CNS Tumours: Exploring Barriers to Registration and Feasibility of Extracting Molecular Characteristics

by

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Abstract

Two concerns regarding the collection of data for brain and other central nervous system (CNS) tumours in Canada are under-reporting of non-malignant tumours and the need for improved reporting of clinically relevant molecular information. The first part of our study, addressing under-reporting, has two objectives: 1) evaluate the impact linkage with hospital discharge, as recorded in Discharge Abstract Database (DAD), has on supplementing case ascertainment for brain tumours, and 2) identify potential barriers for initial registration in the Alberta Cancer Registry (ACR).

Information for all patients with a brain tumour diagnosed and residing in Alberta between 2010 and 2015 were extracted from the ACR. Descriptive statistics were compiled by behaviour and type of registration (originally registered or identified through DAD review). The age-standardized incidence rates and number of cases (observed vs expected) in Alberta were compared to the United States. Phi coefficients (as a measure of correlation) and chi-square tests for the homogeneity of proportions were conducted to examine bivariate relationships of the characteristics of interest. Multiple logistic regression was used to summarize the independent effects on the probability of being identified through DAD review.

The results show 5% of malignant and 35% of non-malignant brain tumours were identified through DAD review. When comparing observed to expected number of non-malignant cases after DAD review, the ACR ultimately captured about 75% of those expected. Cases identified through DAD were statistically significantly ($p \leq 0.05$)

associated with patients over 75 years old at diagnosis (OR=2.5), benign behaviour (OR=2.6), location at diagnosis in Northern Alberta (OR=1.5), non-microscopically confirmed tumours (OR=1.3), no visit to a CancerControl Alberta facility (OR=8.7) and certain histological subtypes, including cranial and spinal nerve tumours (OR=1.7). Given the significant impact DAD review had on case ascertainment of non-malignant brain tumours, it is recommended that DAD review continues on an annual basis while other techniques for case ascertainment are explored. Those characteristics identified as potential barriers to registration should be investigated to further identify possible process improvements in Alberta.

The second part of our study investigates the collection of molecular data for CNS tumours in a new era of personalized patient care. The objectives for this part of the study are: 1) conduct a pilot study to explore the feasibility of electronically extracting molecular parameters for CNS tumours diagnosed in Calgary from CancerControl Alberta's Electronic Medical Record (EMR); and 2) estimate the prevalence of testing for molecular parameters by histological subtype and year of diagnosis.

Analysis involved text mining to extract molecular parameter information from the EMR for all invasive CNS cancers from 2010 to 2015 in the Calgary zone. This information was used to calculate the prevalence of availability of molecular parameter test results by histological subtypes and year of diagnosis. To assess the accuracy of the molecular data extracted, we linked cases to the physician databases and calculated percent agreement and Kappa coefficient.

The results from the pilot study support the feasibility of extracting molecular characteristics for CNS tumours electronically from the EMR. Electronic extraction had a greater chance of missing information, however when information was accessible there was a high percent agreement (~99%) with the physician database. The study also showed Isocitrate dehydrogenase (IDH) testing for gliomas, O^6-methylguanine-DNA methyltransferase (MGMT) testing for glioblastomas, loss of heterozygosity of 1p/19q testing for oligodendroglial tumours, and Alpha Thalassemia/Mental Retardation Syndrome X-linked (ATRX) testing for glioblastomas and astrocytic tumours have varied from 2010 to 2015. However, all four biomarkers had over 75% of relevant subtypes with a test result available in the EMR in 2015. These results support the need to formally collect this information with the possibility of using electronic extraction as a feasible solution to decrease workload.

Preface

This thesis is an original work by Angela C Eckstrand. The research project, of which this thesis is a part, received research ethics approval from Health Research Ethics Board of Alberta, Cancer Committee, Project Name “CNS Tumours: exploring barriers to registration and feasibility of extracting molecular characteristics”, Study Id: HREBA.CC-16-0974, January 5, 2017. A modification to the study, Study Id: HREBA.CC-16-0974_MOD1, was approved on July 20, 2017 and a renewal to the research, Study Id: HREBA.CC-16-0974_REN1, was granted December 17, 2017. No part of this thesis has been previously published.

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List of Acronyms and Abbreviations

ACR	Alberta Cancer Registry
AHS	Alberta Health Services
ATRX	Alpha Thalassemia/Mental Retardation Syndrome X-linked
CBTRUS	Central Brain Tumor Registry of the United States
CAP	College of American Pathologists
CCCR	Canadian Council of Cancer Registries
CIHI	Canadian Institute for Health Information
C-MORE	Cancer Measurement Outcomes Research and Evaluation
CNS	Central Nervous System
CPAC	Canadian Partnership Against Cancer
CT	Computed tomography scan
DAD	Discharge Abstract Database
EMR	Electronic Medical Record
IDH	Isocitrate dehydrogenase
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
MGMT	O^6-methylguanine-DNA methyltransferase
MRI	Magnetic resonance imaging
NAACCR	North American Association of Central Cancer Registries
PCV	Procarbazine-CCNU-vincristine chemotherapy drugs
SEER	Surveillance, Epidemiology and End Results Program
ULI	Unique Lifetime Identifier
WHO	World Health Organization

Chapter 1 Introduction

1.1 Thesis Statement

This thesis will evaluate the completeness of case ascertainment of primary brain tumours in the Alberta Cancer Registry (ACR) by determining the impact hospital discharge data has on case ascertainment. We will look at the distribution of cases by behaviour and type of registration (originally registered or initially missing registration but identified through a review of hospital administrative data, Discharge Abstract Database (DAD)). Barriers to initial registration will also be identified by looking at the difference in characteristics between those originally registered and those identified through DAD review.

A pilot study will also be conducted to look at the feasibility of extracting molecular characteristics of brain and other central nervous system (CNS) tumours from CancerControl Alberta's - Electronic Medical Record (EMR), ARIA MO. Using information extracted from ARIA MO, prevalence of molecular parameters by histological subtype and year of diagnosis will be reported to estimate current testing practices in Alberta.

1.2 Background

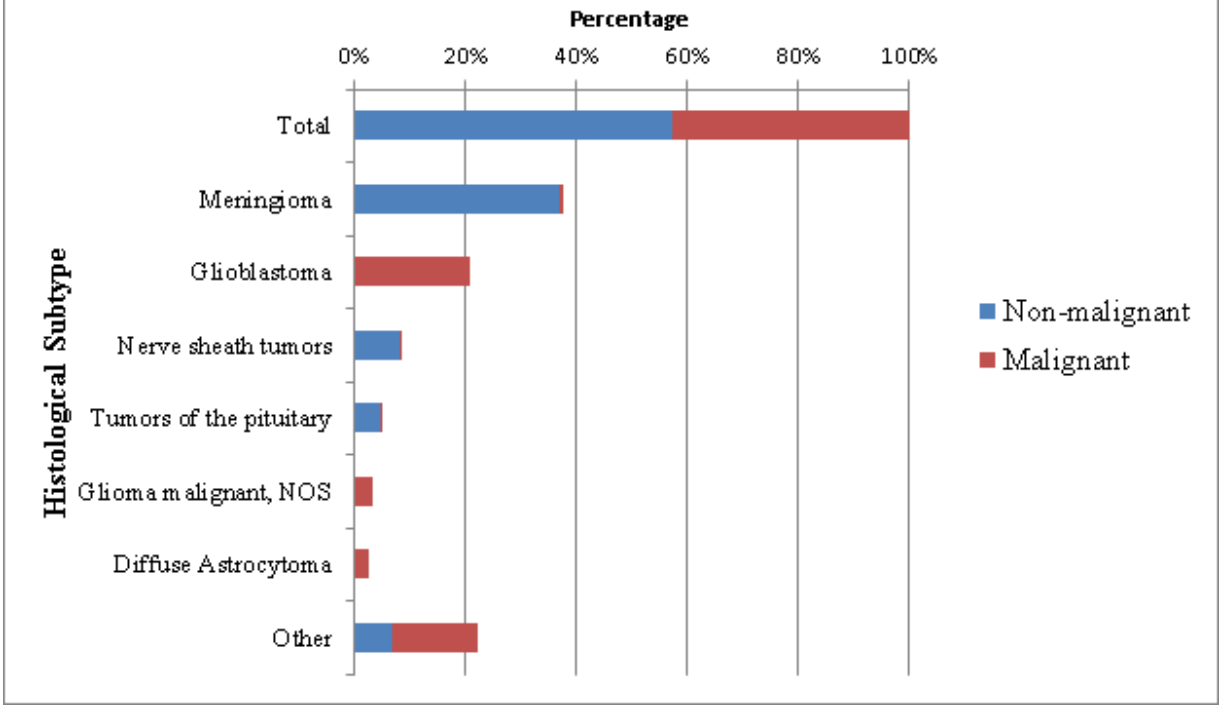
1.2.1 Epidemiology of brain tumours

Brain tumors only account for about 2% of all primary cancers in Canada, however, they have a substantial impact on patients and health care systems due to poor prognosis (Davis, Nagamuthu, Ross, & Megyesi, 2015; Yuan et al., 2016). Although rare in adults, CNS tumours are one of the most commonly diagnosed cancers in children. In Alberta, CNS tumours accounted for 21% of cancer cases for children (ages 0-14) diagnosed 2010 to 2014 and 40% of cancer deaths in the same period (Surveillance & Reporting, 2017). Given the vital functions of the brain, these tumours can drastically impact an individual's quality of life, affecting both physical and cognitive capabilities (Brain Tumour Foundation of Canada, 2017a). Public Health Agency of

Canada (2014) estimates the total national cost, including both direct (drug, hospital and physician care) and indirect (mortality), of brain cancer to be $125,308,100 in 2008. In comparison the total cost for colorectal cancer, which has the highest total cost for a specific cancer type, is $556,334,000. To put this in perspective, the incidence rate ratio of colorectal cancer to brain cancer is approximately 7, where the cost ratio is approximately 4; this indicates that even though colorectal cancer is about 7 times more common than brain cancer, the cost of colorectal cancer to the health care system is only 4 times more. Therefore, even though rare, brain tumours have a high total cost to our health care system. Given the economic and societal impact, research providing a better understanding of the disease is essential.

Malignant brain tumours are fast growing with poorly defined borders and are able to invade adjacent tissue; where non-malignant (benign and uncertain/borderline) brain tumours are slow growing with defined borders and do not invade adjacent tissue (Brain Tumour Foundation of Canada, 2017b). The overall 5-year relative survival of brain and other central nervous system (CNS) tumours is 34.9% for malignant and 90.7% for non-malignant tumours in the United States from 2010 to 2014 (Ostrom et al., 2017). In 2015, 292 cases of malignant and 345 cases of non-malignant brain and other CNS cancers were diagnosed and residing in Alberta (Surveillance & Reporting, CancerControl Alberta, Alberta Health Services, personal communication, February 1, 2018). The most common type of brain and other CNS tumours are meningiomas which account for approximately 38% of all CNS tumours and 65% of non-malignant CNS tumours in Alberta (Figure 1). The most common type of malignant CNS tumours are glioblastomas accounting for approximately 21% of all CNS tumours and 49% of malignant tumours in Alberta. With over 120 subtypes of CNS tumours, many aspects including histological subtype, grade and patient characteristics are considered when treating the patient (Brain Tumour Foundation of Canada, 2017a). Non-malignant tumours can often be managed by observation or surgery; occasionally radiation therapy may also be recommended to stop tumour growth if tumour is inoperable or only partially removed (Brain Tumour Foundation of Canada, 2017a). Malignant brain tumours can grow quickly and tend to be more difficult to remove so often require multimodality treatment methods. Current treatment standard typically includes surgical resection to the extent feasible, followed by radiation therapy and/or chemotherapy (Stupp et al., 2005; Mason et al., 2007).

Figure 1. Distribution of brain and CNS tumours by most common histological subtypes and behaviour, 2010-2015, Alberta



Source: Surveillance & Reporting, CancerControl Alberta, Alberta Health Services, personal communication, February 1, 2018.

Even though many possible risk factors have been proposed for brain tumours, few have been confirmed (McNeill, 2016). Risk factors that have been well established are: ionizing radiation, genetic susceptibility, and allergic and immune-related conditions. Research has shown that radiation exposure for benign conditions or previous cancers can increase the risk of developing brain cancer (Canadian Cancer Society, 2017). Associations have also been made between radiation exposure from atomic bomb survivors and various brain tumours (Preston et al, 2007; Mati et al., 2006). Having a family history of brain cancer or certain inherited conditions can also increase one's risk for brain cancer, even though these are not yet well understood (Canadian Cancer Society, 2017; McNeill, 2006). Lastly, several studies have shown that allergies and autoimmune conditions have been associated with a reduced risk for glioma brain tumours (Brenner et al., 2002; Schoemaker et al., 2006; Schwartzbaum et al., 2003). Overall,

there is still much uncertainty about what causes brain and CNS tumours and more research is needed to clarify the roles other risk factors may have.

1.2.2 Case ascertainment of brain tumours

The quality of the data in Cancer Registries is of utmost importance as it is used by physicians and researchers in understanding disease burden, clinical outcomes and in evaluating trends, as well as, administratively for planning and funding. Quality is dependent on many factors including completeness, accuracy, timeliness and comparability of the data (Cancer Projections Network, 2010). Completeness of registration means that all patients in a population diagnosed with a reportable cancer are being captured in the registry. North American Association of Central Cancer Registries (NAACCR) requires Cancer Registries to have 95% or higher case ascertainment to achieve gold standard (Hofferkamp, 2008). However, NAACCR only looks at overall case ascertainment and does not account for variations based on type of tumour or behaviour. Given the ACR has received gold certification from NAACCR for the last 12 years, we expect high quality data (North American Association of Central Cancer Registries [NAACCR], 2018); however, research has raised concerns regarding the completeness of data for CNS tumours, particularly non-malignant cases, in all provinces and territories (Shaw, Woods, Semenciw, & Megyesi, 2014).

The Alberta Cancer Registry receives notifications for cancer patients independently from laboratories, physicians and vital statistics offices as mandated by the Regional Health Authorities Act - Cancer Registry Regulation (Surveillance & Reporting, 2014; Province of Alberta, 2009). Once initial information is received the registry reviews all information on the patient and if determined to meet the eligibility criteria the patient is entered into the system and transferred to a queue to be coded by trained Cancer Registrars. Coding of new cases is usually not completed until up to two years after initial diagnosis.

