Cost-Effectiveness of Treatment Strategies for Selumetinib to Neurofibromatosis Type I Inoperable Plexiform Neurofibromas Patients Aged 3 to 18

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Table of Contents

ABSTRACT 3
ACKNOWLEDGEMENTS 5
INTRODUCTION 6
LITERATURE REVIEW 9
Neurofibromatosis Type I: An Overview 9
Selumetinib: A Therapy for Neurofibromatosis Type I Inoperable Plexiform Neurofibromas 11
Health Economics and Pharmacoeconomic Evaluation: A Brief Survey 12
Caveats in Pharmacoeconomic Evaluation 18
MATERIALS AND METHODS 20
Time-Dependent Markov Model to Assess Cost Effectiveness 20
Databases and Literature Search 23
Sensitivity Analysis 37
RESULTS 42
Probabilistic Sensitivity Analysis 44
Two-Way Sensitivity Analysis 48
DISCUSSION 51
Limitations and Delimitations 51
Contributions 52
External Validity 53
Future Research 54
CONCLUSION 56
APPENDIX A: FIGURES 67
APPENDIX B: TABLES 76

ABSTRACT

Assessing the cost effectiveness for drugs targeting ultra-rare diseases is complex given the limited clinical evidence for many drugs, yet is growing in importance as the number of these drugs being commercialized is increasing rapidly. Selumetinib is a recently FDA-approved MEK inhibitor for patients aged 3 to 18, with Neurofibromatosis Type I (NF1) Inoperable Plexiform Neurofibromas (PN), a rare genetic disorder, and has been shown in clinical trials to stabilize and contract tumors by up to 20%. As this is an expensive drug with costs ranging from $76,672.03 to $357,802.84CAD (2022) per year of treatment depending on one's body-surface-area, examining its cost-effectiveness to the health system is important; yet made difficult due to the behaviour of the disease largely dependent on one's age. Accordingly, this paper uses the best available clinical evidence, including that of the recent SPRINT clinical trial, to produce a time-dependent Markov model, where costs, utilities and probabilities are based on either the Markov stage, patient age, or both; to evaluate the cost-effectiveness of potential dosing strategies of Selumetinib for NF1 Inoperable PN patients aged 3 to 18. Potential treatment strategies were developed, differing on the number of years a patient would take Selumetinib following clinical response. Incremental cost effectiveness ratios (ICER), representing cost per quality adjusted life year (QALY), were calculated for the strategies, which ranged from $74,671.90 CAD to $255,674.71 CAD. A Monte-Carlo simulation was run in each scenario, assuming a maximum willingness-to-pay threshold of $150,000, which revealed Selumetinib being cost-effective in 70.94% of iterations in the lowest intensity strategy, and in only 6.717% of iterations of the highest intensity. Recognizing this study is limited to understanding the cost-effectiveness of potential treatment

strategies of this drug for this population, this paper hopes to support development of such strategies, along with clinical and epidemiological evidence, in providing an economic perspective. Beyond this application, this paper sets the stage not only for further cost-effectiveness of Selumetinib for other populations, but also of other novel drugs with costs, utilities, and probabilities, in part, based on patient age, through use of the time-dependent Markov model. Future research directions are discussed, based on the limitations of the current study.

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INTRODUCTION

"All models are wrong, but some are useful"

-George Box

Contract negotiation of new pharmaceuticals requires evidence-based valuations of the drug's health benefits in nominal terms, such as to estimate the incremental cost-effectiveness ratio (ICER) of a new drug (Zhang, Zaric and Tuang, 2011), which is also useful in the economic evaluation of potential treatment strategies for novel drugs (Cipriano, Barth and Zaric, 2010). These necessitate that the cost for each quality-adjusted-life-year (QALY) gained from the drug, not otherwise achieved in the standard of care, is within a country's specified maximum willingness-to-pay threshold, which are generally between $50,000 to $150,000 per QALY gained. Cost-effectiveness analysis assists health systems prioritize and maximise health benefits while working within limited financial and societal resources (Folland, Goodman and Stano, 2016), in setting economic boundaries of delivering treatment that delivers a desired health outcome within a willingness-to-pay. In most studies, the ICER is calculated with the assumption of having constant costs and benefits to a patient group, over time. While this may be well suited for analysis of cancers targeting older individuals, this poses limitations for analysis of many new drugs that target genetic conditions on younger patients, where costs and utilities thereby vary substantially with patient age.

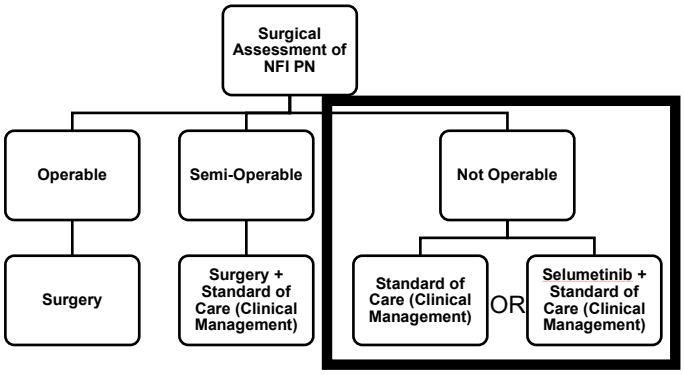
Selumentinib is a recent FDA approved MEK 1/2 inhibitor, for patients with Neurofibromatosis Type I (NF1) of Plexiform Neurofibromas (PN), a rare genetic condition for patients aged 3 to 18 years. This disease is usually diagnosed in young people, for whom 50% with symptomatic PN are inoperable due to the location of the tumor alongside

complex nervous systems (Copley-Merriman, 2021). Until recently, this population was left without treatment aside from clinical management to reduce pain (Anderson et. al, 2021).

Selumentinib has been shown in clinical trials to stabilize or reduce tumor growth by up to 20% (Gross et. al, 2020), significant especially for pediatric patients where tumors grow most frequently in younger ages before plateauing in young adolescence (Dombi, Solomon and Gillespie, 2007). Costs for administering this drug, however, are not cheap, with annualized, gender-weighted costs ranging from over $76,672.03 to $306,688.15 CAD (2022) for patients aged 3 and 18 respectively.

Accordingly, this research responds to calls (see for instance, Copley-Merriman, 2021; Anderson et. al, 2021; Mukhopadhyayet. al, 2021) from recent research on modelling cost-effectiveness of various treatment strategies for Selumetinib plus the Standard of Care (SoC) over the Standard of Care, for the approved population. As many costs and utilities vary by age, this paper develops a time-dependent Markov model, where state transition probabilities, health utilities and treatment costs are allowed to vary depending on the stage, patient age or both, for a set of treatment strategies. The decision model is seen in Figure 1, as below:

Figure 1: Surgical Decision Flowchart, with the decision at hand highlighted in the bordered box.



Data from the SPRINT (Selumetinib in Pediatric Neurofibromas Type I) trial of Selumenitib, a recently FDA-approved MEK inhibitor, for patients aged 3 to 18 with NF1 PN, is used. This drug that has been shown in clinical trials to stabilize and contract tumors by up to 20% (Gross et. al, 2020), which is significant, as tumors grow most frequently in younger ages before plateauing in young adolescence (Dombi, Solomon and Gillespie, 2007). Costs for administering this drug, however, are not cheap, and vary depending on one's body-surface-area, increasing for each year of treatment as one gets closer to the age of 18 (Anderson et. al, 2021), which is naturally correlated with age in younger people. Accordingly, costs and utilities thereby vary depending on age.

This paper proceeds in four parts. First, relevant literature is reviewed with respect to cost- effectiveness in healthcare to highlight the gaps; and the empirical context is outlined. The methodology then follows, where treatment strategies are also discussed. Results, in terms of the ICER in the base case, Monte-Carlo simulations of 100,000 and with changes in the mean age at diagnosis, are then discussed of each treatment strategy along with deterministic two-way sensitivity analysis of the entire model. The results are then discussed as to their contextual, theoretical, and methodological implications for health economics and operations management.

It is widely acknowledged that estimating the cost effectiveness of treatment strategies for NF1 or other rare diseases, and of novel drugs targeting these diseases, are difficult due to limited data and sample sizes. Overall, the goal of this research is to inform cost-effective, evidence-based decision making of healthcare payers, including governments, providers, and insurers (see for instance Galvin et. al, 2021), regarding Selumetinib for NF1 Inoperable PN patients 3 to 18. Accordingly, this study takes a systematic approach but does not include effects to family members' qualities of life nor any of their indirect opportunity costs such as lost wages; and is thereby limited solely to direct costs to the health system and direct utilities to patient quality of life.

LITERATURE REVIEW

Neurofibromatosis Type I: An Overview

Neurofibromatoses are neurological disorders caused by a rare genetic and tumor-predisposing factor combination and come in three distinct phenotypes: Neurofibromatosis Type 1 (NF1), Neurofibromatosis Type 2 (NF2), and Schwannomatosis. NF1 is an autosomal[1] dominant genetic disorder caused by pathogenic variants in the germline NF1 gene (Copley-Merriman, 2021) whereby the NF1 gene encodes neurofibromin, a RAS GTPase-activating tumour suppressor protein that inhibits the mitogen-activated protein kinase (MAPK) signalling pathway. Mutations in the NF1 gene cause uncontrolled cell growth (Menon, Gusella and Sizinger, 1990).

Neurofibromatosis type 1 (NF1) is an incurable genetic disorder affecting 1 in 3000 newborns worldwide. The severity of NF1 signs and symptoms can vary, as can how they manifest in patients (Santo et. al, 2020). NF1 can be complicated by the presence of

[1] The genetic disorder is located on one of the non-sex chromosomes.

tumours known as Plexiform Neurofibromas, (PNs) which are benign peripheral nerve tumours that grow in a plexiform pattern (Carrol and Ratner, 2008) and can become cancerous, malignant peripheral nerve sheath tumors (MPNSTs). A plexiform pattern resembles a plexus, or interconnected network, of thin vessels and nerves which become clustered. In many cases, plexiform neurofibromas causes significant morbidity as they affect multiple nerve branches and plexi, making surgery very complex. Some patients undergo surgical resection to remove or reduce tumour volume though in many cases, the tumor is intertwined with vital structures leaving high probabilities of regrowth (Needle, Canaan and Dattilo, 1997).

