contributes to translational science and barriers associated with the implementation of genomic testing within the context of a multidisciplinary team.

Evaluating the current policy environment with a Canadian lens, it is evident that there is a distinct need to develop an adequate cross-country methodology that will promote the development of reliable evidence-based practice recommendations for the application of genomic testing in pediatric clinical care. We propose that the methodological framework employed in this study to fill the evident need for a generalizable means of developing evidence-based policy. Not only did the deliberative process elucidate a feasible means of addressing the implementation of a novel pharmacogenomic test into care, but it shed

light on the contributing barriers that inhibit the integration of personalized medicine into practice. Future work could include an assessment of whether or not the joint-clinic intervention truly facilitated the integration of the pharmacogenomic test into clinical practice.

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APPENDIX I: INFORMATIONAL PAMPHLETS AND QUESTIONS FOR DELIBERATION

A. Contents of informational pamphlet provided to participants of small-group deliberative stakeholder consultation:

General Information

Personalized Medicine: Pharmacogenomic Testing in Pediatric Oncology

- Literature Review: Critical assessment of current literature concerning the use of personalized medicine, specifically pharmacgoenomic tests, in pediatric oncology
- Cancer is a multifaceted disease that is difficult to treat; traditional methods of diagnosis are not always accurate in predicting disease manifestation and drug effectiveness
- Personalized drug therapy plans can be generated using pharmacogenomic testing
- Slowly being integrated into clinical care, we have seen many obstacles: financial, patient education, policy, autonomy, data ownership etc.

New Laboratory Developed Pharmacogenomic Test

- Test can stratify pediatric patients with HGA into subgroups based on their genetic information
  - Shows high heterogeneity of disease; multiple genetic mutations are recognized as

factors contributing to disease expression

- Harsh "blanket treatments" are not effective for all types
- As many as 20% of pediatric HGA patients could be diagnosed as non-responsive to all current treatment and be moved into palliative care at diagnosis
- This is the first pharmacogenomic test to identify a terminal condition based on an individual's complete resistance to all known therapy.

Knowledge Gap & Contributions

- It is currently unknown to what extent pediatric patients with HGA, and their families, would accept limited therapy (palliation) or a de-escalation of care in exchange for a chance of an increased quality of life.
- We aim to establish the use of this novel pharmacogenomic test as a broader diagnostic treatment and management strategy
- Results of this study are expected to inform the development of communication recommendations surrounding the use of this test in clinical care

B. Questions to be addressed during small-group deliberative stakeholder consultations

- What are the points of agreement and disagreement regarding optimal strategies associated with the implementation of this laboratory derived pharmacogenomic test as a standard of care in pediatric patients with HGA?

- What is the perceived clinical relevance and cognitive impact of the generated strategy recommendations associated with the use of the laboratory derived pharmacogenomic test as a standard of care for pediatric HGA patients?

C. Contents of informational pamphlet provided to participants of final large-group deliberation stakeholder consultation:

The purpose of this project is to establish optimal communication strategies associated with the clinical use of this new laboratory developed pharmacogenomic test targeting terminal pediatric HGA.

1. Points of agreement:

   Communication is the most challenging issue but needs to be a priority.

   Patient and families need coordinated team care, especially the families with a positive test result identifying the group with no viable curative treatment.

2. Points disagreement:

   The timing, integration and role of palliative care in the treatment of patients and families with HGA, particularly for patients and families with a positive test result.

Specific topics to consider:

- Re-naming/branding of palliative care to convey better the role for symptom and pain management, as well as ensuring and maximizing quality of life.
- Minimizing the patients and families feelings of “abandonment”; lack of

"busyness" or isolation from other families.

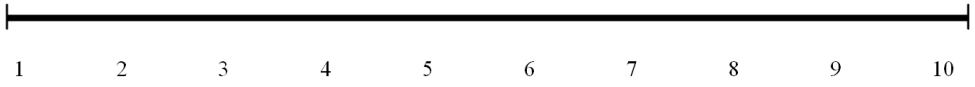
- Account for feelings of professional "failure" when no curative treatment is available and provide support to health professionals for these "difficult conversations" that may only occur rarely.