As both malignant and non-malignant CNS cancers can result in significant mortality and morbidity, these tumours are unique from other cancers in that benign tumours are also reportable to national and international cancer agencies. The Canadian Council of Cancer

Registries (CCCR) recommends all tumours (including benign behaviours) of meninges, brain, spinal cord, cranial nerves and other parts of central nervous system be reported to the Canadian Cancer Registry (Statistics Canada, 2017). Starting in 2007 they also recommend that benign tumours (in addition to the other behaviours already reported) of pituitary gland, craniopharyngeal duct and pineal gland also be reported. The rationale for registering benign and uncertain/borderline CNS tumours in cancer registries has been well documented with reasons for inclusion including: ambiguity of behaviour, differences in etiologies by subtypes, and prognosis being more dependent on type and location of brain tumour than behaviour (Davis, Bruner, & Surawicz, 1997). In February 2007, Bill M235 was passed by the Canadian House of Commons to initiate national standards for the surveillance of malignant and benign brain tumours (Private Members' Bill M235, 2007). However, even with CCCR's recommendations and the passing of legislation for national surveillance, there are still concerns regarding the completeness of data collection for non-malignant CNS tumours. Many European studies found issues of under-reporting of brain tumours in cancer registries, however, there is a lack of similar studies done in North America (Teppo, Pukkala, & Lehtonen, 1994; Pobereskin, 2001; Larsen et al., 2009). Shaw et al. (2014) estimates only 33% of the expected number of non-malignant CNS tumours are being reported in Canada; the expected number of cases was higher than the observed in every province, with the highest ascertainment rates occurring in Manitoba (73%) and Alberta (46%).

Previous work assessing the completeness of pediatric brain tumours in Alberta showed high case ascertainment where 96% of tumours in the physician databases were captured by the ACR (Normandeau, Mehta, Strother, Hatcher, & Davis, 2016). However, one limitation of this study was it assumed all pediatric brain tumour patients would be referred and seen by a specialized physician and therefore logged in selected pediatric physician databases in Calgary or Edmonton. As the ACR is a population-based registry, it also captures patients not seen by a specialized physician and therefore may have been overlooked in that study. The goals of this study are to further assess completeness of brain tumour data for all ages in Alberta by reviewing the impact hospital discharge data, as recorded in DAD, has in case ascertainment for both pediatric and adult populations. As identified by NAACCR, the ultimate goal for all cancer registries would be a case ascertainment of greater than 95% for all reportable tumour types and behaviours.

A study conducted in England found the following factors to be associated with registration of brain tumours: if the patient underwent surgery, received radiotherapy or was over 60 years old (Pobereskin, 2001). The largest under-reporting was for benign tumours in younger patients who did not undergo surgery. The study suggests that since these patients may likely have the best prognosis, this could have a negative influence on survival rates and caution should be used in international comparisons. In this study we also aim to identify barriers to initial registration to gain a better understanding for future case ascertainment efforts in Alberta and for other cancer registries. Identifying limitations of case ascertainment will assist health care systems, specifically cancer registries, on where to focus resources in the future. Standardized registration that ensures high case ascertainment is essential to accurately reflect clinically relevant information, such as evaluation of trends or etiological studies (Davis et al., 1997).

1.2.3 Molecular characteristics in brain tumours

Molecular parameters, also referred to as biomarkers, are measurable physiological indicators that are useful in diagnosis or predictive of treatment response or disease progression. Clinical decisions are already being guided by molecular parameters for certain subtypes of CNS tumours, while molecular research is continuing to discover and validate markers. Research is also using molecular characteristics when pursuing innovative molecular drug treatments (Idbaih, Duran-Pena, Bonnet, & Ducray, 2015). In line with this, the World Health Organization (WHO) recently published new guidelines for CNS tumours that incorporate both histology and molecular parameters in the classification system (Louis et al., 2016). Previously, diagnosis relied only on clinical, radiological and pathological features of tumours, however the new classification, which includes molecular information, is believed to provide more accurate diagnosis and less inter-observer variation by providing more biologically homogeneous and clinically relevant classifications. Molecular information helps ensure proper diagnosis, prognosis and treatment of brain cancer (Idbaih et al., 2015). This is especially true for cases with mixed histological properties, such as anaplastic oligoastrocytomas, where molecular parameters can help distinguish diagnosis and prognosis.

Recently, the CNS tumour subject matter experts in Alberta have identified the following four biomarkers to be used across the province: 1) Isocitrate dehydrogenase (IDH) mutant/wildtype, 2) O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, 3) combined loss of chromosome 1p and chromosome 19q (also known as 1p/19q co-deletion), and 4) Alpha Thalassemia/Mental Retardation Syndrome X-linked (ATRX) status. These biomarkers have been identified as they have been shown to play a role in diagnosis, treatment (predictive value) or prognosis. Predictive markers inform us about response to treatment and what outcomes can be expected based on specific interventions, where prognostic markers inform us about outcomes irrespective of treatment (Siegal, 2016). If a biomarker plays a significant role in prognosis, it is important that clinical trials take this information into account when assessing efficacy of treatments.

Biomarker testing has also been included in Alberta Health Service's (AHS) clinical practice guidelines (Alberta Health Services [AHS], 2017). The 2012 guidelines for CNS tumours, specifically recommended biomarker testing and consideration for:

1) Testing for loss of heterozygosity on chromosomes 1p and 19q for tumours with oligodendroglial characteristics to assist with diagnostic and prognostic decisions (Alberta Health Services [AHS], 2012b).
2) MGMT promoter methylation status to help determine prognosis for Glioblastoma (Alberta Health Services [AHS], 2012a).

In 2016 the guidelines were updated for low grade gliomas to include:

1) IDH and 1p/19q chromosomal loss testing was recommended for all patients with low grade glioma's (Alberta Health Services [AHS], 2016).
2) Possible addition of Procarbazine-CCNU-vincristine (PCV) chemotherapy drugs to radiation for 1p/19q co-deleted tumours based on randomized control trials for anaplastic oligodendrogliomas (AHS, 2016).

IDH mutations are a prognostic marker and have also been found to assist in diagnostic decisions (Rosenfeld, 2013). IDH mutations, especially IDH1, are useful in distinguishing gliomas from other tumour entities; IDH1 mutations occur in 70%-80% of grade II and III astocytomas, oligodendrogliomas, oligoastrocytomas and secondary glioblastomas (grade IV glioblastomas

that progressed from these lower grade tumours) (Brat et al., 2014). Glioma's with IDH mutations are also associated with a significantly better prognosis than IDH-wild type glioma's, adjusting for grade. However, even though presence of IDH1/2 mutation(s) provide a positive prognostic indicator, this has not translated into a predictive role in treatment yet (Rosenfeld, 2013). IDH mutations have also been found to be strongly associated with age (seen in younger patients) and other biomarkers (including 1p/19q co-deletion and MGMT promoter methylation mutations).

MGMT promoter methylation status can assist with diagnostic, prognostic and treatment decisions. As a diagnostic marker, MGMT promoter methylation status can help distinguish between progressions and pseudoprogressions as those with methylation are more likely to develop pseudoprogression than those without methylation in patients with glioblastomas (Brandes et al., 2008; Rosenfeld, 2013). Studies have shown glioblastomas with MGMT promoter methylation have a better overall survival, independent of treatment (Brat et al., 2014). MGMT promoter methylation has also been shown to be predictive of response to temozolomide chemotherapy in glioblastomas where MGMT promoter methylation tumours treated with radiation and chemotherapy have a better overall survival and prolonged progression-free period (Rosenfeld, 2013).

Loss of heterozygosity on 1p and 19q can assist diagnostic, prognostic and treatment decisions. Pathologists can use this information to support a diagnosis of oligodendroglioma tumours as 60%-80% have a combined loss of 1p and 19q chromosomes (Brat et al., 2014). It is also believed to be both a prognostic and predictive marker. Clinical trials have shown anaplastic oligodendroglioma and anaplastic oligoastrocytoma tumours with 1p/19q co-deletion have a better overall prognosis (Cairncross et al., 2006; van den Bent et al., 2006). It is also predictive in that anaplastic oligodendroglial tumours with 1p/19q co-deletion who receive chemotherapy early (vs radiation alone) can double median overall survival, which is not found to be the case for patients with tumours lacking 1p/19q co-deletion (Cairncross et al., 2013; Idbaih et al., 2015; Rosenfeld, 2013).

Lastly, ATRX mutations can also assist in diagnosis and have been found to be a prognostic marker. ATRX mutations are infrequent in primary Glioblastomas and oligodendrogliomas, but frequently found in grade II astrocytomas (67%), grade III astrocytomas (73%) and secondary Glioblastomas (57%) (Brat et al., 2014). ATRX and 1p/19q co-deletion status, which are almost mutually exclusive, are therefore particularly useful for distinguishing mixed gliomas, such as anaplastic oligoastrocytomas who display histological features of both astrocytic and oligodengroglial subtypes (Wiestler et al., 2013). ATRX loss is a predominant feature of astrocytic tumours, where 1p/19q co-deletion is a predominant feature of oligodendroglial tumours. This is important as a more reliable diagnosis allows clinicians to make more informed treatment and prognostic decisions. ATRX loss has also been shown to have a significantly better prognosis in astrocytic tumours (Wiestler et al., 2013).

As molecular research expands, and these characteristics become more imperative in diagnostics and individualized treatment, there is a need for clinicians, laboratories, and cancer registries to collaborate to decide how the information will be captured in the future. By looking at the feasibility of extracting molecular characteristics of CNS tumours from the EMR, we hope to provide some insight into this. We also hope to estimate current testing practices in Alberta to provide some background for future initiatives.

1.3 Why is more work required?

High quality data is essential to accurately understand disease burden and evaluate trends. Health care professionals also rely on complete and accurate data for planning and funding. If the data is incomplete health care systems cannot ensure health care dollars are prioritized where they are most needed. Completeness of Cancer Registries, in particular completeness by tumour site, is largely unreported in literature in Canada, therefore, the extent of missing registration is unknown. As mandated by the Regional Health Authorities Act of Alberta, physicians and laboratories are responsible for sending pathology and radiology reports for reportable conditions to the ACR (Province of Alberta, 2009). However, even though it is mandatory in Alberta to report all brain and other CNS tumours, it is believed non-malignant tumours may be missed. Non-malignant brain tumours can be diagnosed with computed tomography (CT) and magnetic

resonance imaging (MRI) scans, plus biopsy or surgery is not always possible or recommended (Brain Tumour Foundation of Canada, 2014). Given that the primary source of registration is pathology (where the patient has a biopsy or receives surgery and the diagnosis is confirmed by the pathologist), this is one reason why subject matter expert have suggested these tumours may be under-reported. Also, patients who do not receive treatment may have less initial contact with healthcare systems and therefore may be missed. In the United States between 2010 to 2014, approximately 11% of malignant tumours are diagnosed radiologically (where surgery was not performed but patient was diagnosed only by imagining techniques) compared to approximately 50% of the non-malignant tumours (Ostrom et al., 2017). Shaw et al. (2014) estimated an ascertainment rate of 46% for non-malignant CNS tumours in Alberta, suggesting that more than half of the cases are currently not being registered. Surveys with cancer registries in Canada also identified the need to improve case ascertainment procedures and assess the completeness and quality of non-malignant CNS tumours (Davis et al., 2015). Therefore, this study aims to address these recent concerns by evaluating the impact of using DAD to supplement case ascertainment for brain tumours.

Not only is high quality data important for epidemiological studies and operational planning, but it is also important in evaluating performance of cancer registries. Registry certification is completed by NAACCR to ensure the data is of high enough quality to use in analysis (Hofferkamp, 2008). Overall completeness is one of the factors used by NAACCR to evaluate the quality of a Cancer Registry. By estimating the completeness of brain tumours on the ACR, we hope this will be informative and allow for improvements if necessary. We also hope by identifying barriers for initial registration of brain tumours in Alberta, this will help future case ascertainment efforts and assist other Cancer Registries on where to focus resources more appropriately in the future.

The value of molecular medicine is becoming more apparent as it allows for more personalized treatment of patients by providing valuable information for diagnosis, prognosis and treatment (Idbaih et al., 2015). WHO's updated classification system to use molecular parameters for CNS tumours will also provide more precise and clinically relevant classifications in clinical trials, experimental studies and epidemiology studies. It has been suggested that eventually molecular

diagnostics and next-generation sequencing may even replace the current histology directed diagnosis for CNS tumours altogether (Weller et al., 2013). However, the increased use of molecular information in cancer patients also poses many challenges ahead regarding classifying and validating both the laboratory methods and clinical importance of each biomarker (Idbaih et al., 2015). Laboratory methods are still somewhat subjective and results can be difficult to interpret (Ostrom et al., 2016), but research activities for targeted therapies is growing. BCC Research (2016) expects the global CNS biomarker market to reach nearly $5.1 billion by 2020 with large growth in the diagnostic and drug research and development markets as more biomarkers are validated. Research has also suggested the possibility that molecular biomarkers may be detected by non-invasive procedures from radiology that do not require risks from tissue sampling (Brown et al., 2008; Tietze et al., 2018; Park et al., 2018). Rosenfeld (2013) concludes that the clinical value of a biomarker is dependent on many things including the reproducibility and stringency of laboratory measurements for each marker. While these biomarkers play an important role in clinical decisions, until indisputable evidence is available, patients and clinicians will need to use this information weighing in all aspects of care.

Many studies have shown considerable variation in the availability and quality of data in pathology reports (Yunker, Matthews, & Dort, 2008; Wilkinson, Shahryarinejad, Winston, Watroba, & Edge, 2003; Ferrusi et al., 2013). Canadian Partnership Against Cancer has launched the Electronic Synoptic Pathology Reporting Initiative to support implementation of synoptic pathology reports for 5 cancers (Canadian Partnership Against Cancer [CPAC], 2012). Synoptic reporting involves moving from a traditional narrative report to an electronic structured report with standardized information to better inform clinicians and ultimately improve patient outcomes. A systematic review of the effects of implementing synoptic pathology cancer reporting showed that 13 of 14 studies had an increase in overall completeness after implementing synoptic reporting, as well as improved reporting of clinically relevant information (Sluijter, van Lonkhuijzen, van Slooten, Nagtegaal, & Overbeek, 2016). In line with this, tumour-specific site guidelines are published by the College of American Pathologists (CAP) to improve quality of pathology reporting. CAP guidelines have also included an optional CNS Biomarker Reporting Template (which includes the four markers identified in our pilot project) to assist pathologists in providing clinically important elements of biomarker testing (Brat et al.,

2014). The importance of quality pathology reporting (including biomarker testing) is apparent, however the testing practices for molecular characteristics of CNS tumours in Canada is largely unreported in literature. Therefore, this pilot study will be a first step in providing a better understanding of current testing practices in Alberta by assessing the information currently available and extractable from ARIA MO. By using information from pathology reports and physician progress notes already in ARIA MO, we will estimate the prevalence of biomarker testing by histological subtype and year of diagnosis for CNS tumours. We hope this work will then provide feedback to help inform future guidelines regarding the collection of data for molecular testing of CNS tumours in Alberta. We also hope it might assist in future development of reporting systems, such as synoptic pathology reporting and clinical databases.