Common NF1 complications with PN include pain, motor dysfunction, and weakness, among others (Gross, Wolters and Baldwin, 2018). Rare PN comorbidities include vision impairment or loss, bowel and bladder dysfunction and a host of spinal issues (Gross, Singh, and Akshintala, 2018). Complications of those which transform into Malignant Peripheral Nerve Sheath tumors (MPNSTs) include airway or spinal cord compression (Kim, Gillespie and Dombie, 2009; Prada, Rangwala and Martin, 2012), which could result in premature death. The lifetime risk of MPNSTs in NF1 patients ranges from 8% to 13% and symptomatic PN patients with MPNSTs have a 5-year survival rate of just over 40% (Monroe, Dahiya and Gutmann, 2017).

Studies on PN volume changes in children and young adults with NF1 and inoperable, symptomatic or progressive PNs, demonstrate much faster tumour growth in younger patients (Dombi, Solomon and Gillespie, 2007), with growth rates fitting a logarithmic function and plateauing between ages of 16 and 21. A major predictor of PN growth rate, and reduced quality of life, is age, and is unrelated to the PN site or volume

at baseline. To put this into context, tumors grow 35.1 percent per year for patients 3–5 years old, compared to 13.1 percent per year for patients 11–25 years old. The rapid pace of growth has also been linked to increased morbidity (Gross, Singh and Akshintala, 2020). Surface tumours grow faster than deep tumours (Tucker et. al, 2009). These findings highlight the importance of treating younger patients due to the rapid increase in PN sizes. As shown in Appendix B, Table 1, approximately 250 people qill (?) qualify as between 3 and 18 with NF1 Inoperable PN.

Selumetinib: A Therapy for Neurofibromatosis Type I Inoperable Plexiform Neurofibromas

Recent research on Neurofiromin's role in the core MEK signalling pathway has resulted in the development of a new targeted or precision medicine therapy (Anderson et. al, 2021): the mitogen-activate protein kinase 1/2 inhibitor, Selumetinib. Selumetinib was recently approved by the United States *Food and Drug Administration* (FDA) for the treatment of paediatric patients with NF1 who have symptomatic, incurable PN – a population that would otherwise not have effective drug therapies (Copley-Merriman et. al, 2021). This novel APT-independent MEK 1/2 inhibitor is the first and only FDA-approved treatment for patients with NFI PN.

Early results indicate that it is highly likely to target the mitogen-activated protein kinase (MEK) signalling pathway in patients who would otherwise be unable to undergo surgery for an NFI-PN. However, some patients experience side effects from Selumetinib, which are mostly related to their age, with older patients experiencing more complications (Anderson et. al, 2021).

Selumetinib has been granted breakthrough drug status and appears to provide patients with unprecedented and long-lasting reductions in tumour burden, morbidity, and quality of life. The SPRINT trial (Anderson et al., 2021) is currently evaluating the feasibility of using an intermittent dosing schedule to improve patient adherence and satisfaction, as this area is perceived to be difficult (Anderson et. al., 2021) due to difficulties with younger children in swallowing the medication. Nonetheless, medication adherence was in excess of 98% in the SPRINT clinical trial (Gross et. al, 2019). Accordingly, a granule formulation is currently being developed to enhance age-appropriate formulation options for such patients who are unable to swallow whole capsules (Cohen-Rabbie et. al., 2020).

Selumetinib has been associated with serious adverse events in some adult populations (Baldo et al., 2020; Hwang et al., 2020), necessitating routine patient monitoring, and the long-term safety profile is unknown. Selumetinib may also develop resistance. As a result, the drug is primarily used to treat paediatric patients with extremely rapid growth rates; and is currently under further clinical trial for adult patients (clinicaltrials.org #NCT04924608).

Health Economics and Pharmacoeconomic Evaluation: A Brief Survey

Cost is a major factor in the implementation of any new drug therapy and as is the case with many new treatments in the broader field of precision medicine such as Selumetinib. As a result, consideration must be given to which patients will benefit the most from it. A pharmacoeconomic study to assess cost effectiveness on this novel treatment, which has been requested in recent research, has not yet been completed (i.e. Anderson, et. al., 2021; Copley-Merriman, 2021). As reported in Anderson et. al. (2021),

the average wholesale price for Selumetinib is $5443.76 USD for a bottle of 60 capsules of 10 mg and $13 609.44 for a bottle of 60 capsules of 25 mg, according to the IBM Micromedex Redbook database. As the size of the dose depends on body surface area (BSA) and as BSA is tied to age, older patients would on average be far more expensive to treat than younger patients. Treatments range from 30 mg total per day, to 70 mg per day, and a patient is assumed to continue treatment unless complications arise, until the age of 18.

There is a notable gap of literature on NF1 and PN in terms of health-care resource use and costs, indicating a significant data gap. The only study to date, examines medical needs of NF1 patients in France to examine the financial cost of resources used in relation to disease severity (Wolkenstein et. al, 2000). The two most common reasons for hospitalisation for these patients were removal of multiple PNs, and MPNSTs. The early success of Selumetinib in the treatment of PNs serves as proof of concept for MEK inhibitors in this setting, and since its approval, other MEK inhibitors are being investigated for the treatment of various types of Neurofibromatoses, including drugs such as Trametinib, Mirdametinib, and Binimetinib (Galvin et. al, 2021).

As more MEK inhibitors are approved for use in this patient population, comparison studies of efficacy and safety profiles will be necessary. Several studies are also underway to determine the efficacy of Selumetinib in the treatment of other NF-related tumours and in patients with semi-operable PN and adults with PN (Gross, Dombi and Widemann, 2020). However, efficacy of drug compounds needs to also be combined with an evaluation of cost to ascertain the efficiency and cost-effectiveness on new treatments and their effects on health care budgets. In the case of Canada, new drugs

require provincial government approval before being place on public drug formularies and part of the process requires some type of economic evaluation.

Cost-effectiveness analysis (CEA) is a health economics evaluation technique for prioritizing various healthcare strategies to maximise health benefits while working within limited financial and societal resources. (Folland, Goodman and Stano, 2016). In essence, it analyzes the outcomes of a treatment per dollar being spent. This is useful for medical decision-making and healthcare strategy formulation, by directing rational investment toward interventions that result in the greatest health benefits when compared to a set of alternatives (Maru et. al, 2015; Drummond, Schulpher, Claxton, Stoddart, and Torrence, 2015).

The two most frequently used techniques for conducting cost-effectiveness analyses are trial-based and model-based analyses (Maru et. al, 2015), with Model-based methods estimating these from existing data from a variety of sources, whereas trial-based methods use prospectively collected individual patient-level costs and health outcomes from the clinical trial. In this case, uncertainty is quantified using a variety of different assumptions and is more malleable (Gray, Clarke, Wolstenholme, and Wordsworth, 2011).

Systematic studies are limited to direct costs, which as the name implies, includes costs of health care, drugs, physician care, transportation, and social services. Indirect costs are included only when the study is conducted from a social rather than a systematic perspective (Cipriano et. al, 2010) and include the loss or gain of productivity by patients and caregivers. There are some issues with indirect cost calculation, such as lost

productivity among patients and carers. The consensus is that it does influence the outcome, in terms of cost effectiveness.

While costs are clear and directly calculated, there is more debate on calculating "effectiveness" as not all clinical outcomes necessarily directly correlate to improvements in patient quality of life or life expectancy. In North America and Europe, it is common to measure effectiveness in terms of dollars being spent per health outcome with health outcomes often defined in a standardized unit known as a *Quality Adjusted Life Year* (QALY). The QALY is a metric for assessing survival based on the health-related quality of life experienced during a particular annual period. The value index, or weight, is a scale that ranges from 0 (death) to 1 (perfect health). Most of the index items are derived from surveys of the general public to represent public preference for "quality", and surveys administered then to the patient groups on how they asses their health on a number of metrics. Hence, the index captures a preference-based index of health-related qualities of life (Gray, Clarke, Wolstenholme and Wordsworth, 2011). The health consequence associated with the intervention can be measured quantitatively and qualitatively through QALYs, which are given by multiplying the health state by the length of life.

There are some issues with the calculation of QALYs given its foundation in self-reported, or at best, caregiver-reported data. Another measure, *Disability Adjusted Life Years* (DALYs) are primarily concerned with disease burden and are calculated as changes in various morbidities and mortality and represented as an index, with an index weighting for various burdens. While not interchangeable, the consensus is that selection of a QALY or DALY would not materially impact if a treatment is cost-effective or not

(Feng, Kim, Cohen, Neumann and Ollendorf, 2020); though QALYs are much more commonly used.

The willingness-to-pay threshold, which determines whether a health strategy is cost-effective, is the maximum amount of money that the health authority would be willing to pay in exchange for one additional unit of QALY of a particular patient (McDougall et. al, 2020). WTP thresholds are generally derived from WHO criteria and vary by country, though are to be approximately one to three-times a country's GDP. (Do you mean GDP per person?) In the United States, there is no explicit threshold, but implicit thresholds of 100,000–150,000 USD/QALY are used to guide reasonable decisions (Neumann, Cohen and Weinstein, 2014; Liu et. al, 2020). Similarly, there is also no formal cap in Canada, however a threshold of $50,000 or $150,000 per QALY gained has been used in the past (Thokala, Ochalek, Leech and Tong, 2018; Stothard et. al, 2020). Adjusting these numbers for inflation, results in estimates of $53,420.67 to $160,262.01 CAD as per the Bank of Canada Inflation Calculator[2]. This ranking of cost-effective interventions can help health-care decision makers invest wisely to maximise health benefits while staying within budget or minimising cost for a specific health effect.

The major outcome of cost-effectiveness analysis is the incremental cost-effectiveness ratio (ICER), which is used to determine whether a healthcare strategy is cost-effective or not. It is the change in cost divided by the change in effectiveness between compared treatment strategies, generally measured per QALY or DALY. The average incremental cost of one additional unit of health benefit in the health care system

[2] https://www.bankofcanada.ca/rates/related/inflation-calculator/

by shifting from one option to its alternatives is represented by the ICER. If the ICER value for the new strategy is below the threshold, it is considered cost-effective.

In establishing a set of outcomes to be used in a cost-effectiveness analysis, one approach is to use decision analysis in conjunction with Markov simulations. Decision analysis is a mathematical framework for evaluating and determining the best outcome from a set of options (Thokala et. al, 2018). In health technology assessment, decision-analytic models help decision-makers understand the relationship between evaluated health effectiveness and incremental costs. To analyze cost effectiveness on diseases where there is no direct evidence of all parameters currently available, models use variables and structural components that can simulate disease and prognosis patterns from cohort studies or trials (Thokala et. al, 2018). To solve decision problems involving discrete health states in a closed cohort, state transition models are recommended, which are models where health states are changed throughout a patients' lifetime; for either individual patients using Monte Carlo microsimulation or an entire cohort using Markov cohort simulation (Covington et. al, 2007).