APPENDIX II: DEVRIES QUESTIONNAIRE EVALUATION OF OCCURRENCE OF DELIBERATION

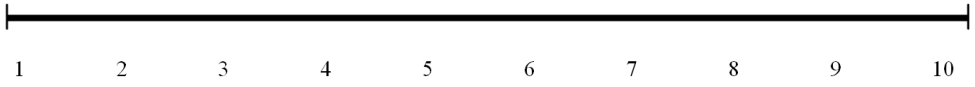
Evaluation of the Democratic Deliberation Session

Thank you for participating in this deliberative stakeholder consultation. Please answer the following questions using a 10 point scale, where 1= Not at all,
10 = Very Much.

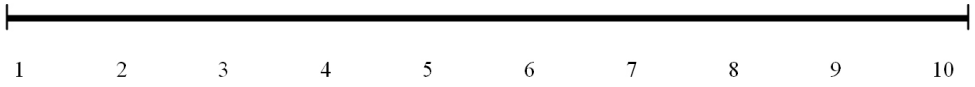
1. Do you feel that your opinions were respected by your group?



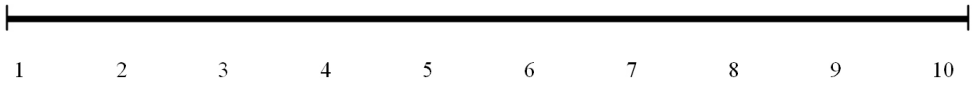
2. Do you feel you were listened to by your facilitator?



3. Do you feel that the process that led to your group's response was fair?

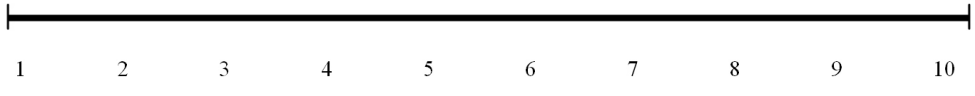


4. How willing are you to abide by the group's final position, even if you personally have a different view?

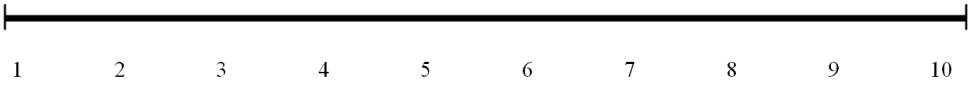


5. How helpful did you find each of the following?

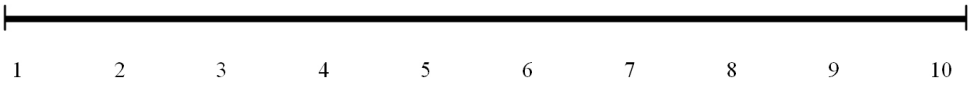
   a. Question and answer interaction with the experts?



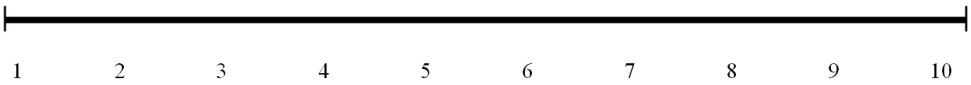
b. The formal presentations given by the experts?



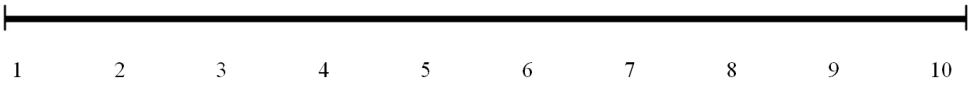
c. Discussing the issues with other participants?



6. How much did attending the session change your *understanding* about the use of this new pharmacogenomic test in pediatric oncology?



7. How much did attending the session change your *opinion* about the use of this new pharamcogenomic test in pediatric oncology?