1.4 Study Objectives and Hypotheses

This study has three major objectives:

Objective 1: Estimate the completeness of brain tumours on the ACR by evaluating the impact of using hospital discharge data, as recorded in DAD, to supplement case ascertainment for brain tumours in Alberta.

- **Hypothesis 1A:** Given the ACR has received gold certification from NAACCR for the past several years and a previous study for pediatric brain tumours showed overall 96% completeness of ACR data compared to physician records, we hypothesize a similar completeness of 95% or higher for malignant brain tumours in Alberta (NAACCR, 2018; Normandeau et al., 2016).
- **Hypothesis 1B:** For non-malignant cases we hypothesize a lower completeness of between 70% to 90% based on previous studies and previous estimates of the expected number compared to the observed number. The difference between malignant and non-malignant cases is believed to be due to difficulties associated with case ascertainment due to unusual and ambiguous terminology (National Cancer Institute, SEER Training Modules, n.d.).

Objective 2: Look at differences in characteristics between those originally registered and those identified through DAD on the ACR to help identify barriers for initial registration of brain tumours in Alberta.

- **Hypothesis 2:** We hypothesize the following characteristics may impact registration of a case: age at diagnosis, histological subtype and behaviour, location at diagnosis, diagnostic confirmation, initial treatment plan (observation, surgery, or radiation therapy) and whether the patient visited a CancerControl Alberta facility.

Objective 3: Conduct a pilot study to explore the feasibility of extracting four molecular parameters (IDH1/2, MGMT, ATRX and 1p/19q status) from pathology reports and progress notes in ARIA MO for CNS tumours diagnosed in Calgary. This will include estimating the prevalence of these molecular parameters by histological subtype and year of diagnosis to better understand the information currently available in the Calgary Zone.

- **Hypothesis 3:** Based on the review of the literature and discussions with subject matter experts, we hypothesize that prevalence of molecular parameters will depend on the molecular parameter and tumour subtype. As far as MGMT promoter methylation and 1p/19q co-deletion status we expect to have a high prevalence as they are included in current practice guidelines and believed to be readily tested. Also, we expect ATRX status to have high prevalence as even though not included in guidelines, it is believed to be readily tested. We expect a lower prevalence for IDH mutant/wildtype as during 2010 to 2015 it was not included in guidelines or considered a standard test in Alberta.

Chapter 2 Methodology

2.1 Data Sources and Variables

The databases used for analysis will be: the Alberta Cancer Registry (provincial population-based cancer registry), Discharge Abstract Database (administrative database that records hospital discharge records), CancerControl Alberta's Electronic Medical Record (clinical database primarily used in treatment of patients), and Physician Database for brain tumours (clinical database kept by the physician tumour group).

The Alberta Cancer Registry is a population-based registry that collects and maintains data on cancer incidence and mortality occurring in Alberta. The ACR was first established in 1942 and includes the following information: demographics (birth date, sex, name, health insurance number), type of cancer (topography and morphology), diagnosis date, diagnosis method, stage at diagnosis, initial treatment information and death information (Alberta Health Services [AHS], 2014). Doctors and laboratories are mandated by the Regional Health Authorities Act of Alberta to notify the ACR of new cancer cases (Province of Alberta, 2009).

The Discharge Abstract Database, maintained by Canadian Institute for Health Information, contains discharge records for Canadian hospitals (requirement of all provinces and territories except Quebec). The database captures demographic, clinical and administrative information for acute care facilities (Canadian Institute for Health Information [CIHI], 2017). The following information is captured: demographics (birth date, sex, health insurance number), institution, admission date, discharge date, length of stay, diagnosis codes (indicates the diagnoses, conditions, problems or circumstances during patient's stay) and diagnosis types (indicates the impact the diagnosis has on the patient's care).

CancerControl Alberta's Electronic Medical Record, ARIA MO, is a clinical database primarily used to assist with the treatment of cancer patients in Alberta. ARIA MO contains information regarding scheduled appointments (including type and date), progress notes (including physician notes and treatment summaries), online prescription orders (for systemic therapy drugs) and drug

administration. ARIA MO was implemented in phases, differing by facility and cancer site, with scheduled appointments being considered reliable starting in 2001. Tom Baker Cancer Centre in Calgary is considered more online than other facilities (such as the Cross Cancer Institute in Edmonton) due to more consistent information being entered, interfaced or scanned into ARIA MO over the use of traditional paper charts. For example, pathology reports in Calgary are interfaced into ARIA MO where for Edmonton and rural communities this is not currently standard and this information is primarily available only in Netcare.

The Physician Database for brain tumours is an excel file containing clinical information and is updated by the oncologists in CancerControl Alberta for the patients they see. This database was only used in this study for assessing the comparability of biomarker information electronically extracted from ARIA MO to manually tracked information in this database.

2.2 Study Population

When the ACR conducted their review, the study population of interest was anyone with an International Classification of Diseases, tenth revision (ICD-10) diagnosis code of D32, D33, D42, D43, C70, C71 or C72 with an admission date from 2010 to 2015. These patients were then linked to the ACR to see if there was a corresponding diagnosis. As the ACR codes topography using International Classification of Diseases for Oncology, third edition (ICD-O-3) in the years of interest, a patient with the following codes were considered to have an equivalent diagnosis: C70, C71, C72 with a behaviour = /0 benign, /1 uncertain/borderline or /3 invasive. Detailed information for ICD-O-3 and corresponding ICD-10 inclusions and exclusions for brain cancers, based on the National Cancer Institute's Surveillance, Epidemiology and End Results Program tables, can be found in Table 18 and Table 19 in the appendix (Surveillance, Epidemiology and End Results Program [SEER], 2014). DAD review was conducted in two parts; the first part focused on benign brain tumours (D32, D33) while the second part focused on uncertain/borderline (D42, D43) and malignant (C70, C71, C72) brain tumours. The time frame of 2010 to 2015 (most recent year of complete data available in the ACR at time of review) was chosen as the ACR, supplemented by the Brain Tumour Foundation of Canada and a Brain Canada grant, allocated enough resources required for this time period for the review.

The study population of interest in this study was patients diagnosed with a brain tumour in Alberta from 2010 to 2015. To assess the impact of DAD on case ascertainment, brain tumours in our study was defined specifically as ICD-O-3 topography of C70, C71 or C72. We also excluded morphologies that when converted into ICD-10 are not specific to brain as listed in Table 19 in the appendix; these morphologies were excluded since they were not included in the DAD review for this project as they would require significant extra resources for a relatively small proportion that would be reportable. The study population was chosen to be consistent with the ICD-10 diagnosis included in the ACR's DAD review.

For the pilot study exploring the availability of molecular characteristics in ARIA MO, the study population of interest includes all patients diagnosed with an invasive CNS tumour residing in Calgary from 2010 to 2015. We limited the pilot study to Calgary as progress notes and pathology reports are consistently being entered or interfaced into ARIA MO for Calgary and therefore electronically available for text mining. Edmonton tends to use traditional paper charts more and therefore the information in ARIA MO is less consistent. For this objective, as we are interested in all invasive CNS tumours, we used a broader definition from the Central Brain Tumor Registry of the United States (CBTRUS) due to the all-inclusive nature. CBTRUS defines brain and other CNS tumours as ICD-O topography codes C70 through C72, C75.1 through C75.3, plus ICD-O topography C30.0 with ICD-O histology codes 9522 and 9523 as per Table 20 in the appendix (Ostrom et al., 2017). For this objective, we have limited the population to only invasive tumours as the majority of patients with non-malignant tumours are not being seen in CancerControl Alberta facilities and therefore have no corresponding information in ARIA MO. Only primary cancer diagnoses were included, as recurrence and metastases are not collected consistently in the ACR. The starting time frame of 2010 was chosen as we only expect biomarker testing to have started in recent years. A closing year of 2015 was chosen as this was the most recent complete data available in the ACR at the time of extraction.

2.3 Data Extraction and Quality Assurance

An ethics application was submitted through the Health Research Ethics Board of Alberta – Cancer Committee and approval was received on January 5, 2017 (Study Id: HREBA.CC-16-0974). Following ethics approval, a research agreement was drafted with AHS and final approval given on January 18, 2017. An amendment to ethics to expand the criteria for biomarker analysis was approved on July 20, 2017 and a renewal to the project was granted December 17, 2017. This granted access to the DAD, ACR, ARIA MO and physician databases allowing the required linkages and chart reviews.

A data request form, along with ethics and research approvals, was then sent to Surveillance and Reporting in Cancer Measurement Outcomes Research and Evaluation (C-MORE) Department which oversees all data requests for cancer information. Analysts within C-MORE, with a strong understanding of ACR and ARIA MO data, were assigned to perform the data extraction and linkage. The data was then quality assured to ensure complete and accurate data before the final results were used in analysis. At the same time, we also submitted a data request to CBTRUS to get counts, age-specific, and age-adjusted incidence rates of brain and CNS tumours (as defined by this study) for 2010 to 2014 in the United States.

Prior to our study, an analyst in C-MORE linked all patients on the DAD with a brain diagnosis admitted from 2010 to 2015 to the ACR using the patient's Unique Lifetime Identifier (ULI) number (number assigned to every person who receives health services in Alberta). For part one of DAD review involving benign brain tumours, patients who were in the DAD but not registered in the ACR with the same brain tumour diagnosis during same time period (2010 to 2015) were identified and a list was provided to the ACR for review. For part two of DAD review involving uncertain/borderline and malignant CNS tumours, patients who were on the DAD but not registered in the ACR with any CNS tumour diagnosis were identified and a list was provided to the ACR for review. The Cancer Registrars in the ACR subsequently reviewed each patient in the list to confirm if the brain tumour diagnosis was eligible to be registered on the ACR. If the case met all eligibility criteria (reportable condition and patient was living in Alberta at time of diagnosis), the Cancer Registrar then registered the missed tumour on the ACR. The criteria used to consider a link equivalent and hence not requiring review was broadened in part two based on the results of part one. For example, a patient who was seen in

hospital in 2010 for a CNS cancer who had a CNS cancer diagnosed in 2009 on the ACR was not considered an equivalent link in part one, however was in part two. Another example, was a patient who was seen in hospital in 2010 for a benign CNS cancer who had an invasive CNS cancer on the ACR was not considered an equivalent link in part one, however was in part two. The rationale for this was that part one of the review showed if the patient was registered on the ACR with a CNS cancer, over 95% of those cases were the same cancer, irrespective of the year of diagnosis or exact type of CNS cancer.

After the ACR finished reviewing and registering all cases as identified through DAD, a C-MORE analyst extracted the cohort for this study. All patients with brain cancer diagnosed from 2010 to 2015 in Alberta were included in the analysis. These patients were initially extracted from the ACR and linked to ARIA MO, using the patient's ACB number (unique identifier for cancer patients), to get additional visit information. They were then re-linked to the original DAD file to flag cases registered as part of DAD review. The final dataset contained information on visits, initial treatment, diagnosis and demographics as per Table 21 in the appendix. Once the final dataset was received from C-MORE, the entire patient list was reviewed to ensure patients fell within the study population and additional quality assurance through chart review was performed as needed.

For the pilot study regarding the feasibility of extracting biomarkers, a C-MORE analyst pulled all patients diagnosed in the Calgary zone with an invasive CNS cancer (as defined by CBTRUS definition) from 2010 to 2015 from the Alberta Cancer Registry. These patients were then linked to ARIA MO to get all visit notes (including progress notes and pathology reports) and corresponding date. The information from visit notes in ARIA MO was provided in text format (as available in the EMR) and analysis involved text mining to explore what information could be extracted. As part of text mining extensive quality assurance was performed; this included chart review to ensure the extracted information was useful and reliable. Any issues and limitations with the data during quality assurance were identified and either the analysis was modified to fix the problem or are identified in the results and discussion.

2.4 Data Analysis

Statistical analyses for this paper was generated using SAS software, Version 3.6 of the SAS System for Unix. Copyright © 2016 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. (SAS Institute Inc., 2016).

2.4.1 Impact of using DAD in case ascertainment of brain tumours

To determine the impact of using DAD to supplement case ascertainment, a frequency table was created with the number and percentage of cases with a brain tumour diagnosed 2010 to 2015 in Alberta by behaviour and type of registration (originally registered or identified through DAD). Overall completeness of case ascertainment was measured using NAACCR's certification criteria as a guideline. NAACCR assigns gold certification when completeness of case ascertainment is 95% or higher and silver certification when 90 to 94% complete (Hofferkamp, 2008).

To investigate cases that may be missed by both the ACR and DAD, we compared age-standardized incidence rates of non-malignant brain tumors (benign and uncertain behaviors) in Alberta to rates from the United States as reported in CBTRUS. We also estimated the expected number of non-malignant brain cases, as defined for this study, from 2010 to 2014 by applying age-specific incidence rates provided by CBTRUS to the Alberta population (Central Brain Tumour Registry of the United States [CBTRUS], 2017). Alberta population data was obtained from Alberta Health Interactive Health Data Application (Government of Alberta, 2017). At the time of this study, CBTRUS rates were available to 2014 diagnosis year, so analysis was restricted to 2010 to 2014 for this portion of the study. This method is similar to the methodology used in previous estimates for all of Canada (Shaw et al., 2014); however, it should be noted that actual rates in Alberta may be higher or lower than those reported in the United States.

2.4.2 Characteristics associated to under-reporting of brain tumours

Characteristics between those originally registered and those identified through DAD review were compared to identify potential barriers associated with originally missing registration. The following characteristics were included in analysis: sex, age group at diagnosis (0-17, 18-59, 60-74, 75+), histological subtype, location at diagnosis (Northern, Central or Southern Alberta), diagnostic confirmation (Microscopically confirmed or Non-microscopically confirmed), surgery, radiation therapy, observation and whether a patient had a visit at a CancerControl Alberta facility. Surgery, radiation therapy and observation indicate if the patient had an initial treatment of interest to the primary, as recorded on the ACR. Chi-square test was used to test for homogeneity of proportions (between those originally registered and identified through DAD) for the characteristics of interest. Because of the suspected collinearity between diagnostic confirmation, treatment plan and visit to CancerControl Alberta facility, we also calculated phi coefficients as a measure of correlation to assist with model selection. After bivariate relationship was examined, we then conducted multivariable logistic regression considering phi coefficients (>0.3) and chi-square analysis ($p \leq 0.05$) in model selection. Odds ratios and 95% confidence intervals for our logistic model were reported to identify the characteristics with the strongest association for cases identified through DAD.