The Markov model, which is used to project long term impact of a new therapy, was introduced in 1983 (Beck and Pauker, 1983) to health economics literature and has been used extensively in decision making for therapies since (Sonnenberg and Beck, 1993). The Markov model is a state transition model that models the probabilistic events occurring over a lifetime, with each stage representing an opportunity for the health state to transition, such as from stability to progression, hospitalization, or death. The Markov model uses a set of discrete, exhaustive, and mutually exclusive health states to represent disease progression over time. Clinical events of most relevance are modelled

in the Markov model, as demonstrated from biomedical literature about certain probabilities for hospitalization, disease progression and death, and the probability of this changing is known as the transition probability. Health costs and utilities are applied to each stage, expressed in DALY or QALY weights and incremental cost. The time horizon is divided into Markovstages. Each Markovstage could be any designated time interval though one year is the most common; that is modelling probabilities of an event occurring each year throughout a lifetime for a patient. A cohort's transition probabilities are independent of previous transitions, including both previous health states' transitions and time spent in the current health state (Covington et. al, 2007).

Caveats in Pharmacoeconomic Evaluation

It is critical to make distinction between cost effectiveness, cost efficiency and cost benefit analysis. In comparison to cost-effectiveness, efficiency refers to how one drug achieving the outcome additional QALYs for a condition, competes against another drug in terms of its relative ICERs. Efficiency thus considers technical, productive, and allocative factors (Reidpath, Olafsdottir, Pokhrel, & Allotey, 2012) as it refers to a program's ability to deliver benefits at the least relative cost. Cost effectiveness is only to see if a drug is cost effective, that is, the additional QALYs gained are within a threshold. Numerous tools are available for evaluating efficiency (Simoens et. al, 2013), generally using a cost-benefit analysis which considers all costs and consequences, including both indirect and direct effects, and political and social repercussions. Typically, these costs and consequences are monetary in nature.

In comparison, cost-effectiveness analysis focuses on a small number of quantifiable outcomes, such as mortality or quality-adjusted life years, and is typically

limited to sectoral effects, in this context, health impacts. Furthermore, because the set of consequences is limited, this method can only determine relative efficiency, not absolute efficiency in terms of generating more value than costs.

Methodologically, there are three major issues for evaluating cost-effectiveness of targeted therapies and precision medicines. To start, there are a lack of models that consider costs of a drug that change throughout one's lifetime, as in most cases, costs of a drug or treatment are assumed static. For therapies targeting growing individuals including pediatric patients and young adults, such as Selumetinib, dosage is based on body-surface area and models must account for these differences, given they greatly change dosing requirements. For adult populations where dosage is based on body surface area, models assume a mean BSA in their analysis, however this does not allow testing sensitivity to parameters well in pediatric patients, such as mean age of diagnosis; nor allow the costs of the drug to change as they age.

There is also a lack of research using changing health utilities based on patient characteristics, as there is an assumption of constant utilities for all patients. Given the exponential growth of PN sizes in the case of NFI PN, primarily based on age of the patient, and not time since treatment, utilities as expressed by the difference between their new health state with Selumetinib and what they would otherwise face with massive tumor growth, clearly modelling utilities appropriately based on their age should be considered. This is also the case several other pediatric genetic conditions and the modelling in this paper may serve further scholarship well on CEA of other new targeted therapies.

MATERIALS AND METHODS

This section describes the empirical data and methods as it applies to assessing the incremental cost-effectiveness of various treatment strategies of Selumetinib plus SoC over SoC alone, using a time-dependent Markov Model. In so doing, it also sets forth a series of propositional statements that may serve as a methodological framework to assess the cost-effectiveness of similar drugs. The time-dependent Markov model differs from the commonly used general Markov Model, as transitions, costs and utilities are all time dependent, where time is substituted for age in this case. The general model, in contrast, assigns probabilities, costs and utilities consistently throughout a patients' lifetime. Accordingly, the time-dependent Markov model is seen as superior for this drug and others; and can be executed using software. In this paper, TreeAge Pro Healthcare 2022 (TreeAge Software, LLC), is used. This package allows a user to enter parameters from biomedical literature, and have an ICER processed easily, as well as have a sensitivity analysis run to measure the robustness of modelling parameters.

Time-Dependent Markov Model to Assess Cost Effectiveness

The health states of the model of the Selumetinib arm include (a) stability, (b) progression, (c) hospitalization, (d) death; whereas the Selumetinib + SoC treatment arm includes all of the above states, though separates progression into (b-i) progression needing treatment and (b-ii) progression without needing treatment. The differentiation here, is that stage (b-i) involves taking Selumetinib for another year and incorporates stable tumor size; whereas (b-ii) involves progression without taking Selumetinib in that stage, thus the tumor is subjected to natural growth rates. This separation was necessary as Selumetinib will stabilize the tumor size though after one takes Selumetinib in period

t, that tumor is subject to natural growth rates in period t+1. The lifetime effects, however, stem from Selumetinib's contraction of tumor size by 20% and from averting tumor growth in ages where the rate of growth is highest (i.e. 7 years of age and under). Natural rates of growth are in the double-digits for those years, compared to just 0.7% in adult years.

Base-case results are run, followed by a Monte Carlo simulation cohort of 100,000 patients, with similar characteristics to the SPRINT clinical trial, which are suggested to be representative of the population of patients with NFI, to discern the ICER and assess the percentage of iterations where each treatment strategy would be cost-effective or not. All enter in the pre-progression health stage, with costs and utilities being reflective over a lifetime horizon; meaning that the benefits of treatment one year are assessed against its lifetime benefits to quality-of-life. Patients will remain in the present state or shift to the next feasible state and would not be able to transition after states involving death (state d). The model assumes also, that once the disease progresses, it cannot return to the pre-progression health state, and is modelled below in Figure 2 for the SoC arm, and Figure 3 for the Selumetinib + SoC arm.

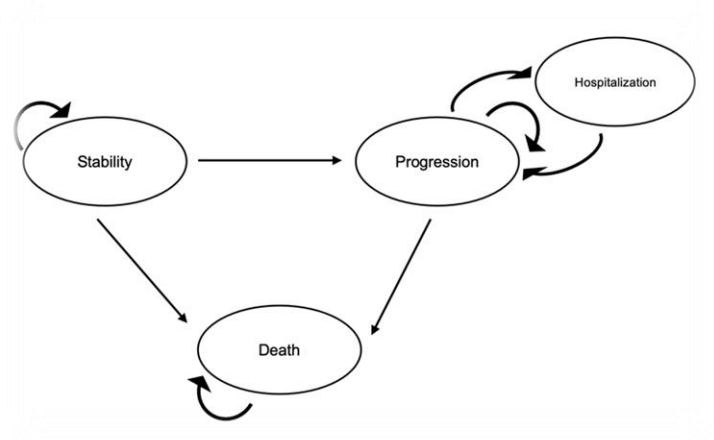


Figure 2: Markov Model for the Standard of Care

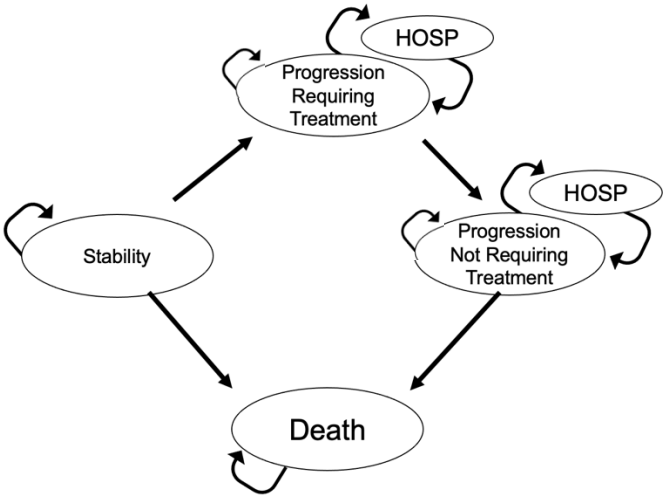


Figure 3: Markov Model for Selumetinib + Standard of Care Strategies

The model considers annual stages, which is the standard in pharmacoeconomic evaluation. The Markov process assumes a lifetime horizon and parameterized with the distributions of Canadian life expectancy and adjusted from NF1 life expectancy being eight years shorter as literature suggests. The Markov model is run until 99.9% of the cohort was absorbed into one of the death-related health states (state d).

The absolute maximum willingness-to-pay threshold was set to $150,000 in 2022 CAD per QALY gained, which is the upper limit as per the 2020-2023 *Value Assessment Framework* and is appropriate to be used given it is a rare condition. Setting this as the maximum, allows the percentage of iterations to be compared against the greatest reasonable threshold. It is noted this translates to approximately $100,000 USD in 2017.

To achieve comparability, all costs were converted to Canadian 2022 dollars using the *Bank of Canada Inflation Calculator*. A stage rectification for costs and utilities was used, whereby the model accrues at the start of each stage, and transitions happen at the end of each stage. All costs, including hospitalizations and treatments, and utilities,

are discounted by 1.5%, in alignment with standards by the *Canadian Agency for Drugs and Technologies in Health*.

$$PV = \frac{FV}{(1 + 0.015)^t}$$

where PV= present value, FV= future (discounted) value of utility or of cost, t=cycles and r=1.5%.

Databases and Literature Search

The model is aimed to be useful, and while aimed to be as accurate as possible, the accuracy would only be as strong as the model's assumptions. Data to represent the effect of Selumentinib was gleaned from the most recent Phase II trial's *Supplementary Data File*. The research used for parameter estimates for costs and to develop health utilities not expressed in trial data, were found through extensive literature search on *MEDLINE* and *BioMed Central*, which are leading databases for biomedical literature. Specific publications were selected for their longitudinal data, demonstrating changes in health states throughout one's lifetime, namely, through decreased tumor burden; and for correlations between quality-of-life and tumor burden, as the drug is only shown to effect quality and not longevity insofar. This enables conversion into EQ-5D-5L health state utilities which take into consideration utilities based on improvements to between pain and self-reported quality of life.

Treatment Strategies

As a rare and heterogenous disease, it is assumed a precision dosing strategy would be adopted. It is assumed that a durable and stable response is 20% reduction in tumor volume and no growth at or above 20% during anytime of the treatment. It is also assumed, that after a patient discontinues Selumetinib, their PN will grow at natural rates. In the SPRINT trial, most patients received a durable and stable response, patients were

allowed to discontinue Selumetinib treatment after one year following a stable and durable response, meaning 20% contraction of tumor size and no new tumor growth. Accordingly, all reasonable treatment strategies would be to suggest that all patients must go through at very minimum one year of treatment following a treatment year where response was realized, for a minimum 2 total years of treatment. Conceivably, exceptions should be made for all children 7 years of age and under, as the expected growth rates are in excess of 15%, to which they would be subjected to should they discontinue Selumetinib and may diminish any benefit gained. At the maximum, since the mean age of diagnosis is 10 and maximum age the disease is approved for is 18, a maximum of 7 years following a response (for a minimum of 8 years of treatment).