APPENDIX III: INSTITUTIONAL ETHICS APPROVAL DOCUMENTS & CONSENT FORMS

A. Ethics Approval from Research Ethics Board at Montreal Children's Hospital

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

Montreal Children's Hospital
McGill University Health Centre

Feb. 12, 2015

Dr. N. Jabado
Hematology Department
MUHC - Montreal Children's Hospital
Room B-336

Re: MCH003-26 **Research in Pediatric Brain Disorders -** Perspectives on the Optimal Implementation Strategies for a Pharmacogenomics Test for Paediatric Glioblastoma

Dear Dr. Jabado,

We are writing in response to your correspondence requesting Research Ethics Board review of an amendment for the research study referenced above.

We are pleased to inform you that approval for the following documents was provided on Feb. 12, 2015 via expedited review and will be reported at the REB meeting on March 9, 2015:

- MUHC eReview Revision to an Approved Study form (to add a consent for health professionals and 2 questionnaires in order to determine a communication strategy for a pharmacogenomics laboratory derived test pediatric patients with HGA)
- Protocol - Stakeholder Perspectives on Communication Strategy Surrounding a Novel Pharmacogenomic Test for Pediatric Neuroblastoma: A Mixed Methods Study, (no version./date)
- Questionnaires, English version (no date)
    - Evaluation of the Democratic Deliberation Session
    - Information Assessment Method (PUSH version)
- Health professional Consent form, English version Oct. 15, 2014

Should any revision to the study, or other unanticipated development occur prior to the next required review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to REB approval for the amendment.

Sincerely,

Jane McDonald, MD
Chairperson, Research Ethics Board

Page 1 of 1

2300 rue Tupper, Montréal QC CANADA H3H 1P3 Téléphone : 514 412-4400
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B. Ethics Approval from the McGill University Institutional Review Board.

McGill

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3655 Promenade Sir William Osler #633
Montreal, QC H3G 1Y6

Faculté de médecine
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Tel/Tél: (514) 398-3124

November 25, 2014

Dr. Gillian Bartlett-Esquilant
Department of Family Medicine
5858 Cote des Neiges, Suite 300
Montreal, Quebec H3S 1Z1

RE: IRB Study Number A11-B64-14B
Perspectives on the optimal implementation strategies for a pharmacogenomics test for pediatric glioblastoma

Dear Dr. Bartlett-Esquilant,

Thank you for submitting the above-referenced study for an ethics review, on behalf of your Master's candidate, Laura Crimi.

As this study involves no more than minimal risk, and in accordance with Articles 2.9 and 6.12 of the 2nd Edition of the Canadian Tri-Council Policy Statement of Ethical Conduct for Research Involving Humans (TCPS 2) and U.S. Title 45 CFR 46, Section 110 (b), paragraph (1), we are pleased to inform you that approval for the study (November 2014) was provided by the IRB Co-Chair on November 24, 2014, valid until **November 2015**. The study proposal will be presented for corroborative approval at the next meeting of the Committee and a certification document will be issued to you at that time.

Kindly revise the contact information in the consent form to "Ilde Lepore, Ethics Officer at McGill at 514-398-8302" before initiating the study.

A review of all research involving human subjects is required on an annual basis in accord with the date of initial approval. The annual review should be submitted at least one month before **November 2015**. Please inform the IRB promptly of any modifications that may occur to the study over the next twelve months.

Sincerely,

Carolyn Ells, PhD
Co-Chair
Institutional Review Board

cc: Laura Crimi
A11-B64-14B

C. Consent Form

McGill

GE^{3}LS: Patient and Stakeholder Engagement Project

HEALTH PROFESSIONAL CONSENT FORM

Title of Research Project:	Stakeholder Perspectives on Communication Strategy Surrounding a Novel Pharmacogenomic Test for Pediatric Neuroblastoma
Principal Investigator:	Gillian Bartlett, Associate Professor, Department of Family Medicine, McGill University
Co-investigators:	Dr. Nada Jabado, Department of Pediatrics, Montreal Children's Hospital, Montreal, QC Dr. Peter Nugus, Assistant Professor, Department of Family Medicine, McGill University Laura Crimi, MSc Candidate Department of Family Medicine, McGill University
Institution:	McGill University
Project sponsored by:	Genome Canada, CIHR, Genome Quebec

RESEARCH PROJECT DESCRIPTION

A new personalized medical treatment for pediatric oncology patients has been developed at Montreal Children's Hospital and may become the new standard is pediatric high-grade astrocytoma (HGA). HGA is the leading cause of death in children under the age of 20. This type of cancer affects 500 children and young adults every year; 90% of them die within the first 3 years of diagnosis.