2.4.3 Feasibility of extracting biomarkers from ARIA MO

Analysis involved text mining to extract molecular parameter information from the free-text information in ARIA MO for all invasive CNS cancers (as defined by CBTRUS definition) from 2010 to 2015 in the Calgary zone. Review was conducted on four molecular parameters: 1) IDH mutant/wildtype, 2) 1p/19q co-deletion, 3) ATRX, and 4) MGMT promoter methylation. These parameters have been chosen as they were identified by CNS tumour group subject matter experts in Alberta to be used across the province. After the molecular data was extracted, prevalence of availability of molecular parameter test results was calculated by histological subtypes and year of diagnosis. The annual percent change was calculated using the Joinpoint Regression Program modelling proportion of available test results from 2010 to 2015 (Statistical Research and Applications Branch, National Cancer Institute, 2017).

After results were compiled using electronic extraction from ARIA MO, we linked the cases to the physician databases (who manually input this information) and calculated percent agreement and Kappa coefficient to assess the accuracy of the molecular data extracted through ARIA MO. Landis and Koch (1977) guidelines for interpretation of Kappa coefficient were used to quantify agreement after correcting for chance. A kappa statistic score of 0.81 or better was almost perfect agreement, 0.61 to 0.80 was substantial agreement, 0.41 to 0.60 was moderate agreement, 0.21 to 0.40 was fair agreement, 0.00-0.20 was slight agreement and <0.00 was poor agreement.

2.5 Data Limitations

A limitation of this study was the lack of alignment between ICD-O-3 (used in the registry system) and ICD-10 (used in DAD). Due to these differences we had to exclude some morphology codes as they fall into ICD-10 categories not specific to CNS tumours. These codes would require significant extra resources to review for a relatively small proportion of cases that would be reportable and therefore they were not selected for review in this project. Another limitation of our study is that even though a patient was being seen in hospital from 2010 to 2015, their actual diagnosis date could be years before; consequently, it is likely we are not getting the entire impact of DAD review.

A limitation of using ARIA MO to extract information for biomarkers is only patients who are seen at a CancerControl Alberta facility have information available in ARIA MO. Even for patients seen at a CancerControl Alberta facility, there are challenges due to inconsistencies of information. For this study, we chose to restrict our population to patients diagnosed in Calgary as progress notes and pathology reports are consistently being entered or interfaced into ARIA MO and therefore electronically available for text mining. Another challenge discovered after initial review was not all pathology reports interfaced into ARIA MO have data that can be electronically extracted. As such we expanded the initial criteria to include not only pathology reports but physician progress notes to assist in getting a better overall picture of the feasibility of extracting this information from ARIA MO. Lastly, text mining has the potential of wrong

interpretations and possibility of misconstruing information, therefore the results are only estimates and final review and confirmation should be conducted before being used otherwise.

Chapter 3 Case Ascertainment Results and Discussion

3.1 Impact of using DAD in case ascertainment of brain tumours

3.1.1 Results

There was a total of 3524 brain tumours, defined as ICD-O topography of C70-C72, diagnosed in Alberta from 2010 to 2015. However, 98 patients were excluded as they were diagnosed with morphologies outside the scope of this study. A detailed breakdown of excluded morphology codes can be found in Table 19 of the appendix. After applying the exclusions, a total of 3426 tumours were included in the final cohort for this part of the study. Table 1 shows the percentage of those originally registered compared to those identified through DAD review by tumour behaviour.

Table 1. Brain tumours, Alberta, 2010-2015, by type of registration and behaviour

Type of Registration	Behaviour			Total, n (%)
	Benign, n (%)	Uncertain/ Borderline, n (%)	Malignant, n (%)	
Originally Registered	999 (62)	251 (81)	1427 (95)	2677 (78)
Identified through DAD	612 (38)	57 (19)	80 (5)	749 (22)
Total	1611	308	1507	3426

For all behaviours combined, 749 of the 3426 brain cases (22%) on the ACR were identified through DAD review (Table 1). The highest percentage of cases identified through DAD were for benign tumours with 612 of the 1611 cases (38%) found after DAD review. For uncertain or borderline tumours, 57 of the 308 cases (19%) were identified through DAD. For malignant tumours, 80 of the 1507 cases (5%) were identified through DAD. Using NAACCR certification criteria, the ACR would not receive gold (≥95% completeness) or silver (90 to 94% completeness) certification for benign or uncertain/borderline brain tumours. However, the ACR would receive gold certification for malignant brain tumours as defined in this study.

As described in Section 2.4.1, we calculated age-standardized incidence rates in Alberta and expected number of non-malignant brain tumours from 2010 to 2014 applying the CBTRUS age-specific rates to the Alberta population. From these calculations, Table 2 was obtained.

Table 2. Age-standardized incidence rates and number of cases (expected and observed) of non-malignant brain tumors, 2010-2014[1,2]

Year	Rate, United States	Rate (with DAD review), Alberta	Expected Number, Alberta	Observed Number without DAD Review, Alberta	Observed Number with DAD Review, Alberta
2010	11.04	8.64	401	196	311
2011	11.10	8.12	414	187	302
2012	11.12	8.86	429	222	345
2013	11.08	8.42	442	225	332
2014	10.84	7.97	448	229	329
			2134	1059	1619

[1]Rates are per 100,000 people and age-adjusted to the 2000 US Standard Population
[2] Non-malignant includes benign and uncertain behaviours

Even after DAD review, Alberta's age-standardized incidence rates for non-malignant tumors are lower than are reported in the United States (Table 2). Using CBTRUS rates, we would expect 2134 non-malignant brain cases were expected from 2010 to 2014. Without DAD review, the ACR would have captured 1059 of the 2134 expected non-malignant brain cases (50%). After DAD review and additional coding of missed cases, the ACR now captured 1619 of the 2134 expected non-malignant cases (76%). The number of cases on the ACR is considerably better aligned with those expected after DAD review, albeit still lower than expected assuming Alberta and United States rates are similar.

3.1.2 Discussion

The results confirm our hypothesis that malignant brain tumours had a 95% or higher completeness of case ascertainment. Also, as suspected we see a difference between malignant and non-malignant case ascertainment. Under-reporting for uncertain/borderline brain cases in the ACR (19%) was in line to our original hypothesis of 10 to 30% of non-malignant cases being initially missed, however, the overall severity of under-reporting for benign cases in the ACR

(38%) was more than hypothesized. Overall, the impact of DAD in case ascertainment was found to be considerable for non-malignant brain tumours. These findings align with previous suspicions based on surveys with registries in Canada that work is needed to improve case ascertainment procedures of non-malignant brain tumours (Davis et al., 2015).

Previous studies done in Scotland and England, found approximately 50% under-reporting of CNS tumours, with the greatest difference in benign cases (Counsell, Collie, & Grant, 1997; Pobereskin, 2001). In comparison, the results in Alberta for all behaviours combined was 22% under-reporting for the brain tumours of interest in this study. Another similar study done in Finland, looking at patients in the hospital discharge registry from 1985 to 1988 but not the Finland cancer registry, found 1.4% under-reporting for malignant CNS, but 19.4% under-reporting for non-malignant CNS (Teppo et al., 1994). The results in Alberta were similar for malignant brain tumours with 5% under-reported, but were worse for non-malignant brain tumours with 35% of cases under-reported.

Given the observed number of brain cases in Alberta after DAD review is around 75% of the expected number assuming similar rates to CBTRUS, this is an indication that Alberta could still be missing some cases. It should be noted that the actual rates in Alberta may be higher or lower than in the United States and therefore the CBTRUS rates can only be used as an approximation (as they may actually be an over or under estimate of the true number of cases for Alberta). One reason Alberta could still be missing cases is we only reviewed discharge abstracts from 2010 to 2015. Some patients may only be followed in outpatient clinics and not in DAD or some may only be admitted years after diagnosis when symptoms worsen or disease progresses. Consequently, we would suspect with each annual DAD review there will be more cases caught in past diagnosis years and the impact even greater.

The next step could be to investigate a way to catch cases even before they are seen in hospital, possibly by looking for better ways to catch them when initially diagnosed (for example looking at electronic linkages with radiological data or physician billing data). Also, if synoptic pathology reporting was implemented in the future it could be possible to electronically capture these cases earlier in the process. In Norway it is believed that significant increase in

completeness since the 1990's is in part due to the Norwegian system allowing reminders to be sent to clinicians based on the Norwegian hospital discharge files (Larsen et al., 2009). Three times a year, physicians and hospitals receive a reminder for any cancer diagnosis they have failed to report or not provided enough information for registration. It is believed that this trace back system has had the largest impact on cases with a low proportion of morphologically verified tumours such as CNS, which were previously missed or only picked up as death certificate initiated cases. One possible long-term solution to the problem could be to implement a similar technique in Alberta. A new provincial clinical information system is being rolled out in Alberta over the next five years with the goal of better access to health information for both the patient and provider (Alberta Health Services, 2018). Having one provincial system and better access to information may also assist with cancer registration in the future.

3.2. Characteristics associated to under-reporting of brain tumours

3.2.1 Results

After evaluating the impact of using DAD for case ascertainment, we compared the characteristics between cases originally registered and cases identified through DAD review in an attempt to understand why initial registration was missed. As malignant brain tumours were relatively complete, we have focused the results in this section on non-malignant tumours where the majority of under-reporting occurred. Table 3 shows the results of chi-square test for homogeneity of proportions between the 1250 cases originally registered and 669 cases identified through DAD for the characteristics of interest.

Table 3. Chi-square test for homogeneity of type of registration for characteristics of non-malignant brain tumours, Alberta, 2010-2015[1]

Characteristic	Originally Registered, n (%)	Identified through DAD, n (%)	All Cases, n	p
Sex				0.56
Female	783 (65)	428 (35)	1211	
Male	467 (66)	241 (34)	708	
Age at Diagnosis				**<0.001**
0-17	53 (83)	11 (17)	64	
18-59	601 (68)	287 (32)	888	
60-74	371 (71)	150 (29)	521	
75 and over	225 (50)	221 (50)	446	
Behaviour				**<0.001**
0 Benign	999 (62)	612 (38)	1611	
1 Uncertain/Borderline	251 (81)	57 (19)	308	
Histological Subtype				**0.05**
Tumours of Neuroepithelial Tissue	83 (75)	28 (25)	111	
Tumours of Cranial and Spinal Nerves	180 (61)	116 (39)	296	
Tumours of Meninges	944 (65)	507 (35)	1451	
All Other	43 (70)	18 (30)	61	
Location at Diagnosis				**<0.001**
Southern Alberta	627 (70)	266 (30)	893	
Central Alberta	163 (67)	80 (33)	243	
Northern Alberta	459 (59)	322 (41)	781	
Unknown	1 (50)	1 (50)	2	
Diagnosis Confirmation				**<0.001**
Microscopically confirmed	774 (68)	356 (32)	1130	
Non-microscopically confirmed	476 (60)	313 (40)	789	
Surgery				**0.002**
Yes	689 (68)	319 (32)	1008	
No	561 (62)	350 (38)	911	
Radiation Therapy				**<0.001**
Yes	68 (99)	1 (1)	69	
No	1182 (64)	668 (36)	1850	
Observation				**0.002**
Yes	270 (59)	188 (41)	458	
No	980 (67)	481 (33)	1461	
Visit to CancerControl Alberta				**<0.001**
Yes	425 (92)	38 (8)	463	
No	825 (57)	631 (43)	1456	
Total	**1250 (65)**	**669 (35)**	**1919**	

[1] Non-malignant includes benign and uncertain behaviours

Chi-square test for homogeneity found identification through DAD to be significantly associated ($p \leq 0.05$) with age group at diagnosis, behaviour, histological subtype, location at diagnosis, diagnostic confirmation, whether the patient's initial treatment was surgery, radiation therapy, or observation and whether a patient visited a CancerControl Alberta facility (Table 3). Sex was not statistically significantly different between the two groups.

Given we know that age impacts treatment decisions (for example those over 75 years old are less likely to get surgery), multiple logistic regression was performed to rule out potential confounding. Also, because of the suspected collinearity of treatment plan with diagnostic confirmation and visit to CancerControl Alberta facility, we calculated phi coefficients as a measure of correlation between these binary variables. Phi coefficients are summarized in Table 4.

Table 4. Phi coefficient measuring the correlation between diagnostic confirmation, treatment types and visit information

	Diagnostic Confirmation	Surgery	Observation	Radiation Therapy
Diagnostic Confirmation	-			
Surgery	0.88	-		
Observation	-0.44	-0.59	-	
Radiation Therapy	-0.04	-0.04	-0.11	-
Visit to CancerControl Alberta Facility	-0.07	-0.05	0.05	0.32

Surgery is highly correlated to diagnostic confirmation with a phi coefficient of 0.88 (Table 4); this is expected as patients having surgery get a biopsy, and therefore have a microscopically confirmed diagnosis. We also see that observation is moderately negatively correlated with diagnostic confirmation and surgery, which again was predicted as only those who do not have a specific treatment plan (i.e. surgery or radiation therapy) would have observation coded as initial treatment. We also see a moderate correlation between radiation therapy and visit to CancerControl Alberta facility, which is expected as radiation therapy is done only in CancerControl facilities if treated in Alberta. Therefore, to avoid collinearity and overfitting, our multivariable logistic model excluded treatment variables (surgery, observation, radiation

therapy), but included all other characteristics that were statistically significant with the chi-square test for homogeneity. As such the following co-variates were included in the logistic model: age group at diagnosis, behaviour, histological subtype, location at diagnosis, diagnostic confirmation and whether the patient visited a CancerControl Alberta facility. Odds ratios and 95% confidence intervals for the multiple logistic model can be found in Table 5.