Accordingly, the following are adopted as reasonable treatment strategies:

- Treatment Strategy 1, representing a maximum expected duration of treatment, would see treatment of all patients for a maximum of 7 years of treatment following a response (representing 8 years total), so long as the patient taking Selumetinib is 18 or younger, and given that all children 7 years of age or below must take Selumetinib.
- Treatment Strategy 2, representing the median expected duration of treatment, would see treatment of all patients for a maximum of 4 years of treatment following a response (representing 5 years total), so long as the patient taking Selumetinib is 18 or younger, and given that all children 7 years of age or below must take Selumetinib.
- Treatment Strategy 3, representing the minimum expected duration of treatment, would see treatment of all patients for a maximum of 1 year of treatment following

a response (representing 2 years total), so long as the patient taking Selumetinib is 18 or younger, and given that all children 7 years of age or below must take Selumetinib.

The various lengths will have different cumulative costs; obviously with *Treatment Strategy 3* having the lowest cumulative costs, due to less treatment years involved. All strategies, however, would have the same utilities from the drug, aside from more peace of mind with a longer duration of Selumetinib treatment. In each of the above strategies, the age of the patient, and when they receive a response, are allowed to vary, hence making them "precision dosing strategies".

Model Parameters

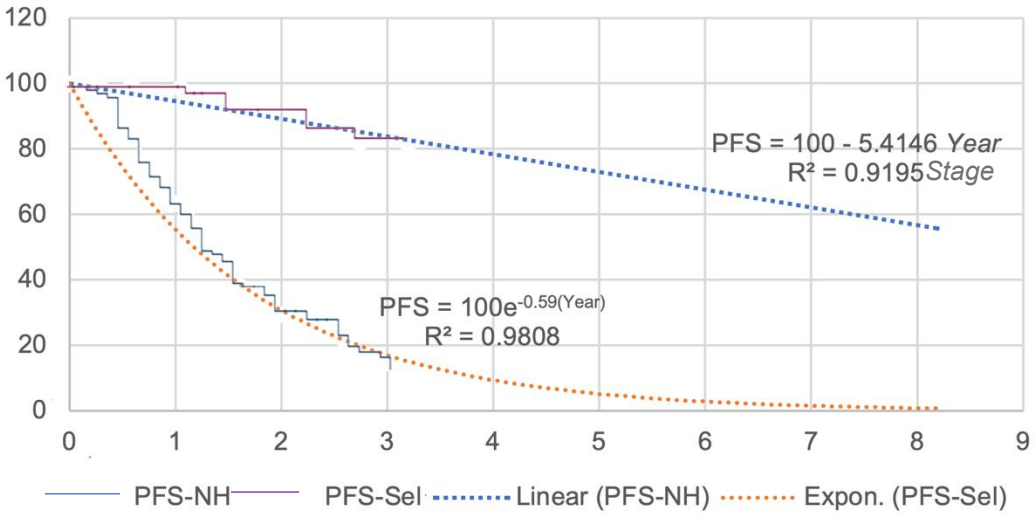
Transition Probabilities

To estimate annual state-dependent transition probabilities, Kaplan–Meier probability free survival estimates were gleaned from the clinical trial (Gross et. al, 2020). Using WebPlotDigitizer[3] to extract values from the graph and preforming OLS, the mean Progression Free Survival (PFS) from the observed time of the clinical trial (3 years) is approximately 94.58% per year and can be modelled as 100%-5.4146% per year, in the treatment group with an exponential function predicting natural history. As the trial has not considered its impact on mortality, probabilities to the death were assumed to be consistent with Canadian mortality rates, adjusted for eight years before natural death per sex, since patents with NF1 PN live on average eight years less than their gender-segmented average (Kenborg et. al, 2020; Mansocco et. al, 2011; Evans et. al, 2011; Genet, 2001).

[3] https://apps.automeris.io/wpd/

Overall survival is assumed to be the same in both cases, and results are extracted from previous literature. Mortality is not shown be impacted by Selumetinib at this time, given it has only been shown to slow tumor growth and impact morbidities, not reduce malignancy of tumors and hence affect mortality. Ongoing clinical trials are examining its effect on these issues, using mouse models (trials run on rodents), but their results are not assumed. Using parameters of the SPRINT trial data, and assuming a Weibull distribution of survival (Fleurence and Hollenbeck), transition probabilities were produced. To ensure the model predictions are accurate, Kaplan-Meier curves for PFS generated from SPRINT trial supplementary data, were then overlaid with the model projections for PFS in the natural history and Selumenitib categories to ensure the Markov model is simulated correctly, as demonstrated in Figure 3.

Figure 3: PFS Curve: Selumetinib vs. SoC



Between the progression arms in the Selumetinib trial, the age of the patient and previous cycles' treatments of Selumetinib of the patient are used to determine their transition probability. It is assumed everyone who does not die of natural death would need to undertake 2 years at minimum, of Selumetinib, unless dying of natural death. Accordingly, moving from the initial cycle of Seluemtinib treatment to the second cycle of Selumetinib treatment is gleaned from the following formula:

$$p_{StabToProgCost_{Age}} = 1 - p_{death_{Age}}$$

where Age is Initial Age_at_Diagnosis + _Stage, and where _Stage represents the Markov Stage.

In determining whether or not a patient would have to undergo further years of Selumetinib treatment, age is also used to determine the probability. Namely, in all strategies, the following served as guidelines:

- if the patient is 7 year of age or under, significant progression (i.e. 15%+ growth) could arise in the natural stage, meaning Selumetinib would need to be taken during these early years for its positive effects unless the patient dies;
- As long as a patient takes Selumetinib for 1 year, a patient would only need to take it for a maximum of 7 (in the case of strategy 1), 4 (in the case of strategy 2) and 1 more time respectively, (in the case of strategy 3), unless they are progressing further or the patient dies;
- a patient cannot take Selumetinib unless the drug is approved from the population, hence, is capped at age 18.
- A patient would need to take it again if their disease progresses (with progression defined as 15% growth in tumor size).

Accordingly, it is modelled by the following formula:

$$p_{ProgNoCostToProgCost_{age}} = \begin{matrix} 1 - p_{death_{age}}, if\ Age\ 1\ to\ 7 \\ 1\ -\ PFS - p_{death_{age}}, if\ Age\ 8\ to\ 18\ AND\ TreatmentMAX\ \leq\ \_Cycle, \\ 0\ if\ Age\ 18 \end{matrix}$$

Where TreatmentMAX is the number of maximum treatment years a patient would be permitted, and expected, to take Selumetinib following a stable response, by age 18.

Death Probabilities

There is some early analysis that shows differences in the probabilities based on patient characteristics, as expressed in differences of standardized mortality ratios (SMR), which are ratios between observed deaths in a population and that which would be expected based on age- and sex-specific characteristics in the natural unaffected population. The higher an SMR is above 1, the higher the expected deaths whereas 1

implies equality with the rate of mortality among all people. Findings (Duong et. al, 2011) suggest SMR is highest in younger patients with NF1, such as those aged 10 to 20 with an SMR of 5.2 (CI 2.6-9.3 P<0.001), compared to those aged 20 to 40 with a SMR 4.1 (CI 0.2-6.4, p<0.001) and an overall SMR is 2.02 (CI 1.6-2.6, p<0.001) for the disease. Early evidence also suggests gender differences, with women more likely to die earlier than men from these tumors. While there are differences in ages at diagnosis between genders, and given that women live longer than men overall, studies find median survival is approximately 8 years lower than of the gender in the general population (Kenborg et. al, 2020; Mansocco et. al, 2011; Evans et. al, 2011; Genet, 2001). These rates are used to calculate death rates, using as a base, expected deaths in Canada[4].

Costs

Direct costs to the Canadian health care are estimated, using the wholesale costs of the drug in 2022 USD, Selumetinib, and converted to 2022 CAD using the exchange rate at the time of writing, as 1.294. The dosing schedule was observed from SPRINT trial supplementary data (Gross et. al, 2020). Costs are obtained from the IBM Micromedex Redbook Database, as reproduced in Anderson et. al, 2021; and cost of administration was assumed to be very little, since it involves only an oral pill. The cost reported was $13,027 for 60 capsules of 25mg, which converts to $10.855USD per milligram, or $14.0474483 CAD. Per milligram prices were identical for various sizes of packages and pills.

[4] www.150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310071001

The cost of Selumenitib was approximated by ages based on their respective mean body surface areas and is allowed to change throughout a simulated patient's life. Using data from Health Canada on height and weight for different ages of Canadian boys and girls aged 3 to 19, body-surface area (BSA) was calculated using the Mosteller formula and matched, using the dosing schedule, to the appropriate dose. For simplicity, this study only considers cost effectiveness for patients receiving the full dose of the drug, and it does not consider dose reductions for adverse reactions given uncertainty as to the effect of the drug under reduced dosing. This study also does not consider costs relating to the Standard of Care as both strategies are assumed to use the same drugs, with the Selumetinib treatment group taking the novel drug in addition, not in place of, existing clinical management.