HGA patients typically undergo aggressive treatment, including brain resection and full brain radiation therapy, both of which are linked to a low quality of life and a high morbidity. Pediatric HGA is currently incurable and are often located in such a way to make surgical removal of the tumour impossible. As current treatment only provides a very short increase in survival for these patients, significant work has been done to increase the etiology, biologic and genomic understanding, particularly the genomic composition of the tumour. With genotyping, it has been shown that HGA is a heterogeneous disease with several different genetic mutations that can contribute to the expression of HGA. For a subset of patients with a specific genetic variation in the tumour, there is no current oncologic treatment option that has any impact on the tumour. A pharmacogenomic laboratory derived test is being developed which can be used genotype distinct mutations in the tumour and identify this specific mutation that occurs in ~20% of all pediatric HGA patients.

The introduction of this test into clinical care would help the families and health care professionals determine a treatment strategy that would optimize survival and health related quality of life for the pediatric patients. For the group with the mutation that is resistant to current treatment options (including therapies currently in Phase III clinical trials), this would result in the introduction of palliative care at diagnosis.

What is currently unknown is what information is needed regarding the test results and how this should be communicated to the children and their families to ensure that the de-escalation of therapy and introduction of palliative care is seen as an acceptable course for pediatric HGA patients.

You have been identified as a health professional working at Montreal Children's Hospital who may be implicated by the implementation of the test. You are being invited to participate in this study

conducted by researchers from McGill University to help us determine the communication needs around the integration of this new pharmacogenomics test as a standard of care for pediatric patients with HGA.

Consent to participate in the deliberative stakeholder consultation regarding the use of anew pharmacogenomic laboratory derived test in pediatric HGA.

If you agree to participate, you will be asked to attend a half-day deliberative stakeholder consultation session. An expert panel will begin the session by presenting relevant information about the test and current standards of clinical care. Following the expert panel there will be an open question period. After the open question period, there will be small-group discussions that will last approximately 1.5 hours. The conclusions of the small group discussions will be discussed in a final large-group sessions (1 hour).

The study will happen at the Montreal Children's Hospital. We anticipate that a total of 15-20 participants, including: pediatric oncologists, pediatric palliative care physicians (and residents), clinical nurse specialist and social workers. There is no risk associated with participation in this study.

Consent to participating in the evaluation of two different surveys

If you agree to participate, you will be asked to answer two short questionnaires during the deliberative consultation, which are aimed at evaluating the success of the deliberations and the cognitive impact of implementing this pharmacogenomics test as a new standard of care in paediatric oncology. The questionnaires will be given at the conclusion of the expert panel and at the end of the deliberations, the questionnaires will take no more than 5 minutes.

Participant's rights

Your participation is completely free and voluntary. Your decision to participate or not to participate will have no adverse effect on your employment with the hospital or university. You may take the time necessary to reflect on your decision and discuss your participation in the project with persons close to you before giving us your answer. You are free to withdraw from the study at any time.

If you have any questions regarding your rights as a research participant, you may contact any member of the research team.

Confidentiality and anonymity of patients and physicians

Only Dr. Gillian Bartlett will have access to participants' identification. Information gathered will remain strictly confidential and will only by used for this project. No individual data shall be divulged in the course or subsequent reporting of the results of the research in order to insure confidentiality of physicians and other healthcare professionals.

Consent statement and signatures

I have familiarized myself with the consent form and have received a copy. I have had the opportunity to ask questions that have been answered. Upon reflection, I agree to participate in this research project.

This consent is valid until _____. This consent is strictly voluntary and will cease to take effect if I decide to withdraw from the study by advising a member of the research team. I do not waive my legal rights by signing this consent form.

Health Professional's Signature	Date
Health Professional's Name (please print)	
Principal Investigator's Signature	Date

The research project was approved by the Institutional Review Board of McGill University on

APPENDIX IV: CONCEPTUAL FRAMEWORK