Table 5. Multiple logistic regression model for characteristics associated with being identified through DAD for non-malignant brain tumors, Alberta, 2010-2015[1]

Characteristic	Odds Ratio (95% confidence interval)	p
Age at Diagnosis		
0-17	1.00 (reference)	**-**
18-59	1.76 (0.78 - 3.98)	0.18
60-74	1.26 (0.54 - 2.92)	0.59
75 and over	2.50 (1.07 - 5.86)	**0.04**
Behaviour		
1 Uncertain	1.00 (reference)	-
0 Benign	2.59 (1.69 - 3.97)	**<0.001**
Histological Subtype		
Tumours of Meninges	1.00 (reference)	**-**
Tumours of Neuroepithelial Tissue	1.71 (0.93 - 3.16)	0.09
Tumours of Cranial and Spinal Nerves	1.70 (1.27 - 2.29)	**<0.001**
All Other	2.15 (1.02 - 4.51)	**0.04**
Diagnostic Confirmation		
Microscopically confirmed	1.00 (reference)	**-**
Non-microscopically confirmed	1.34 (1.05 - 1.71)	**0.02**
Location at Diagnosis		
Southern Alberta	1.00 (reference)	**-**
Central Alberta	1.07 (0.77 - 1.48)	0.69
Northern Alberta	1.47 (1.18 - 1.82)	**<0.001**
Alberta, Unknown	3.95 (0.13 - 122.24)	0.43
CancerControl Alberta Visit		
Yes	1.00 (reference)	**-**
No	8.66 (6.02 - 12.48)	**<0.001**

[1] Non-malignant includes benign and uncertain behaviours

As shown in Table 5, one of the strongest predictors for registration was if a patient had a visit at a CancerControl Alberta facility; patients who did not visit CancerControl Alberta were 8.66

times more likely to be identified through DAD than those who did, after adjusting for age group at diagnosis, behaviour, histological subtype, diagnostic confirmation and location at diagnosis ($p<0.001$). We also see differences in the likelihood of registration depending on a patient's location and age at diagnosis. Cases in Northern Alberta (Edmonton and North Zone) were 1.47 times more likely to be identified through DAD than cases in Southern Alberta (Calgary and South Zone) after adjusting for co-variates ($p<0.001$). Older patients (75 years and over) are 2.50 times more likely to be identified through DAD than pediatric patients (0-17) after adjustment ($p=0.04$).

The multivariable logistic model also showed differences based on behaviour, histological subtype and diagnostic confirmation of the tumour. After adjusting for age group at diagnosis, histological subtype, diagnostic confirmation, location at diagnosis and visit to CancerControl Alberta facility, we see benign cases are 2.59 times more likely to be identified through DAD than uncertain/borderline cases ($p<0.001$). Also, tumours of cranial and spinal nerves and all other tumours are 1.70 and 2.15 times, respectively, more likely to be identified through DAD than tumours of meninges ($p<0.001$ and $p=0.04$, respectively). Cases not diagnosed microscopically are 1.34 times more likely to be identified through DAD than those microscopically confirmed after adjusting for co-variates ($p=0.02$).

3.2.2 Discussion

Patients visiting CancerControl Alberta facilities being more likely to be registered is not surprising as they have direct contact with oncological healthcare professionals. A similar study done in England, compared an independent brain tumour database with the cancer registry and found the strongest predictor of registration as having an operation (Pobereskin, 2001). Correspondingly, we also see microscopic diagnostic confirmation was predictive of likelihood of registration. This is not surprising given most notifications for registration of a cancer primary originate from pathology reports sent to the ACR. Prior to this study subject matter experts believed radiological and clinically diagnosed cases were being missed; even though statistically those cases were more likely to be missed, what is surprising is there was still a large

number (356 cases) of microscopically confirmed brain tumours missed (Table 3). This may imply that not only are tumours being missed due to diagnostic imaging techniques and limited contact with the healthcare system, but a need for further communication with pathologists submitting notifications.

That same study done in England found an age greater than 60 years was a strong predictor of registration (Pobereskin, 2001). They suggested that this could be due to the fact that those over 60 years may have longer stays in hospital, which could increase the ascertainment rate. However, our results differ in that older patients (75+) were more likely to be originally missed and identified through DAD than pediatric patients (0-17) even after adjustment for other co-variates. Preferential registration of younger patients aligns with a previous study done in Alberta, which found a strong overall case ascertainment of pediatric brain tumours in the ACR compared to the pediatric physician databases (Normandeau et al., 2016). This is likely attributable to the specialized care and extra attention the pediatric population often receive.

Lastly, the fact that location at diagnosis was a strong predictor for registration was surprising. As the Alberta Cancer Registry is provincially mandated and standard rules apply at a provincial level, we did not expect to see differences by location at diagnosis. However, given the north and south function differently operationally, reasons for this difference need to be investigated further. There could be possible difference in coding practices, accessibility of information (for example we know Tom Baker Cancer Centre in Calgary tends to be more electronic), or in notifications for registration (such as different laboratories sending different information to the ACR).

Chapter 4 Pilot Study for Biomarkers Results and Discussion

4.1 Results

4.1.1 Prevalence of biomarker information by histological subtype

The final dataset of all visit notes (including pathology and physician notes) in ARIA MO was provided by C-MORE on October 6, 2017. Using CBTRUS' all inclusive definition as per Table 20 in the appendix, there were a total of 541 invasive CNS cancers diagnosed in Calgary Zone from 2010 to 2015. As previously outlined, we have limited the population to only invasive tumours for this objective as the majority of patients with non-malignant tumours are not being seen in CancerControl Alberta and therefore have no corresponding information available in ARIA MO. Histological subtypes have been classified using CBTRUS histological subtype groupings as outlined in Table 22 in the appendix. Table 6 to 9 show the prevalence of the availability of four biomarkers of interest (IDH1/2, MGMT, 1p/19q and ATRX) by histological subtype as extracted electronically from ARIA MO.

Table 6. Prevalence and percent distribution of availability of IDH1/2 test result by histological subtype using ARIA MO, 2010-2015, Calgary

Histological Subtype	Availability of IDH1/2 test based on electronic extraction		Total
	No CancerControl Alberta Visit or IDH1/2 test result not found, n	IDH1/2 test result found, n (%)	
Glioma	239	226 (49)	465
Pilocytic Astrocytoma	13	1 (7)	14
Diffuse Astrocytoma	8	11 (58)	19
Anaplastic Astrocytoma	10	24 (71)	34
Unique Astrocytoma variants	6	0 (0)	6
Glioblastoma	165	152 (48)	317
Oligodendroglioma	4	11 (73)	15
Anaplastic oligodendroglioma	2	14 (88)	16
Oligoastrocytic tumours	2	9 (82)	11
Ependymal tumours	13	0 (0)	13
Glioma malignant, NOS	16	3 (16)	19
Other Tumours of Neuroepithelial Tissue[1]	5	2 (29)	7
Embryonal tumours	23	0 (0)	23
Tumours of Meninges	15	0 (0)	15
Lymphomas and Haemopoietic Neoplasms	20	0 (0)	20
All Other	12	0 (0)	12
Total	314	227 (42)	541

[1]One of seven cases in Other Tumours of Neuroepithelial Tissue is considered Glioma as defined by CBTRUS

IDH1/2 results can be found electronically in ARIA MO for 42% of patients included in our cohort (Table 6). IDH mutation status is particularly helpful in diagnosing grade II or III astrocytoma, oligodendroglioma, oligoastrocytoma, or secondary glioblastomas (Brat et al., 2014). It is also helpful in determining prognosis for glioma patients (Rosenfeld, 2013). Similarly, AHS (2016) recently recommended testing of IDH mutation for all patients with low-grade gliomas in their clinical practice guidelines. When limiting histological subtypes to gliomas in Table 6, we see 49% of patients diagnosed in Calgary from 2010 to 2015 have an IDH result electronically extractable in ARIA MO. As it was not believed to be a standard test during our study time frame, we hypothesized a relatively low prevalence for IDH testing

practices. With about half the patients in our cohort having an extractable test the results are in par with our original hypothesis.

Table 7. Prevalence and percent distribution of availability of MGMT test result by histological subtype using ARIA MO, 2010-2015, Calgary

Histological Subtype	Availability of MGMT test based on electronic extraction		Total
	No CancerControl Alberta Visit or MGMT test result not found, n	MGMT test result found, n (%)	
Glioma	209	256 (55)	465
Pilocytic Astrocytoma	13	1 (7)	14
Diffuse Astrocytoma	10	9 (47)	19
Anaplastic Astrocytoma	10	24 (71)	34
Unique Astrocytoma variants	6	0 (0)	6
Glioblastoma	127	190 (60)	317
Oligodendroglioma	6	9 (60)	15
Anaplastic oligodendroglioma	3	13 (81)	16
Oligoastrocytic tumours	4	7 (64)	11
Ependymal tumours	12	1 (8)	13
Glioma malignant, NOS	17	2 (11)	19
Other Tumours of Neuroepithelial Tissue[1]	6	1 (14)	7
Embryonal tumours	23	0 (0)	23
Tumours of Meninges	15	0 (0)	15
Lymphomas and Haemopoietic Neoplasms	20	0 (0)	20
All Other	12	0 (0)	12
Total	284	257 (48)	541

[1]One of seven cases in Other Tumours of Neuroepithelial Tissue is considered Glioma as defined by CBTRUS

MGMT results can be found electronically in ARIA MO for 48% of patients included in our cohort (Table 7). MGMT promoter methylation status is particularly helpful in determining prognosis and treatment decisions for glioblastomas (Rosenfeld, 2013). Table 7 shows 60% of glioblastoma patients diagnosed in Calgary from 2010 to 2015 have an MGMT result electronically extractable in ARIA MO. When looking at other gliomas (not including

glioblastomas) in Table 7 about 45% (66/148) have an MGMT result extractable from ARIA MO. These results confirm our original hypothesis that MGMT promoter methylation would have a high prevalence for relevant subtypes, as it is believed to be readily tested in Calgary.

Table 8. Prevalence and percent distribution of availability of 1p/19q loss of heterozygosity test result by histological subtype using ARIA MO, 2010-2015, Calgary

Histological Subtype	Availability of 1p/19q test based on electronic extraction		Total
	No CancerControl Alberta Visit or 1p/19q test result not found, n	1p/19q test result found, n (%)	
Glioma	382	83 (18)	465
Pilocytic Astrocytoma	14	0 (0)	14
Diffuse Astrocytoma	14	5 (26)	19
Anaplastic Astrocytoma	15	19 (56)	34
Unique Astrocytoma variants	6	0 (0)	6
Glioblastoma	302	15 (5)	317
Oligodendroglioma	1	14 (93)	15
Anaplastic oligodendroglioma	0	16 (100)	16
Oligoastrocytic tumours	0	11 (100)	11
Ependymal tumours	13	0 (0)	13
Glioma malignant, NOS	16	3 (16)	19
Other Tumours of Neuroepithelial Tissue[1]	6	1 (14)	7
Embryonal tumours	23	0 (0)	23
Tumours of Meninges	15	0 (0)	15
Lymphomas and Haemopoietic Neoplasms	20	0 (0)	20
All Other	12	0 (0)	12
Total	457	84 (16)	541

[1]One of seven cases in Other Tumours of Neuroepithelial Tissue is considered Glioma as defined by CBTRUS

Testing for loss of heterozygosity for 1p/19q results can be found electronically in ARIA MO for only 16% of patients included in our cohort (Table 8). Testing for 1p/19q co-deletion and ATRX are particularly useful in distinguishing mixed glioma subtypes as co-deletion of 1p/19q is a

predominant feature of oligodendroglial tumours, where loss of ATRX protein is a predominant feature of astrocytic tumours (Wiestler et al., 2013). Loss of heterozygosity of 1p/19q is also helpful in prognostic and treatment decisions for tumours with oligodendroglial features (AHS, 2012b). Table 8 shows 98% (41/42) of oligodendroglial tumours diagnosed in Calgary from 2010 to 2015 have a 1p/19q test result electronically extractable from ARIA MO. AHS (2016) also recently recommend 1p/19q testing for all patients with low grade gliomas in their clinical practice guidelines. However, when looking at other low-grade (WHO grade I and II) gliomas, not including oligodendroglial tumours, we see only 9% have a 1p/19q test result (data not shown). This suggests that testing for 1p/19q for oligodendroglial tumours is highly prevalent as originally hypothesized and in line with 2012 recommendations (AHS, 2012b); however, testing for other low-grade gliomas is not prevalent which is expected given that testing was not recommended until 2016 (AHS, 2016).

Table 9. Prevalence and percent distribution of availability of ATRX test result by histological subtype using ARIA MO, 2010-2015, Calgary

Histological Subtype	Availability of ATRX test based on electronic extraction		Total
	No CancerControl Alberta Visit or ATRX test result not found, n	ATRX test result found, n (%)	
Glioma	364	101 (22)	465
Pilocytic Astrocytoma	13	1 (7)	14
Diffuse Astrocytoma	13	6 (32)	19
Anaplastic Astrocytoma	20	14 (41)	34
Unique Astrocytoma variants	6	0 (0)	6
Glioblastoma	253	64 (20)	317
Oligodendroglioma	11	4 (27)	15
Anaplastic oligodendroglioma	10	6 (38)	16
Oligoastrocytic tumours	7	4 (36)	11
Ependymal tumours	13	0 (0)	13
Glioma malignant, NOS	17	2 (11)	19
Other Tumours of Neuroepithelial Tissue[1]	6	1 (14)	7
Embryonal tumours	23	0 (0)	23
Tumours of Meninges	15	0 (0)	15
Lymphomas and Haemopoietic Neoplasms	20	0 (0)	20
All Other	12	0 (0)	12
Total	439	102 (19)	541

[1]One of seven cases in Other Tumours of Neuroepithelial Tissue is considered Glioma as defined by CBTRUS

Similar to loss of heterozygosity for 1p/19q, ATRX results can only be found electronically in ARIA MO for 19% of patients included in our cohort (Table 9). As mentioned above, ATRX testing is particularly useful in distinguishing mixed glioma subtypes, but is also useful in distinguishing primary Glioblastomas from secondary Glioblastomas (Brat et al., 2014). Also, ATRX protein loss is believed to influence prognosis in astrocytic tumours (Wiestler et al., 2013). AHS' (2017) current clinical practice guidelines do not include recommendations for ATRX testing, however subject matter experts believed it was readily tested in Calgary. Table 9 shows 20% of glioblastomas and 30% (25/84) of all astrocytic tumours diagnosed in Calgary

from 2010 to 2015 have an ATRX test result electronically extractable from ARIA MO. This suggests that testing is not as prevalent as originally hypothesized for ATRX mutation.

4.1.2 Prevalence of biomarker information by year of diagnosis, for relevant histological subtypes

Prevalence of biomarkers by year of diagnosis was summarized for all CNS cancers as well as only histologically relevant subtypes as per results in section 4.1.1. To see results for all CNS cases refer to Tables 23 – 26 in the appendix. Tables 10 – 13 below show the prevalence of the four biomarkers of interest as extracted electronically from ARIA MO by year of diagnosis for histologically relevant subtypes only. Joinpoint Regression Program modelling proportion of available test results from 2010 to 2015 was used to calculate the annual percent change (Statistical Research and Applications Branch, National Cancer Institute, 2017).

Table 10. Glioma prevalence and percent distribution of availability of IDH1/IDH2 test result using ARIA MO by year of diagnosis, 2010-2015, Calgary[1]

Availability of IDH1/2 test based on electronic extraction	Year of Diagnosis						Total, n (%)
	2010, n (%)	2011, n (%)	2012, n (%)	2013, n (%)	2014, n (%)	2015, n (%)	
No CancerControl Alberta Visit or IDH test result not found	63 (89)	52 (71)	41 (57)	28 (38)	31 (42)	24 (24)	239 (51)
IDH test result found	8 (11)	21 (29)	31 (43)	46 (62)	42 (58)	78 (76)	226 (49)
Total	71	73	72	74	73	102	465

[1]Included ICD-O-3 Morphologies codes are 9380-9384, 9391-9460.