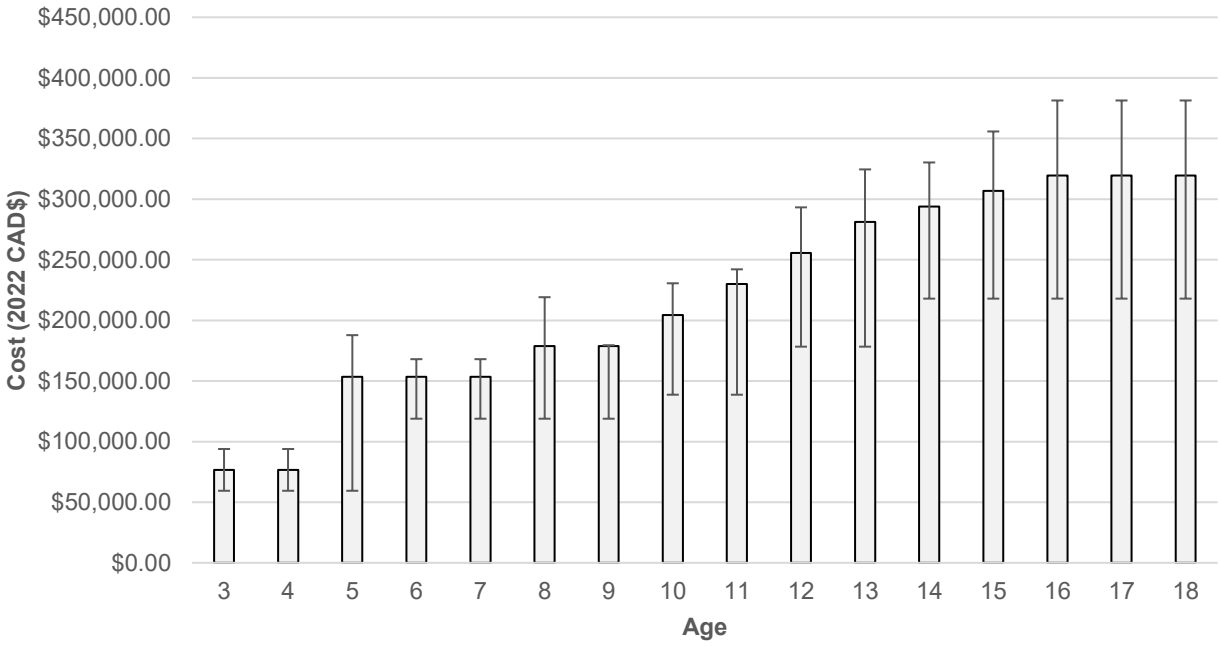
$$BSA(m^2) = \sqrt{\frac{height(cm) * weight(kg)}{3600}}$$

Table 1: Calculated Wholesale Cost of Selumetinib per BSA, 2022 USD and 2022 CAD

BSA Min	BSA Max	Weighted mg / day	Cost-US	Cost-CAN
	0.69	15	$59,435.69	$76,672.04
0.7	0.89	30	$118,871.38	$153,344.07
0.9	1.09	35	$138,683.27	$178,901.42
1.1	1.29	45	$178,307.06	$230,016.11
1.3	1.49	55	$217,930.85	$281,130.80
1.5	1.69	60	$237,742.75	$306,688.15
1.7	1.89	65	$257,554.65	$332,245.49
1.9		70	$277,366.54	$357,802.84

Using the BSA estimates above, mean BSA for each age, as well as the 10th and 90th percentile, treatment costs reflecting an average across both genders, were calculated, and are reflected in the Figure 5 below:

Figure 5: Cost of Treatment of Selumetinib Based on Age, 3-18, Canada (10th/90th Percentile)



Once a patient is diagnosed, that patient grows, and so too will their costs of annual treatment, until they discontinue Selumetinib at age of 18. For simplicity the model does not consider those who experience hepatic impairment, strong or moderate CYP3A4 inhibitors or fluconazole, gastrointestinal toxicity, skin toxicity, increased creatine phosphokinase (CPK), ocular toxicity, cardiomyopathy. This study only considers cost effectiveness for patients receiving the full dose of the drug, and it does not consider dose reductions for adverse reactions given uncertainty as to the effect of the drug under reduced dosing.

Accordingly, treatment costs for consideration of the ICER thus take the cumulative incremental costs, in this case, being represented by the cumulative cost of Selumetinib treatments from age at diagnosis until the end of their treatment, is represented by the below formula, accounting for those 18 only get one year of treatment, at most, since they will be become ineligible at the age of 19.

$$NominalTreatment\ Cost = \sum Cost_{age} + Cost_{age+Cycle} + \cdots Cost_{age_{final}}; if\ Age < 17; Cost_{age} if\ Age = 18$$

where age= age at diagnosis+Cycle, andstage is defined as an annual (yearly) Markovstage, representing current patient age in a particular Markovstage.

To account for potential growth in the price of Selumetinib relative to inflation,

$$RealTreatmentCost\ =\ NominalTreatmentCost * RealDrugPrice$$

where *RealDrugPrice* allows for an increase/decrease in price relative to inflation, with the value of 1 representing no change.

Hospitalization

There are two major studies which examined hospitalization of NF1 patients, among pediatric patients with NF1 PN in America (N=301; Yang et. al, 2020) and of NF1 across the lifespan, in the Netherlands (N=2467; Kenborg et. al, 2020). Given the lifetime horizon is adopted in this research, the later study is most useful for estimating costs and rates of hospitalization, to which, risk ratios, and hazard ratios are gleaned as well as a mean cost of hospitalization. Risk ratios are probabilities of hospitalization for NF1 patients compared to the general population. The higher the ratio, the higher the risk; and a rate of 1 indicates they are equally at risk to the general population. While risk ratios do not consider the timing of the event, hazard ratios consider the chance of the event happening a specified time, usually one year. This study makes sense as approximately

half of the NF1 population will be PN patients, and the American study mentioned no significant difference between patients with NF1 and NF1 PN in terms of hospitalization (Yang et. al, 2020) aside from surgery.

Costs of hospitalization are reflected in Canada, using the Canadian Institute of Health Information's Patient Cost Estimator[5]. Using Kenborg et. al, 2020's supplementary appendix of 127 most common hospitalization issues, this paper took the excess hospitalizations for the NF1 population across all age groups compared to the population for the Canadian population. It converted all costs for the line items in the appendix, to matching ones in the CIHI calculator, using descriptions. To get an average excess hospitalization cost for the NF1 population, the following formula, which takes a weighted average of each hospitalization cost given their marginal occurrence to the NF1 population over the general population, was used:

$$Hosp_{age} = \frac{\sum Hosp_{Cost} * Hosp_w}{\sum Hosp_w} * p_{Hosp_{age}}, where\ Hosp_w = \frac{Hosp_{Nf1} - Hosp_{Gen}}{\sum Hosp_{Nf1} - Hosp_{Gen}}$$

where *Hosp.* refers to a specific intervention, and p represents probability of hospitalization at a specific age. (Perhaps you can explain what you are summing over as there is no index variable in your equation.)

Risk ratios, and hazard ratios are gleaned as well as a mean cost of hospitalization. Risk ratios are probabilities of hospitalization for NF1 patients compared to the general population. The higher the ratio, the higher the risk; and a rate of 1 indicates they are equally at risk to the general population. While risk ratios do not consider the timing of the event, hazard ratios consider the chance of the event happening a specified time, usually one year. Inpatient hospitalisation, same-day surgery, physician services, home and

[5] https://www.cihi.ca/en/patient-cost-estimator

community care, diagnostic tests, and outpatient prescription drugs were all considered for hospitalization of common hospitalizations for PN1 patients. No outpatient medications, ER visits, or ambulatory care costs were included.

As this study considers only inoperable patients, hospitalization incidences involving or related to surgery of malignant sheath tumors were not included given the study used considers all NF1 patients, which accounted for 0.11% of all hospitalizations among the NF1 population. The list represented 99.67% of all hospitalizations for the NF1 population, excluding surgeries.

Utilities

To approximate the health utilities using the best available clinical evidence, parameters are approximated by considering the impact of the drug on incremental QALYs. In the case of Selumetinib, the major clinical outcome is significantly reduced tumor volume, which has been shown to positively impact pain and motor morbidities in clinical trial with a minimally clinically significant difference in most patients (Gross et. al, 2020). Research has shown that tumor burden and morbidity are indeed interrelated (Wolters et. al, 2015). In addition to the size of the tumor, the rate of tumor growth has been shown to impact increase pain, with those having >20% growth requiring increased pain medication (Gross et. al, 2018). Interestingly, in the case of NF1, the rate of tumor growth correlates strongly with age (Dombi et. al, 2007), and not necessarily puberty (Dagalakis et. al, 2014). The formula for tumor growth rates, among those under 25, is as follows:

$$Tumor\ Growth_n = \big(1.36 * EXP(-0.31 * Age)\big), for\ age = 1\ to\ 25;$$

Selumetinib has been shown, in the clinical trial, to obtain a minimally clinically significant difference by a mean of 2 points in pain, with 38% of patients reported through

MCID scale in terms of pain interference. Pain interference has been shown to be a major function impacting quality of life for patients with NF1 inoperable PN. When pain is measured using the PROMIS pain interference index, correlates with overall quality of life are found as 0.7, with quality of life measured by the EQ-ED-5L scale, among Canadian patients (Hamoy-Jimenez, Kim, Suppiah, et. al, 2020). Pain, is seen as largely dependent upon the size of the tumor. Merker et. al (2014) provide a regression analysis on how quality of life decreases throughout one's life with NFI, with total tumor burden (TTB), as the natural logarithm of the percentage of body mass to which the tumor occupies, being a primary predictor to pain interference as reported by caregivers (0.29, $p<0.05$) (Merker et. al, 2014). It is also widely acknowledged in literature, of the relationship between tumor size and pain being directly related in the case of NF1 (Sanagoo et. al, 2019).

Based on the growth model of tumors and using a WebPlotDigitizer image showing whole body tumor volume (mL) for ages 1 to 64, tumor size was modelled for each age, in the baseline case. Given the impact of Selumetinib is primarily a reduction in 20% volume over the course of its use. As the SPRINT trial suggests the drug contracts the tumor at a stable 20%, the size was seen to level during the duration of the treatment. After treatment, the Selumenitib group, like the SoC group, were subjected to the growth rates for each subsequent age they live, however, these growth rates are much smaller than those early in the patient lifecycle. Reports suggest, in adolescence through adulthood, an average of 0.74% each year on median, which was smoothed with the model predicting tumor growth for those under the age of 25.

Given the modelled tumor sizes, utilities were mapped using the EQ-ED-5L Crosswalk Index Value Calculator for Mac[6]. Various median EQ-ED-5L values reported in literature for various tumor sizes of NF1 individuals calibrated the model. To contextualize the numbers, the mapped index value in the base case was 0.728 for a fictional 18-year-old or younger. The model assumed to perfect health at birth, which is the standard assumption in the literature. The EQ-5D-5L scores for various ages through both, Selumetinib and Natural History cohorts were then mapped, assuming the 0.7 correlation between pain and quality of life.

Accordingly, the health utility representing pain and motor functions can be assumed as the difference between their natural progression in the base case, compared to the average marginal effect of Selumetinib upon stabilization. Data from the clinical trial suggests that once this health state is achieved, it is relatively stable in patients (Gross et. al, 2020).

The modelled QALY values were calculated as below, for ages 3 to 22, though all ages, up to 100, were assigned a utility using the same formulae. For each of these ages, it is assumed also that a post-hospitalization decrement of 0.1 assigned to the year of the hospitalization, is applied. This assumption is tested in subsequent sensitivity analysis.

$$QALY_{year} = Effect * (TumSoC_n - TumSel_n) * ProjectedGrowth_n$$

The above values do not take into consideration the utility that would come lifetime effects of potential averted tumor size, that would then later grow. Accordingly, the total tumor size averted for each year was calculated as the cumulative effect from pain morbidities from the difference in tumor size from age at diagnosis, to the next age,

[6] https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/

subjected to its growth rates. This value represents the lifetime benefit of the averted tumor size, considering its potential increase in size. The QALY value for Selumetinib treatment, before discounting, was therefore:

$$QALY_{Selu} = QALY_{Selu_{Age_i}} + LifetimeUtilityWithTreatment_{Selu_{Age_i}}$$

In a similar way, the QALYs in the Selumetinib arm for progression without treatment, adjust for the size of the tumor under the most recent cycle, subjected to natural growth upon no longer being treated for that year.

The Markov Model then calculates an ICER based on the probabilities below, as calculated by:

$$ICER = \frac{\Delta\ Cost}{\Delta\ Utility} = \frac{Cost_{Sel.+SoC} - Cost_{SoC}}{Utility_{Sel.+SoC} - Utility_{SoC}}$$

Sensitivity Analysis

Analysis examining the percentage of cost-effective iterations for smaller thresholds of $50,000 and $100,000 per QALY gained, as well as those up to $300,000 per QALY gained, are also examined through a cost-acceptability curve of each strategy.

Probabilistic sensitivity analysis using the parameter distributions and a willingness to pay at $150,000 per QALY gained, in 2022 Canadian dollars will enable a health payer to then see the robustness of the model. As per the recommendation of the International Professional Society for Health Economics and Outcomes, deterministic (DSA) and probabilistic (PSA) sensitivity analysis, is run to test variable uncertainty and the robustness of the expected results. To this end, important model assumptions in parameters are changed in DSA to analyse their impact on model outcomes.

In addition to model assumptions, two-way deterministic sensitivity analysis is also run to understand the boundaries where Selumenitib would be cost-effective if its price climbs greater than the rate of inflation. As NF1 PN is a form of cancer, it is also important to note the rising costs of cancer in Ontario; for which recent research suggests, from 2010 to 2020, a (Tadrous, Shakeri et. al, 2021) reported average annual inflation of drugs at 6%, which is three times the average inflation rate of all goods and services during the same period; though similar to inflation rates at the time of writing (6.7%). Underlying reasons for the former observation are expensive new drugs, expanded treatment options, and increasing needs for supportive care given that people live long. Given this, it is also important to assess how it changes should the mean age at diagnosis change. Given the costs are highly different for people of different age groups, not only would the wholesale price of the drug to inflation be accounted for but the mean age as this can significantly change the costs in terms of demand for higher or lower doses.

Beta distributions, for probability distributions on probabilities, were used for the utilities, and gamma distributions are applied to describe all costs as they are normally positively skewed. All parameter distributions are assumed to be equal, and 1000 Monte-Carlo simulation iterations are run on all sample ranges. According to WTP criterion of $150,000/QALY gained, PSA will then deem a percentage of these iterations as cost-effective, which would then suggest that the use of Selumentinib should be discontinued. An overall incremental cost ratio was developed given the respective distributions, as seen in Table 5, adapting the original definitions in Table 2. The TreeAge Pro model schematics are seen in figures 4 and 3.

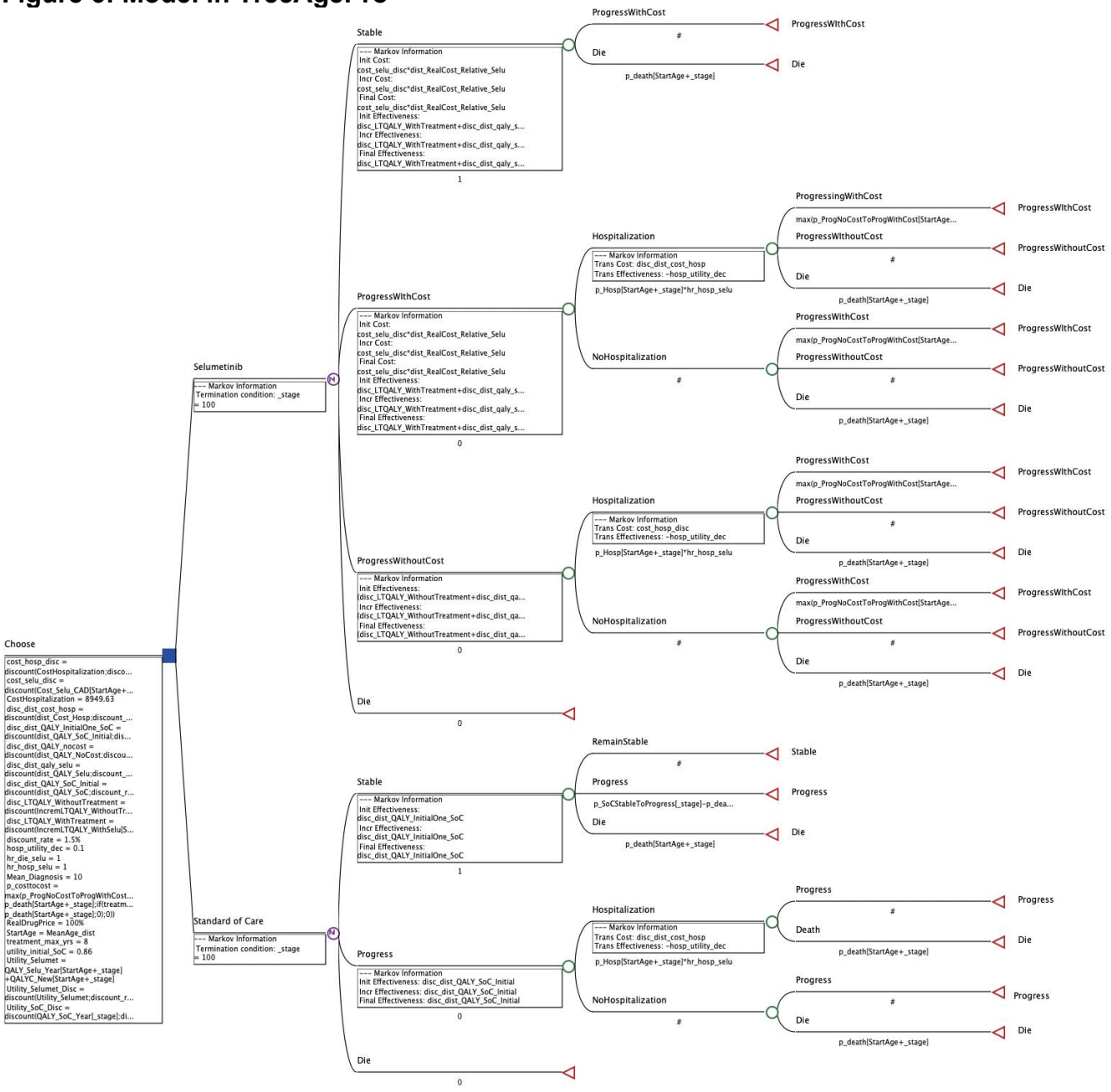
Table 2: Variable Definitions in TreeAge Pro

Name	Root Definition
cost_hosp_disc	discount(CostHospitalization;discount_rate;_stage)
cost_selu_disc	discount(Cost_Selu_CAD[StartAge+_stage]*RealDrugPrice;discount_rate;_stage)
CostHospitalization	8949.63
disc_dist_cost_hosp	discount(dist_Cost_Hosp;discount_rate;_stage)
disc_dist_QALY_Initial One_SoC	discount(dist_QALY_SoC_Initial;discount_rate;_stage)
disc_dist_QALY_nocost	discount(dist_QALY_NoCost;discount_rate;_stage)
disc_dist_qaly_selu	discount(dist_QALY_Selu;discount_rate;_stage)
disc_dist_QALY_SoC_Initial	discount(dist_QALY_SoC;discount_rate;_stage)
disc_LTQALY_Without Treatment	discount(IncremLTQALY_WithoutTrtmnt[StartAge+_stage];discount_rate;_stage)
disc_LTQALY_WithTreatment	discount(IncremLTQALY_WithSelu[StartAge+_stage];discount_rate;_stage)
discount_rate	1.5%
hosp_utility_dec	0.1
hr_die_selu	1
hr_hosp_selu	1
Mean_Diagnosis	10
p_costtocost	max(p_ProgNoCostToProgWithCost[StartAge+_stage]-p_death[StartAge+_stage];if(treatment_max_yrs-2>_stage;if(StartAge+_stage<18.01;1-p_death[StartAge+_stage];0);0))
RealDrugPrice	100%
StartAge	MeanAge_dist
treatment_max_yrs	8
utility_initial_SoC	0.86
Utility_Selumet	QALY_Selu_Year[StartAge+_stage]+QALYC_New[StartAge+_stage]
Utility_Selumet_Disc	discount(Utility_Selumet;discount_rate;_stage)
Utility_SoC_Disc	discount(QALY_SoC_Year[_stage];discount_rate;_stage)

Table 3: Variable Distributions

Type	**Name**
Gamma	dist_RealCost_Relative_Selu
Gamma	dist_Cost_Hosp
Beta	dist_QALY_SoC
Beta	dist_QALY_SoC_Initial
Beta	dist_QALY_Selu
Normal	MeanAge_dist

Figure 6: Model in TreeAgePro



RESULTS

Base-Case Cost-Effectiveness Results

The base case represents results for one who contracts NF1 at the age of 10 and follows their treatment strategy. The data for Selumentinib clearly indicate the vast difference in costs and utilities based on age. Costs of treatment grow quickly from ~$76,672.04 CAD at its lowest BSA-based dose, to ~$357,802.94 CAD at its highest BSA-based dose. This implies costs to treat younger patients are much lower than those who are older.

Since Selumetinib provides increased progression-free-survival and contracts tumors by 20%, taking the drug will have lifetime effects in terms of QALYs, given the most rapid growth of tumors are in the early years. Using the input parameters, the simulation in TreeAgePro Healthcare 2022, calculates an overall ICER of each strategy. As discussed earlier, the ICER considers exclusively the incremental cost over the standard of care, which in this case, reflects treatment costs over costs of excess hospitalizations since drugs (i.e pain killers) consumed are assumed to be the same in all stages; compared to the incremental effectiveness reflected by the total QALYs in the Selumetinib + SoC arm compared to those in the SoC arm.