IDH status has been shown to be both diagnostic and prognostic for glioma subtypes, therefore we have included all gliomas in Table 10. Prevalence of IDH1/2 results electronically extracted from ARIA MO show a significant increase over the six year time frame with an annual percent change of 25.0% between 2010 to 2015 (data not shown). Table 10 shows only 11% of glioma patients diagnosed in Calgary had an extractable test in 2010, however this grew to 76% in 2015.

Table 11. Glioblastoma prevalence and percent distribution of availability of MGMT test result using ARIA MO by year of diagnosis, 2010-2015, Calgary[1]

Availability of MGMT test based on electronic extraction	Year of Diagnosis						Total, n (%)
	2010, n (%)	2011, n (%)	2012, n (%)	2013, n (%)	2014, n (%)	2015, n (%)	
No CancerControl Alberta Visit or MGMT test result not found	16 (36)	15 (33)	29 (57)	27 (47)	24 (50)	16 (23)	127 (40)
MGMT test result found	29 (64)	31 (67)	22 (43)	31 (53)	24 (50)	53 (77)	190 (60)
Total	45	46	51	58	48	69	317

[1]Included ICD-O-3 Morphologies codes are 9440, 9441, 9442/3.

As MGMT promoter methylation status has been shown to be prognostic and predictive for treatment particularly for glioblastomas, we have limited prevalence by year of diagnosis to this subtype (Rosenfeld, 2013). Table 11 indicates that testing for MGMT in glioblastomas diagnosed in Calgary has varied from 2010 to 2015. The annual percent change was not significantly different during the time frame (data not shown). However, in 2015 testing was the highest with 77% of patients with glioblastomas diagnosed in Calgary having a test result extractable in ARIA MO.

Table 12. Oligodendroglial tumours and low-grade glioma prevalence and percent distribution of availability of 1p/19q loss of heterozygosity test result using ARIA MO by year of diagnosis, 2010-2015, Calgary[1]

Availability of 1p/19q test based on electronic extraction	Year of Diagnosis						Total, n (%)
	2010, n (%)	2011, n (%)	2012, n (%)	2013, n (%)	2014, n (%)	2015, n (%)	
No CancerControl Alberta Visit or 1p/19q test result not found	8 (50)	4 (33)	6 (50)	1 (14)	6 (50)	7 (41)	32 (42)
1p/19q test result found	8 (50)	8 (67)	6 (50)	6 (86)	6 (50)	10 (59)	44 (58)
Total	16	12	12	7	12	17	76

[1]Included ICD-O-3 Morphologies codes are 9380-9384, 9391-9460 with a recorded WHO grade of 1 or 2 or codes 9450, 9451, 9460, 9382.

As co-deletion 1p/19q status is helpful for diagnosis, prognosis and treatment decisions particularly for tumours with oligodendroglial characteristics, we have included all these

subtypes in Table 12. Table 12 also includes all low-grade gliomas; even though AHS' clinical practice guidelines did not include 1p/19q testing for low-grade gliomas in our study period, we have included these in Table 12 to give an idea of past testing practices (AHS, 2016). Because we know 1p/19q testing is occurring for 98% of oligodendroglial tumours (Table 8 in section 4.1.1), we know that the majority of the cases not being tested from 2010 to 2015 in Table 12 are other low-grade gliomas; this is expected given testing was only recommended starting in 2016. Table 12 indicates testing for 1p/19q has varied from 50 to 86% of patients diagnosed with low-grade gliomas in Calgary having an extractable test result. The annual percent change was not statistically different from 2010 to 2015 (data not shown).

Table 13. Astrocytic tumours and glioblastoma prevalence and percent distribution of availability of ATRX test result using ARIA MO by year of diagnosis, 2010-2015, Calgary[1]

Availability of ATRX test based on electronic extraction	Year of Diagnosis						Total, n (%)
	2010, n (%)	2011, n (%)	2012, n (%)	2013, n (%)	2014, n (%)	2015, n (%)	
No CancerControl Alberta Visit or ATRX test result not found	54 (95)	58 (97)	66 (99)	63 (91)	51 (81)	20 (24)	312 (78)
ATRX test result found	3 (5)	2 (3)	1 (1)	6 (9)	12 (19)	65 (76)	89 (22)
Total	57	60	67	69	63	85	401

[1]Included ICD-O-3 Morphologies codes are 9421, 9425, 9400, 9410, 9411, 9420, 9401, 9381, 9384, 9424, 9440, 9441, and 9442/3

As ATRX status is helpful for diagnosis of glioblastomas (primary vs secondary), as well as diagnosis and prognosis of astrocytic tumours, we have included these subtypes in Table 13. Table 13 suggests that testing for ATRX for glioblastoma and astrocytic tumours was minimal in patients diagnosed in Calgary until recently. The annual percent change increased significantly between 2010 to 2015 by 112.4% annually (data not shown). In 2015, 76% of patients with glioblastoma and astrocytic tumours diagnosed in Calgary had a test result electronically extractable from ARIA MO.

4.1.3 Quality assurance using physician database

Because information from notes in ARIA MO are in text format, analysis involved text mining to extract biomarker information. As text mining has a high possibility of computer error, accuracy of the data extracted from ARIA MO was assessed by comparing the results to the physician databases (who manually track such information). The physician dataset for biomarker information was provided on November 11, 2017. Our results were then linked to the physician database by ACB Number, which is a unique identifier for each patient seen in CancerControl Alberta. Of the 541 patients on our database only 287 patients were also on the physician database. Reasons for differences between the physician database and the ACR include differences in defining and capturing CNS cases; as these differences have been previously documented for Alberta's pediatric population (Normandeau, 2015), our results only focus on cases in both databases. For the 287 patients on both databases, we compared results of biomarker information to estimate accuracy of computer-generated results compared to manual review. Table 14 – 17 below summarize the percent agreement between the physician database and electronic extraction using ARIA MO for each biomarker of interest.

Table 14. Percent agreement between physician database and electronic extraction for IDH1/2

Type of Agreement	n (%)
Same Results	122 (43)
Both Databases no results	35 (12)
Physician Database Results, Electronic Extraction Missing	91 (32)
Physician Database Result More Detailed (i.e. information on both markers)	24 (8)
Electronic Extraction Results, Physician Database Missing	5 (2)
Electronic Extraction Result More Detailed (i.e. information on both markers)	7 (2)
Discrepant Results	3 (1)
Total	287

Table 14 shows that 55% of compared cases had the same results for IDH1/2 for both the physician databases and information electronically extracted from ARIA MO; with 12% of those cases having no result on either database and 43% having the same result. Also, only about 1%

of the cases had a discrepancy in the result between the two databases. With a percent agreement of 55% and a kappa statistic of 0.30, we concluded there was fair agreement between the physician database and electronic extraction from ARIA MO for IDH1/2. The biggest discrepancy was due to a large percentage of cases (40%) missing information through electronic extraction but having information in the physician database. Some possible reasons for this are that the results might not have been interfaced into ARIA MO (a full chart review using other systems to get the information, such as Alberta Netcare, was required to get the information) or it could be that they are not in a readable format in ARIA MO. When the results were examined by diagnosis year, we see that electronic extraction appears to be improving over time with only 11% having more information in the physician database in 2015 (data not shown).

Table 15. Percent agreement between physician database and electronic extraction for MGMT

Type of Agreement	n (%)
Same Results	181 (63)
Both Databases no results	43 (15)
Physician Database Results, Electronic Extraction Missing	49 (17)
Electronic Extraction Results, Physician Database Missing	9 (3)
Discrepant Results	5 (2)
Total	287

For MGMT, 78% of compared cases had the same result in the physician database as using electronically extracted information from ARIA MO; 63% of those cases had results, where 15% for both databases had missing results (Table 15). We also see a small percent of discrepant MGMT results between the two databases (2%). A moderately high percentage of cases (17%) have a result in the physician database but not electronic extraction. However, similar to IDH1/2, we see that electronic extraction appears to be improving over time with only 11% of cases having more information in the physician database in 2015 (data not shown). Therefore, it is possible that as time goes on more information is being added to ARIA MO in an extractable format. With a percent agreement of 78% and a kappa statistic of 0.67, we concluded there was substantial agreement between the physician database and electronic extraction from ARIA MO for MGMT status.

Table 16. Percent agreement between physician database and electronic extraction for LOH 1p/19q

Type of Agreement	n (%)
Same Results	42 (15)
Both Databases no results	229 (80)
Physician Database Results, Electronic Extraction Missing	10 (3)
Electronic Extraction Results, Physician Database Missing	3 (1)
Discrepant Results	3 (1)
Total	287

Table 16 shows that 95% of compared cases had the same results for loss of heterozygosity on chromosomes 1p and 19q for both the physician databases and electronic extraction using ARIA MO; with 80% of those cases having no result on either database. We also see that about 1% of the cases had a discrepancy in the result for 1p/19q and about 3% had a result in the physician database but not electronic extraction. With a percent agreement of 95% and a kappa statistic of 0.82, we concluded there was almost perfect agreement between the physician database and electronic extraction from ARIA MO for loss of heterozygosity of 1p/19q.

Table 17. Percent agreement between physician database and electronic extraction for ATRX

Type of Agreement	n (%)
Same Results	46 (16)
Both Databases no results	228 (79)
Physician Database Results, Electronic Extraction Missing	5 (2)
Electronic Extraction Results, Physician Database Missing	7 (2)
Discrepant Results	1 (0.3)
Total	287

For ATRX, 95% of compared cases had the same results for both the physician database and electronic extraction from ARIA MO; with almost 80% of those cases having no result on either database (Table 17). We also see that less than 1% of the cases had a discrepancy in the result for ATRX and only 2% of cases had a result in the physician database but not electronic extraction. With a percent agreement of 95% and a kappa statistic of 0.85, we concluded there

was almost perfect agreement between the physician database and electronic extraction from ARIA MO for ATRX mutations.

4.2 Discussion

4.2.1 Quality of electronic extracting of biomarkers using ARIA MO

The aim of this pilot study was to investigate the feasibility of extracting molecular characteristics electronically from information currently available in ARIA MO. The above results firstly showed that we were able to extract biomarker results from ARIA MO. Secondly, by using the physician's database to assess the accuracy of extracted data we were able to conclude that text mining of visit notes to extract biomarker test results for CNS cancers was highly accurate (with around 1% discrepancy compared to the physician database) and should be explored further. As could be expected, electronic extraction had a greater chance of missing information than manual review conducted in the physician database. This was especially true for MGMT and IDH1/2 with about 17% and 40% of cases, respectively, having more information in the physician database. Using Landis and Koch (1977) guidelines for interpretation of Kappa statistic we found that IDH status had fair agreement, MGMT status had substantial agreement and 1p/19 loss of heterozygosity and ATRX status had almost perfect agreement. We also noticed that electronic extraction appeared to be improving over time with only 11% for both IDH 1/2 and MGMT having more information in the physician database in 2015 (data not shown). Therefore, it is possible that with time more information is being added to ARIA MO in an extractable format. Overall, the above pilot study supports the feasibility of extracting molecular characteristics electronically through ARIA MO and suggests this should be looked into further as it may be able to supplement the work already occurring to help reduce workload.

There are known limitations in our pilot study. The first limitation being that we were only able to extract information for patients who were seen at a CancerControl Alberta facility. Those who do not have a visit at CancerControl Alberta, would not have their information in ARIA MO and therefore test results would not be available for extraction in this study; this was about 13% of

our population of patients with CNS cancer (data not shown). Also, not only did the information have to be within ARIA MO, it also had to be in an extractable format (some interfaces do not allow for information to be extracted). Therefore, the results above are only a representation of what information is electronically available for extraction and can only provide broad estimates. However, by including not only pathology notes but all visit notes we decreased the likelihood that the test result would be missed (as if it was not extractable through a pathology report, it is often stated within a physician note).

There are also known limitations that come with text mining. Text mining involves searching for meaning and patterns within unstructured text to provide useful interpretations. Due to the nature of unstructured text fields, there is always the possibility of misconstruing information and potential of wrong interpretations. Therefore, it is important that results are reviewed and confirmed, which often entails manually examining the text under study. Text mining involves balancing the overall classification accuracy with false positive rates (Fuller & Dursun, 2012).

Furthermore, because CNS is a relatively rare cancer, one could assume relatively fewer oncologists are seeing these patients and therefore likely more consistent in visit note summaries. We assume this is favorable when electronically extracting information from ARIA MO. Therefore, our results might not be applicable to other cancer types; as data increases, it is likely that the selection algorithm would need to increase in complexity and need to accommodate more scenarios, which might not be as accurate. However, with new initiatives underway in Canada to support electronic synoptic pathology reporting, moving to more structured standardized information may help (CPAC, 2012). Based on previous studies (Sluijter et al., 2016), we would expect that synoptic reporting would increase the quality of molecular data electronically extracted for CNS cancers and also allow for molecular characteristics to be more easily extracted for more common cancers.

4.2.2 Testing practices in Alberta

Once we confirmed it was feasible to extract molecular characteristics from ARIA MO, the goal was to use this information as a first step in understanding current molecular testing practices for

CNS cancers in Alberta. Therefore, prevalence of biomarker testing for patients with CNS cancer diagnosed in Calgary from 2010 to 2015 was estimated using the information electronically extracted from ARIA MO. As mentioned above, the results are only a representation of what information is electronically available for extraction and therefore caution should be used when making conclusions. For example, patterns across time could be due to differences in actual testing or could be due to differences in how the information is available in ARIA MO.

Using electronic extraction from ARIA MO, IDH testing for gliomas appears to have substantially increased in the last six years going from 11% in 2010 to over 75% in 2015 (Table 10). Similarly, ATRX testing for glioblastoma and astrocytic tumours, was minimal until 2015 where we see over 75% of cases with a test result available in ARIA MO (Table 13). Testing for loss of heterozygosity of 1p/19q for oligodendroglial tumours diagnosed in Calgary from 2010 to 2015 was 98% of all cases, but much less (<10%) when looking at other low-grade gliomas as recently recommended by AHS (Table 12). MGMT testing appears to be inconsistently used for glioblastomas diagnosed in Calgary from 2010 to 2015 with the lowest at 43% of cases in 2012 to 77% of cases in 2015 (Table 11). Overall these results help provide a better understanding of information currently available in ARIA MO and support the belief that IDH1/2, MGMT, 1p/19q and ATRX are readily being tested for relevant subtypes, especially in more recent years.

Comparing our results to Ostrom et al. (2016) who reported average percent of completion for MGMT, 1p deletion and 19q deletion in SEER registries from 2010 to 2012, we see similar patterns by histology group, however we see a much higher percent of completion. For MGMT the highest average percent of completion reported in their study was 14% for glioblastomas, compared to 60% we see in our results for years 2010 to 2015. Also, for oligodendroglial tumours they saw around 40 to 55% completion for 1p deletion and 19q deletion where we found 98% completion. Our results show that testing for IDH1/2, MGMT, 1p/19q and ATRX is becoming increasingly prevalent in Alberta therefore supporting a need to collect this information.

There are many challenges ahead regarding validating and classifying the laboratory methods and clinical importance of each biomarker (Idbaih et al., 2015). One limitation of testing for these markers is that laboratory methods are still somewhat subjective and results can be difficult to interpret (Ostrom et al., 2016). Also, some clinicians may treat all patients similarly regardless of status of these markers and thus the test would not be relevant. However, with WHO's recently updated guidelines for CNS tumour classification the incorporation of these biomarkers into cancer registration will be critical as they will become a primary factor for classification (Louis et al., 2016). Also, when making a diagnosis, molecular information can provide valuable information not always known with histology, such as using ATRX mutations as a marker to help differentiate primary glioblastomas, where mutation is uncommon, from secondary glioblastomas, where mutation is frequent (Brat et. al, 2014). As the value of molecular medicine in diagnostics, prognostics and predictive value for treatment becomes more apparent, so does the need for formally collecting this information. Our study further supports the need to collect this information as well as a need to better coordinate efforts between clinicians and cancer registry staff to make the ACR more clinically relevant.

Chapter 5 Conclusion

5.1 Summary of Findings

5.1.1 Summary of findings - Impact of using DAD in case ascertainment of brain tumours

For benign brain tumours, 38% were identified through DAD review. This decreased to 19% for brain tumours with uncertain or borderline behaviours and only 5% for malignant brain tumours. The completeness of brain case ascertainment demonstrated by the ACR were in line with the original hypothesis for malignant cases and also confirms our hypothesis that there is a difference between malignant and non-malignant case ascertainment. These findings align with previous surveys with Canadian registries that work is needed to improve case ascertainment procedures of non-malignant CNS tumours (Davis et al., 2015).

Because overall case ascertainment of brain tumours on the ACR cannot be measured due to the inability to estimate the true number of cases missing, we used CBTRUS incidence rates to estimate the total number of expected tumours. When applying CBTRUS rates to the Alberta population, an estimated 2134 non-malignant brain tumour cases were expected from 2010 to 2014. The ACR would have only captured 50% of the expected non-malignant brain cases without DAD review. After additional coding of missed cases through DAD review, the ACR ultimately captured about 75% of the expected non-malignant cases. The actual rates in Alberta may be higher or lower than in the United States and therefore the CBTRUS rates can only be used as an approximation (as they may actually be an over or under estimate of the true number of cases for Alberta). However, this provides some indication that Alberta may still be missing some cases; however, given the observed number of brain cases in Alberta after DAD review is considerably more aligned with the expected number, Alberta appears to be getting much closer to capturing all brain tumours of interest in this study.

5.1.2 Summary of findings - Characteristics associated to under-reporting of brain tumours

Bivariate comparisons found identification through DAD to be significantly associated with: age group at diagnosis, behaviour, histological subtype, location at diagnosis, diagnostic confirmation, whether the patient's initial treatment was surgery, radiation therapy, or observation and whether a patient visited a CancerControl Alberta facility ($p \leq 0.05$). However, because of correlation of treatment types with diagnostic confirmation and whether a patient visited a CancerControl Alberta facility, we excluded treatment information in the logistic model. The multiple logistic regression model found cases being identified through DAD to be significantly associated with: patients 75 years and older (OR=2.5), benign behaviour (OR=2.6), location at diagnosis in Northern Alberta (OR=1.5), non-microscopically confirmed tumours (OR=1.3) and no visit to a CancerControl Alberta facility (OR=8.7). There were also differences in probability of registration depending on histological subtypes.

5.1.3 Summary of findings – Feasibility of extracting biomarkers from ARIA MO

The aim of this pilot study was to investigate the feasibility of extracting molecular characteristics electronically from information currently available in ARIA MO. The findings of this study confirm that we were able to extract biomarkers from ARIA MO for CNS cancers. Text mining of visit notes to extract test results was quite accurate when the information was available, with only approximately 1% discrepancy when compared to the physician database. However, electronic extraction had a greater chance of missing information than manual review conducted in the physician database. This appeared to get better with time indicating more information may be extractable in recent years. Overall, the above pilot study supports the feasibility of extracting molecular characteristics electronically and suggests that this should be investigated further.

When estimating the prevalence of testing for molecular parameters in Calgary from 2010 to 2015 by relevant histological subtype using electronic extraction, the following findings were observed:

- 98% of oligodendroglial tumours had a 1p/19q loss of heterozygosity test result extractable, but less than 10% of other low-grade gliomas had an available test result

- For gliomas, IDH1/2 testing appears to have substantially increased in the last six years going from approximately 10% in 2010 to 75% in 2015
- MGMT testing appears to be inconsistently tested for glioblastomas with the lowest at 43% of cases in 2012 to the highest at 77% of cases in 2015
- Minimal testing of ATRX for glioblastoma and astrocytic tumours was seen until 2015 where over 75% of cases had a test result available

Overall, these results align with our hypothesis that in recent years MGMT and 1p/19q are readily being tested in Calgary for relevant subtypes. Even though ATRX is not included currently in the clinical practice guidelines our results support that in 2015 it was being readily being tested. Similarly, we found that IDH1/2 was being tested, especially in 2015, even though not adapted in the clinical practice guidelines until 2016 (AHS, 2016). These results support the need to formally collect this information with the possibility of using electronic extraction as a feasible solution to decrease workload. This work can be used to inform guidelines and subsequent electronic reporting systems for CNS cancers.

5.2 Limitations of Study

A limitation of this study was the lack of alignment between ICD-O-3 (used in registry systems) and ICD-10 (used in DAD). Due to these differences we had to exclude some of the morphologies codes that are typically included in the CBTRUS CNS definitions. Table 19 in the appendix lists those codes that were excluded as they fall into ICD-10 categories not specific to CNS cancers and therefore not selected for review in this project. For example, ICD-O-3 morphology 9161/0 Acquired tufted hemangioma would translate to D18.0 Haemangioma of any site in ICD-10. As these codes are not specific to CNS tumours, they would require significant extra resources to review for a relatively small proportion of cases that would actually be a CNS tumour and considered to be a reportable condition. However, given they account for only 4% of CNS tumours in the United States (CBTRUS, 2017), we assume it would be a relatively small proportion of cases and not a huge impact when studying all CNS tumours.

Another limitation of our study is we only reviewed discharge abstracts from 2010 to 2015, therefore we suspect the estimated impact of DAD review could be underestimated in our study. Even though a patient was being seen in hospital from 2010 to 2015, many were diagnosed years prior. Some patients may only be followed in outpatient clinics and not in DAD or some may only be admitted years after diagnosis when symptoms worsen or disease progresses. Consequently, we would suspect with each annual DAD review there will be more cases caught in past diagnosis years and the impact even greater.

For the pilot study extracting molecular characteristics from the EMR, there are many known limitations. These include: 1) ability to only extract information for patients who were seen at a CancerControl Alberta facility, 2) information had to be in ARIA MO in an extractable format, 3) text mining has the possibility of misconstruing information and potential of wrong interpretations, and 4) as CNS is a relatively rare cancer, we assume this is favorable for consistency and simplicity of the selection algorithm, so our results might not be applicable to other cancer types. Therefore, the results are only a representation of what information is electronically available for extraction and caution should be used when making conclusions. For example, patterns across time could be due to differences in how the information is available in ARIA MO or differences in actual testing practices.

5.3 Implications of Findings

This study will provide a measure of accuracy of surveillance estimates as well as provide physicians and researchers with a better understanding of the completeness of brain tumours in the ACR. Given the significant impact DAD review had on non-malignant brain tumour case ascertainment, previous studies that included non-malignant tumors would have under estimated the burden of disease. It is also likely similar problems exist in other cancer registries that do not perform hospital or radiological database linkages and therefore special consideration into case ascertainment procedures should be given for studies including non-malignant CNS tumours. These types of studies are important not only for epidemiological studies and operational planning, but also in evaluating performance of cancer registries. DAD review has already had significant impact on improving completeness of case ascertainment of brain tumours in Alberta.

There were 749 cases of brain tumours diagnosed from 2010 to 2015 that have been added to the ACR and available for future studies.

This study has also identified characteristics that reflect potential barriers to registration for non-malignant brain tumours. By identifying these barriers, the ACR can investigate these further to identify possible process improvements and assist with allocation of resources in the future. Key implications regarding the potential barriers to registration identified in this study are:

- Given under-reporting was more common older patients, one implication of this is the impact it could have on reporting of survival rates (if these patients are less likely to survive their disease).
- Non-microscopically confirmed tumours were more likely to be under-reported implying there is a need for further communication with radiologists and laboratories submitting notifications for these tumours.
- Even though statistically more likely to be initially missing non-microscopically confirmed tumours, surprisingly there was still a large number of microscopically confirmed brain tumours initially missed. This may also imply a need for further communication with pathologists as well.
- Lastly, the fact that location at diagnosis was a strong predictor for registration was surprising given the ACR is provincially mandated. Reasons for this difference need to be investigated further; there could be possible difference in coding practices, accessibility of information, or in notifications for registration.

As far as feasibility of extracting molecular characteristics electronically through ARIA MO, the results from our pilot study support this ability and we conclude there is a need to explore this further. We acknowledge that electronic extraction has a greater chance of missing information, however when information was accessible it had a high percent agreement. We also noticed that electronic extraction appeared to be improving over time, therefore, it is possible with time more information is being added to ARIA MO in an extractable format. Overall, we conclude that electronic extraction of molecular characteristics should be investigated as a source to supplement efforts in data collection to reduce overall workload.

5.3 Recommendations

Given Alberta's review of DAD cases found a large number of under-reported non-malignant brain tumours, it is recommended that other provinces and territories review their procedures for case ascertainment as well. Since, Alberta had the second highest estimate of completeness of case ascertainment in Canada (after Manitoba), DAD review might have an even greater impact on other provinces and territories in Canada (Shaw et al., 2014). We also recommend that DAD review for brain and CNS tumours in Alberta continues on an annual basis while other techniques for case ascertainment are explored. Also, characteristics identified as potential barriers to registration should be investigated to further identify possible process improvements.

Even though this study estimated completeness of case ascertainment based on review of DAD compared to the ACR, it is still unclear how many cases may have been missed by both DAD and ACR. Methodology was used to estimate the number of expected cases, assuming similar rates in the United States to Alberta, but there is still uncertainty involved with this method. Therefore, completeness of case ascertainment in this study is only an estimate and could be an under or over estimate of the true value. Further investigation could include looking at cases that are in physician billing data or linkages with diagnostic imaging databases if available.

Considerations for the future would be to clarify the definition of primary brain tumours to be included in DAD review, such as expanding the selection criteria of DAD to include additional sites such as pituitary glands, craniopharyngeal duct, and pineal gland. Also, similar studies could be done to assess the impact of using DAD in case ascertainment of other cancers with higher risk of being under-reported, such as hematological cancers (Teppo et al., 1994; Phekoo, Moller, Richards, & Schey, 2002). One limitation of using DAD, is there are known ICD code accuracy errors due to: quality of information at admission, communication between patient and provider, clinician's knowledge of illness and attention to detail, discrepancies in records, coder training/experience, and quality-control efforts (O'Malley et al., 2005). Therefore, manual review of cases in DAD is required which involves an extensive amount of resources. So while

using DAD to catch missed cases is valuable, especially for cancer sites with known case ascertainment issues, it may not be the best use of resources for all cancer sites.

As the value of molecular medicine becomes more apparent, so does the need for formally collecting this information. The importance in diagnosis is evident when looking at WHO's recently published guidelines for CNS tumour classification that incorporate both histology and molecular parameters in the system (Louis et al., 2016). This study supports the need to collect molecular information further by showing that in Calgary testing for IDH, MGMT, 1p/19q and ATRX are readily being conducted and becoming more prevalent in recent years. This study also demonstrates a need to better coordinate efforts between clinicians and cancer registry staff to make the ACR more clinically relevant. As noted by Chen et al. (2014) using population-based central cancer registries to collect data has numerous strengths. Pre-existing laws and infrastructure often allow Cancer Registries to more timely collect additional data. Cancer Registries already have well-established standard rules and codes for tumour reportability and coding, in addition to staff with extensive experience. Another important feature is that Cancer Registries are population-based and therefore findings from research can be generalized to the entire population. Even though there are great advantages to having the cancer registry collecting additional data, there are also limitations including additional training and resources required that potentially could cause delays of routine registry data collection. Therefore, it is important that Cancer Registries work closely with health care providers to ensure that Cancer Registry and clinical data requirements are aligned to support changing needs related to program operations, surveillance and research (MacIntyre & MacKay, 2018). Even though this work has known limitations as previously mentioned, we hope this will help provide some feedback to inform future guidelines and data collection needs for molecular testing of CNS tumours.