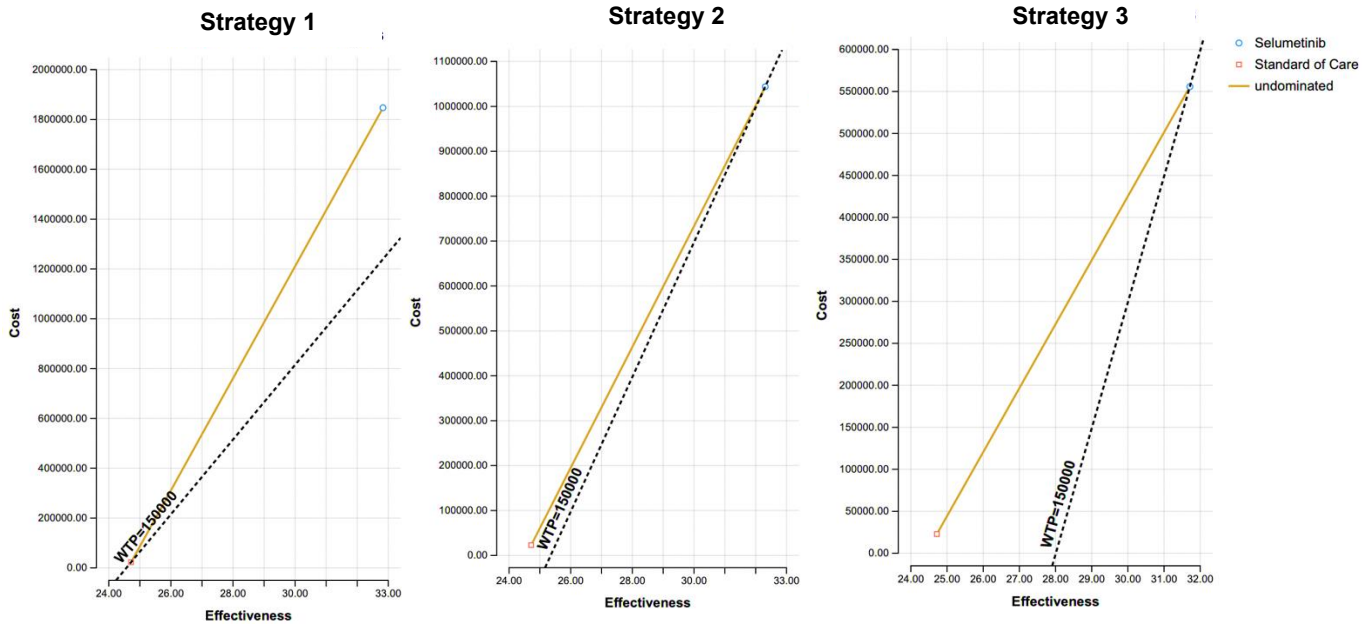
The ICERs calculated, in 2022 CAD, are $224,915.81 for treatment strategy 1, $134,491.57 for treatment strategy 2, and $76,189.40 for treatment strategy 3. The ICERs are compared to the $150,000 threshold in ICER Planes, represented in Figure 7. From this figure, strategies 2 and 3 are within the $150,000CAD per year threshold, and 3 is the only one with a base-case ICER within the thresholds of $100,000 and $150,000. Not surprisingly, this demonstrates high sensitivity in the ICER value to the maximum number

of years one would need to take the drug following a clinical response. Cumulative costs range from $1,857,459 to $555,684.32, which is the primary influence to the calculated ICER. From the below graph, it shows $22,768.03 would be the cost of hospitalizations that would occur in the base-case, which is subtracted from each of the strategies to gain incremental costs. The shortest strategy (3) results in 6.99 QALYs gained at a cumulative incremental cost of $532,916.29. This is only just over 1 QALY lower than the longest strategy, which gains 8.11 QALYs, at a cumulative incremental cost nearly four-times the amount at $1,8234,691.81.

Table 4: Estimated ICERs per Strategy

Strategy	**Standard of Care**	**Strategy 1**	**Strategy 2**	**Strategy 3**
Cost of Hosp. & Incremental Drugs, Discounted	$22,768.03	$1,847,459.84	$1,043,713.19	$555,684.32
Incremental Cost, Discounted		$1,824,691.81	$1,020,945.15	$532,916.28
Median QALYs per patient - Total, Discounted	24.71	32.83	32.31	31.71
Incremental Effectiveness (Incremental QALYs gained), Discounted		8.11	7.59	6.99
Incremental Cost Effectiveness Ratio (ICER), Discounted		$224,915.81	$134,491.56	$76,189.40
Monetary Benefit of Effect (QALYs * WTP Threshold of 150000)		$1,216,500.00	$1,138,500.00	$1,048,500.00
Net Monetary Benefit		-$608,191.81	$117,554.85	$515,583.72

Figure 7: ICER Planes by Strategy



Probabilistic Sensitivity Analysis

The ICER however, is calculated based on numerous assumptions. These include:

(a) the mean age of diagnosis and age demographics being like those of the participants of the SPRINT trial,

(b) real costs will remain the same throughout a patient's lifetime;

(c) a discount rate of 1.5%;

(d) calculated excess hospitalization costs;

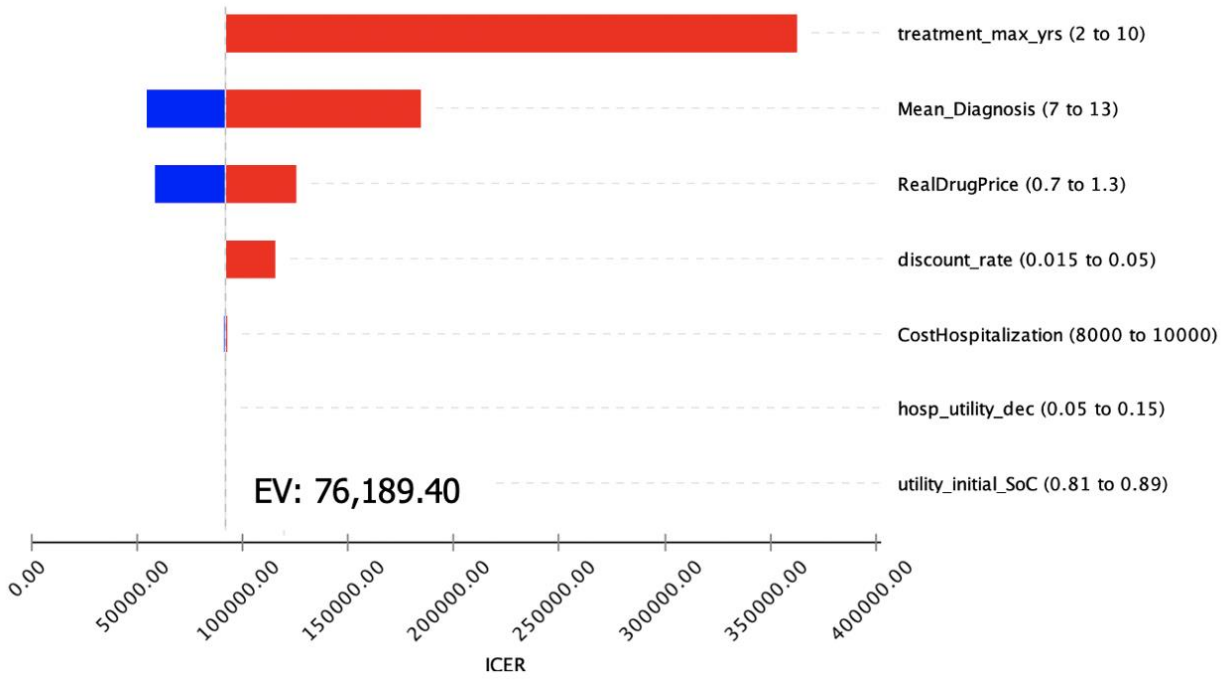
(e) A negative impact of 0.1 QALYs per hospitalization;

(f) An initial utility pre-diagnosis of normal (average) health; and

Accordingly, it is important to run sensitivity analysis to examine how the model may change with changes in the assumptions. As demonstrated in the Tornado analysis below (Figure 8), where red indicates that, as the variable increases, so too would the ICER, while blue indicates that, as the variable increases, the ICER decreases; the model

is most sensitive to potential changes in the mean age at diagnosis, though all have an ICER below $200,000. This makes sense as younger patients are more inexpensive to treat and result in stronger utilities given the tumor growth rates averted. The results also indicate it was sensitive to the discount rate is also another point of model sensible sensitivity that can increase the ICER of the strategy, namely as the more discounted future years are, the greater the ICER and the less cost-effective the strategy becomes. Some cost-effectiveness analyses include 3%, however, this study used the Canadian standard of 1.5%, considered conservative globally.

Figure 8: Tornado Diagram: Selumetinib vs. SoC



The probabilistic sensitivity analysis modelled all the assumptions in input values to determine the robustness of these estimates. A 10,000 stage Monte-Carlo simulation was performed, where in each simulation, a random value according to the chosen distributions were taken, for each variable. The ICER Scatterplots (Figure 9, 10 and 100 for strategies 1, 2 and 3 respectively), where red represents the strategy was cost

prohibitive and green suggests it was cost-effective. Overall, they suggest in strategy 1, only 6.717% of iterations were cost-effective, that is, had an ICER lower than the WTP set at $150,000. This is compared to 30.685% in strategy 2 and 70.94% in strategy 3. Clearly, thus, only strategy 3 is cost effective over the Standard of Care more than not and hence should be the only one adopted if one's objective is to be cost-effective at the $150,000 per QALY gained level, given the others would not represent a good use of health resources.