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Appendix

Table 18. Brain Tumour ICD-O-3 Topography and Behaviour Inclusions and corresponding ICD-10 Codes[1]

ICD-O-3 Topography	ICD-O-3 Behaviour	ICD-O-3 Description	ICD-10 Conversion	ICD-10 Description
C70	/0	Benign meninges	D32	Benign neoplasm of meninges
C71	/0	Benign brain	D33	Benign neoplasm of brain and other parts of CNS
C72	/0	Benign spinal cord, cranial nerves, and other parts of central nervous system		
C70	/1	Uncertain meninges	D42	Neoplasms of uncertain or unknown behaviour of meninges
C71	/1	Uncertain brain	D43	Neoplasms of uncertain or unknown behaviour of CNS
C72	/1	Uncertain spinal cord, cranial nerves, and other parts of central nervous system		
C70	/3	Malignant meninges	C70	Malignant neoplasms of meninges
C71	/3	Malignant brain	C71	Malignant neoplasms of brain
C72	/3	Malignant spinal cord, cranial nerves, and other parts of central nervous system	C72	Malignant neoplasms of spinal cord, cranial nerves and other parts of CNS

[1]Table adapted from Surveillance, Epidemiology and End Results Program. (2014, August 5). ICD conversion programs. Retrieved from https://seer.cancer.gov/tools/conversion/

Table 19. Brain Tumour ICD-O-3 Morphology Exclusions and corresponding ICD-10 Codes[1]

ICD-O-3 Morphology	ICD-O-3 Description	ICD-10 Conversion	ICD-10 Description
9590-9992 /3	Tumours of haematopoietic and lymphoid tissue, malignant	C81-C96, D45, D46	C81-C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue D45 Polycythaemia vera D46 Myelodysplastic syndromes
9590-9992 /1	Tumours of haematopoietic and lymphoid tissue, uncertain	D47, D76.0, L41.2	D47 Other neoplasms of uncertain or unknown behaviour of lymphoid, haematopoietic and related tissue D76.0 Langerhans' cell histiocytosis, not elsewhere classified L41.2 Lymphomatoid papulosis
9050-9055 /0	Mesothelioma, benign	D19	Benign neoplasms of mesothelial tissue
9050-9055 /3	Mesothelioma, malignant	C45	Mesothelioma
9140/3	Kaposi Sarcoma	C467	Kaposi Sarcoma of other sites
9100/0	Hydatidiform mole, NOS	O01.9	Hydadidiform mole, unspecified
9100/1	Invasive hydatidiform mole	O01.9	Hydadidiform mole, unspecified
9103/0	Partial hydatidiform mole	O01.9	Hydadidiform mole, unspecified
9540/1	Neurofibromatosis, NOS	Q85.0	Neurofibromatosis (non-malignant)
8850/0	Lipoma, NOS	D17.9	Benign lipomatous neoplasm, unspecified
8851/0	Fibrolipoma	D17.9	Benign lipomatous neoplasm, unspecified
8852/0	Fibromyxolipoma	D17.9	Benign lipomatous neoplasm, unspecified
8854/0	Pleomorphic lipoma	D17.9	Benign lipomatous neoplasm, unspecified
8856/0	Intramuscular lipoma	D17.9	Benign lipomatous neoplasm, unspecified
8857/0	Spindle cell lipoma	D17.9	Benign lipomatous neoplasm, unspecified
8860/0	Angiomyolipoma	D17.9	Benign lipomatous neoplasm, unspecified
8861/0	Angiolipoma, NOS	D17.9	Benign lipomatous neoplasm, unspecified

8862/0	Chondroid lipoma	D17.9	Benign lipomatous neoplasm, unspecified
8870/0	Myelolipoma	D17.9	Benign lipomatous neoplasm, unspecified
8880/0	Hibernoma	D17.9	Benign lipomatous neoplasm, unspecified
8881/0	Lipoblastomatosis	D17.9	Benign lipomatous neoplasm, unspecified
8711/0	Glomus tumor, NOS	D18.0	Haemangioma, any site
8712/0	Glomangioma	D18.0	Haemangioma, any site
8713/0	Glomangiomyoma	D18.0	Haemangioma, any site
9120/0	Hemangioma, NOS	D18.0	Haemangioma, any site
9121/0	Cavernous hemangioma	D18.0	Haemangioma, any site
9122/0	Venous hemangioma	D18.0	Haemangioma, any site
9123/0	Racemose hemangioma	D18.0	Haemangioma, any site
9125/0	Epithelioid hemangioma	D18.0	Haemangioma, any site
9130/0	Hemangioendothelioma, benign	D18.0	Haemangioma, any site
9131/0	Capillary hemangioma	D18.0	Haemangioma, any site
9132/0	Intramuscular hemangioma	D18.0	Haemangioma, any site
9141/0	Angiokeratoma	D18.0	Haemangioma, any site
9142/0	Verrucous keratotic hemangioma	D18.0	Haemangioma, any site
9150/0	Hemangiopericytoma, benign	D18.0	Haemangioma, any site
9160/0	Angiofibroma, NOS.	D18.0	Haemangioma, any site
9161/0	Acquired tufted hemangioma	D18.0	Haemangioma, any site
9170/0	Lymphangioma, NOS	D18.1	Lymphangioma, any site
9171/0	Capillary lymphangioma	D18.1	Lymphangioma, any site
9172/0	Cavernous lymphangioma	D18.1	Lymphangioma, any site
9173/0	Cystic lymphangioma	D18.1	Lymphangioma, any site
9174/0	Lymphangiomayoma	D18.1	Lymphangioma, any site
9175/0	Hemolymphangioma	D18.1	Lymphangioma, any site
8247/3	Merkel cell carcinoma	C44.9	Malignant neoplasm of skin, unspecified

[1]Table adapted from Surveillance, Epidemiology and End Results Program. (2014, August 5). ICD conversion programs. Retrieved from https://seer.cancer.gov/tools/conversion/

Table 20. Central Brain Tumour Registry of the United States (CBTRUS), Brain and Other Central Nervous System ICD-O-3 Topography and Morphology Inclusions[1]

ICD-O-3 Topography	ICD-O-3 Description	ICD-O-3 Morphology
C70	Meninges	All
C71	Brain	All
C72	Spinal Cord, Cranial Nerves and Other CNS	All
C751	Pituitary gland	All
C752	Craniopharyngeal duct	All
C753	Pineal gland	All
C300	Nasal Cavity	9520 Olfactory neurogenic tumor 9521 Olfactory neurocytoma 9522 Olfactory neuroblastoma 9523 Olfactory neuroepithelioma

[1] Table based off Table 1 of Ostrom, Q. T., Gittleman, H., Liao, P., Vecchione-Koval, T., Wolinsky, Y., Kruchko, C., & Barnholtz-Sloan, J. S. (2017). CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. *Neuro-Oncology, 19*(S5), 1-88. doi:10.1093/neuonc/nox158

Table 21. List of variables and description requested from C-MORE for data analysis

Variable Name	Description
ACB Number	The number which uniquely identifies a client of a CancerControl facility and appears on the patient's paper medical chart/report/microfiche.
Malignancy Number	Primary number counter indicating the order of reportable conditions coded for a patient.
Gender	The gender of the client.
Age at Diagnosis	Age of the patient at diagnosis.
Zone at Diagnosis	Zone of the usual residence of the patient at time of diagnosis.
Diagnosis Date	To identify the first date the primary is recognized by the medical system (by the most definitive method), which leads to a treatment decision.
ICD-O-3 Topography	The code representing the anatomical location of the primary. Refer to ICD-O-3 for cases diagnosed 2001 to present.
ICD-O-3 Morphology	The 5 digit code representing the cell type(s) and behaviour of the tumour. Refer to ICD-O-3 for cases diagnosed 2001 to present.
Diagnostic Method	How the primary was established which reflects the date of diagnosis. Values from high to low priority are: cytology, histology, laboratory, surgery, radiology, clinical, death certificate, and unknown.
Diagnostic Confirmation	The most definitive method of diagnosis. Values are: positive histology, positive cytology, positive histology plus, autopsy only, positive laboratory test/marker study, direct visualization without microscopic confirmation, radiography and other imaging without microscopic confirmation, clinical diagnosis including physical findings, death certificate only, and method of diagnosis unknown.
Initial Treatment Types	The method(s) used to treat the primary site. Indicates all initially planned treatment to the primary.
Initial Treatment Dates	The start date of a particular treatment modality.
Visit CancerControl Alberta	Flag to indicate if a patient visited a CancerControl Alberta facility for the primary of interest.
Facility Visited	Name of the CancerControl Alberta facility the patient visited for the primary of interest.
DAD Flag	Flag to indicate if the case was a part of DAD review.

Source: Alberta Cancer Registry Coding Manual, CancerControl Alberta, Alberta Health Services, personal communication, April 26, 2018

Table 22. Central Brain Tumour Registry of the United States (CBTRUS), Brain and Other Central Nervous System Tumour Histology Groupings[1]

Main Histology Group	Histology Subtype	ICD-O-3 Histology Code
Tumors of Neuroepithelial Tissue	Pilocytic astrocytoma[2]	9421, 9425
	Difuse astrocytoma[2]	9400, 9410, 9411, 9420
	Anaplastic astrocytoma[2]	9401
	Unique astocytoma variants[2]	9381, 9384, 9424
	Glioblastoma[2]	9440, 9441, 9442/3
	Oligodendroglioma[2]	9450
	Anaplastic oligodendroglioma[2]	9451, 9460
	Oligoastrocytic tumors[2]	9382
	Ependymal tumors[2]	9383, 9391, 9392, 9393, 9394
	Glioma malignant, NOS[2]	9380, 9431, 9432
	Choroid plexus tumors	9390
	Other neuroepithelial tumors[2]	9363, 9423, 9430, 9444
	Neuronal and mixed neuronal-glial tumors[2]	8680, 8681, 8690, 8693, 9412, 9413, 9442/1,9492 (excluding site C75.1), 9493, 9505, 9506, 9522, 9523
	Tumors of the pineal region	9360, 9361, 9362, 9395
	Embryonal tumors	8963, 9364, 9470, 9471, 9472, 9473, 9474, 9480, 9490, 9500, 9501, 9502, 9508
Tumors of Cranial and Spinal Nerves	Nerve sheath, non-malignant and malignant	9540, 9541, 9550, 9560, 9561, 9570, 9571
	Other tumors of cranial and spinal nerves	9562
Tumors of Meninges	Meningioma	9530, 9531, 9532, 9533, 9534, 9537, 9538, 9539
	Mesenchymal tumors	8324, 8800, 8801, 8802, 8803, 8804, 8805, 8806, 8810, 8815, 8824, 8830, 8831, 8835, 8836, 8850, 8851, 8852, 8853, 8854, 8857, 8861, 8870, 8880, 8890, 8897, 8900, 8901, 8902, 8910, 8912, 8920, 8921, 8935, 8990, 9040, 9136, 9150, 9170, 9180, 9210, 9241, 9260, 9373
	Primary melanocytic lesions	8720, 8728, 8770, 8771
	Other neoplasms related to the meninges	9161, 9220, 9231, 9240, 9243, 9370, 9371, 9372, 9535

Lymphomas and Hemopoietic Neoplasms	Lymphoma	9590, 9591, 9596, 9650, 9651, 9652, 9653, 9654, 9655, 9659, 9661, 9662, 9663, 9664, 9665, 9667, 9670, 9671, 9673, 9675, 9680, 9684, 9687, 9690, 9691, 9695, 9698, 9699, 9701, 9702, 9705, 9714, 9719, 9728, 9729
	Other hemopoietic neoplasms	9727, 9731, 9733, 9734, 9740, 9741, 9750, 9751, 9752, 9753, 9754, 9755, 9756, 9757, 9758, 9760, 9766, 9823, 9826, 9827, 9832, 9837, 9860, 9861, 9866, 9930, 9970, 9971[3]
Germ Cell Tumors and Cysts	Germ cell tumors, cysts and heterotopias	8020, 8440, 9060, 9061, 9064, 9065, 9070, 9071, 9072, 9080, 9081, 9082, 9083, 9084, 9085, 9100, 9101
Tumors of Sellar Region	Tumors of the pituitary	8040, 8140, 8146, 8246, 8260, 8270, 8271, 8272, 8280, 8281, 8290, 8300, 8310, 8323, 9492 (Site C75.1 only), 9582
	Craniopharyngioma	9350, 9351, 9352
Unclassified Tumors	Hemangioma	9120, 9121, 9122, 9123, 9125, 9130, 9131, 9133, 9140
	Neoplasm, unspecified	8000, 8001, 8002, 8003, 8004, 8005, 8010, 8021
	All Other	8320, 8452, 8710, 8711, 8713, 8811, 8840, 8896, 8980, 9173, 9503, 9580, 8821[3]

[1] Table based off Table 2 of Ostrom, Q. T., Gittleman, H., Liao, P., Vecchione-Koval, T., Wolinsky, Y., Kruchko, C., & Barnholtz-Sloan, J. S. (2017). CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. *Neuro-Oncology, 19*(S5), 1-88. doi:10.1093/neuonc/nox158

[2]All or some of this histology is included in the CBTRUS definition of gliomas, including ICD-O-3 histology codes 9380-9384, 9391-9460.

[3]ICDO-3 Histology Code added for this study (as not originally on CBTRUS table).

Table 23. Prevalence and percent distribution of availability of IDH1/IDH2 test result using ARIA MO by year of diagnosis for All CNS Histological Subtypes, 2010-2015, Calgary

Availability of IDH1/2 test based on electronic extraction	Year of Diagnosis						Total, n (%)
	2010, n (%)	2011, n (%)	2012, n (%)	2013, n (%)	2014, n (%)	2015, n (%)	
No CancerControl Alberta Visit or IDH test result not found	76 (90)	60 (74)	58 (65)	41 (47)	41 (49)	38 (32)	314 (58)
IDH test result found	8 (10)	21 (26)	31 (35)	46 (53)	42 (51)	79 (68)	227 (42)
Total	84	81	89	87	83	117	541

Table 24. Prevalence and percent distribution of availability of MGMT test result using ARIA MO by year of diagnosis for All CNS Histological Subtypes, 2010-2015, Calgary

Availability of MGMT test based on electronic extraction	Year of Diagnosis						Total, n (%)
	2010, n (%)	2011, n (%)	2012, n (%)	2013, n (%)	2014, n (%)	2015, n (%)	
No CancerControl Alberta Visit or MGMT test result not found	44 (52)	40 (49)	64 (72)	44 (51)	46 (55)	46 (39)	284 (52)
MGMT test result found	40 (48)	41 (51)	25 (28)	43 (49)	37 (45)	71 (61)	257 (48)
Total	84	81	89	87	83	117	541

Table 25. Prevalence and percent distribution of availability of 1p/19q loss of heterozygosity test result using ARIA MO by year of diagnosis for All CNS Histological Subtypes, 2010-2015, Calgary

Availability of 1p/19q test based on electronic extraction	Year of Diagnosis						Total, n (%)
	2010, n (%)	2011, n (%)	2012, n (%)	2013, n (%)	2014, n (%)	2015, n (%)	
No CancerControl Alberta Visit or 1p/19q test result not found	73 (87)	66 (81)	79 (89)	71 (82)	72 (87)	96 (82)	457 (84)
1p/19q test result found	11 (13)	15 (19)	10 (11)	16 (18)	11 (13)	21 (18)	84 (16)
Total	84	81	89	87	83	117	541

Table 26. Prevalence and percent distribution of availability of ATRX test result using ARIA MO by year of diagnosis for All CNS Histological Subtypes, 2010-2015, Calgary

Availability of ATRX test based on electronic extraction	Year of Diagnosis						Total, n (%)
	2010, n (%)	2011, n (%)	2012, n (%)	2013, n (%)	2014, n (%)	2015, n (%)	
No CancerControl Alberta Visit or ATRX test result not found	81 (96)	78 (96)	88 (99)	81 (93)	70 (84)	41 (35)	439 (81)
ATRX test result found	3 (4)	3 (4)	1 (1)	6 (7)	13 (16)	76 (65)	102 (19)
Total	84	81	89	87	83	117	541