Figure 9: ICER Strategy for Strategy 3

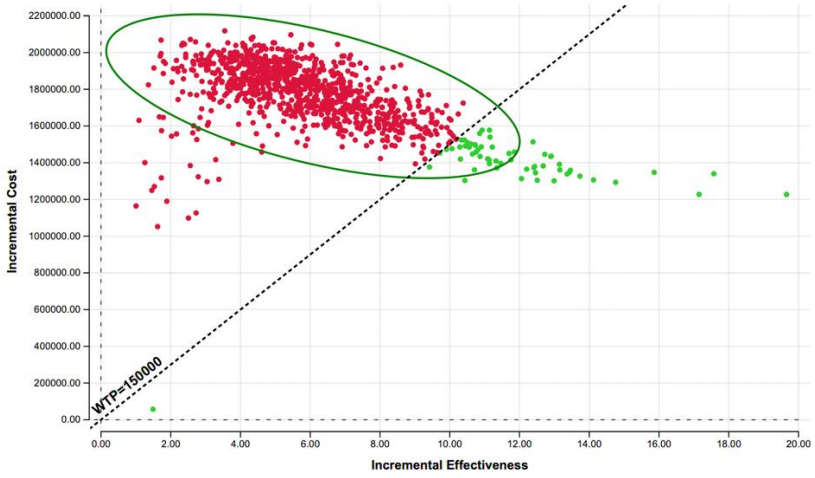


Figure 10: ICER Strategy for Strategy 2

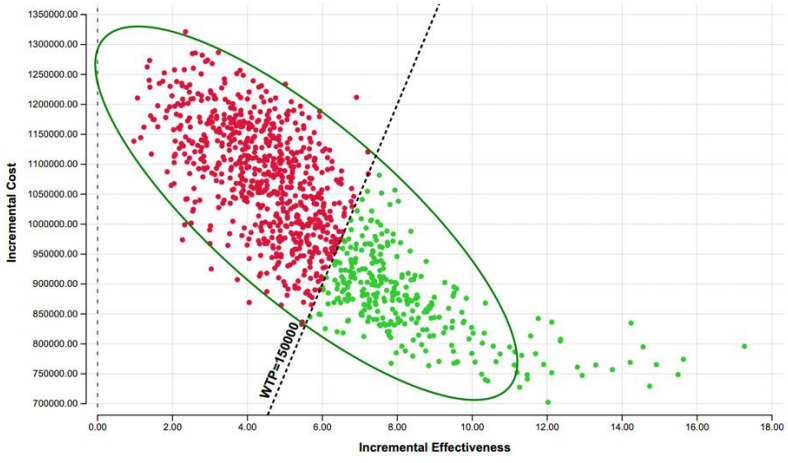
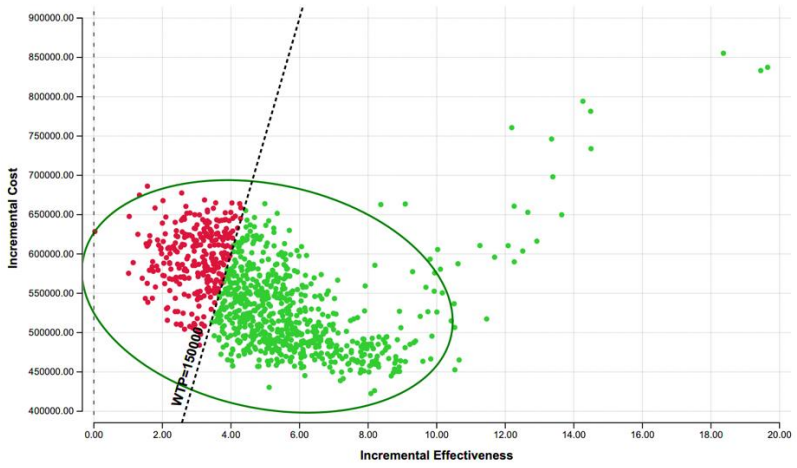


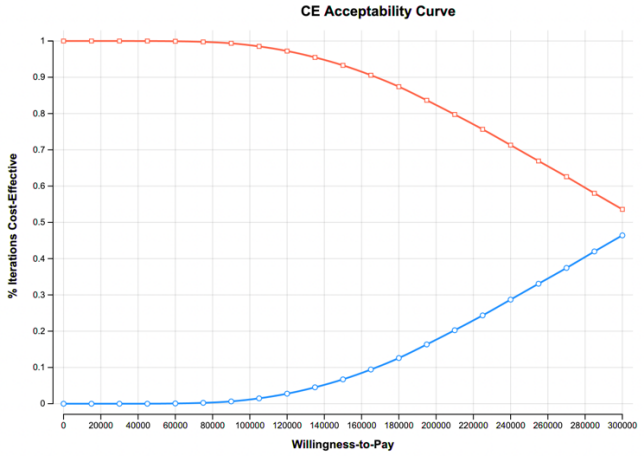
Figure 11: ICER Plane for Strategy 3

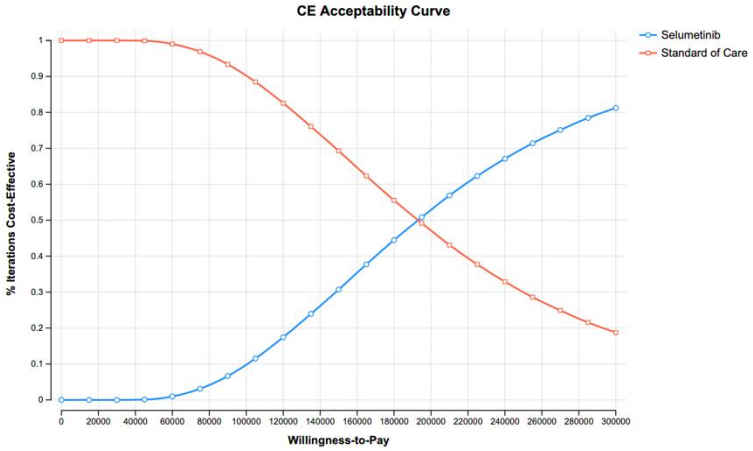


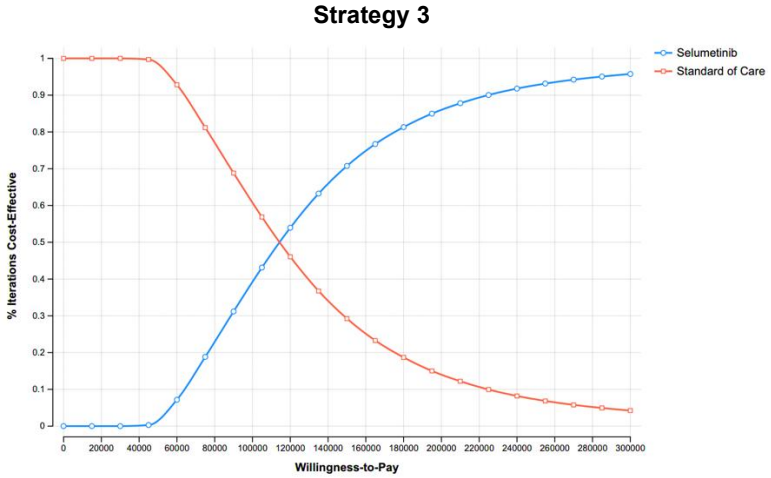
The Cost-Acceptability Curves compares the likelihood of each of the strategies, given the distributions to each uncertainty and their probabilities, of being cost-effective over the SoC. As demonstrated in Figure 12, for strategy 1, the Selumetinib arm does not become more cost effective over the SoC than not at any threshold below $300,000 per QALY gained, suggesting the strategy is very cost prohibitive. In strategy 2, however, the Selumetinib arm becomes more cost effective over the SoC at $183,300 per QALY. The most cost-effective strategy is seen in strategy 3, where the strategy becomes more acceptable over the SoC at $112,000 per QALY gained, which is only one demonstrated to be probably within the $150,000 per QALY WTP threshold. Through trial-and-error, the number of MAX Treatment years is 3.83 before it is parity between strategies at the $150,000 per QALY threshold.

Figure 12: Cost-Acceptability Curves

Strategy 1 **Strategy 2**







Two-Way Sensitivity Analysis

Sensitivity analysis was run to see the impact of the two most sensitive variables to the model: *mean age at diagnosis* (StartAge) and the real cost of the drug relative to inflation at the ICER threshold of a $150,000 WTP per QALY gained for strategy 3. In Figures 13 to 15, the line separating orange and blue area highlights where the ICER is equal to the willingness to pay, with the blue area suggesting where Selumenitib is cost effective; and the orange area suggesting that to which the SoC is cost-effective. This suggests that, as the median age at diagnosis increases, and as real costs for Selumetinib rise beyond current levels in real dollars, the less cost-effective the strategy is to the point of the line intersecting the two areas. Interestingly, it seems never cost-effective when the

mean age at diagnosis approaches close to 18, likely, due to the little lifetime utility a patient aged 18 would receive given the relatively small tumor growth as a percentage of body mass. Figure 15, that real drug costs could rise 50%, and the strategy would still be cost-effective if the mean age at diagnosis does not exceed 16; or up to 240% if mean age at diagnosis is 13 or below. The other strategies were also examined with results showing greater sensitivity to both parameters in Figures 13 and 14 for strategies 1 and 2, respectively.

Figure 13: Two-Way Sensitivity Analysis for Strategy 1

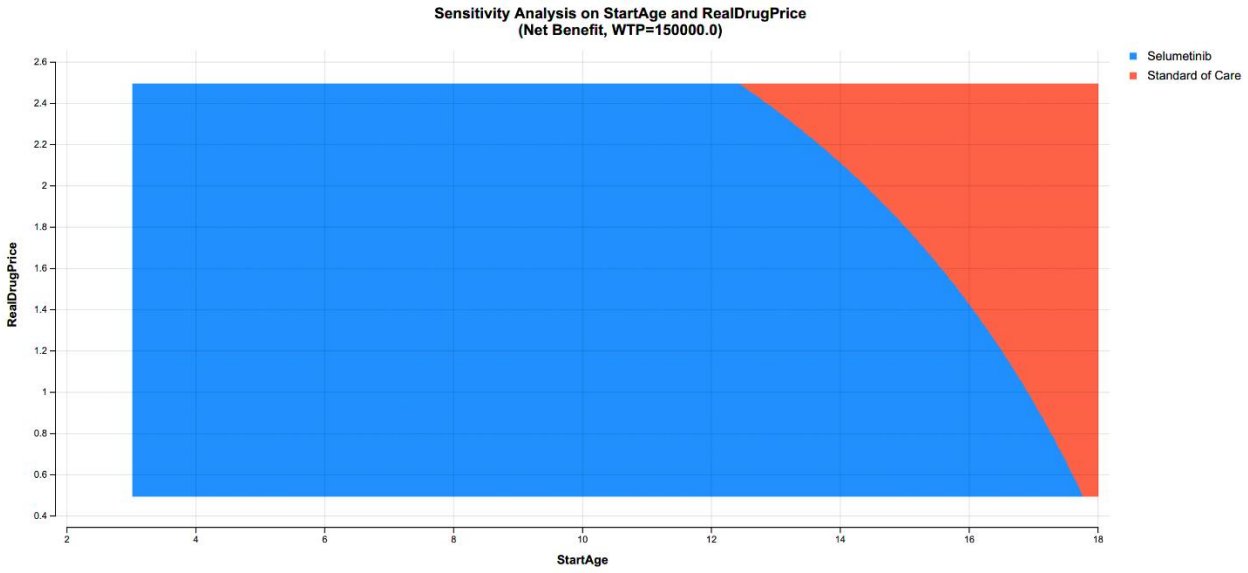


Figure 14: Two-Way Sensitivity Analysis for Strategy 2

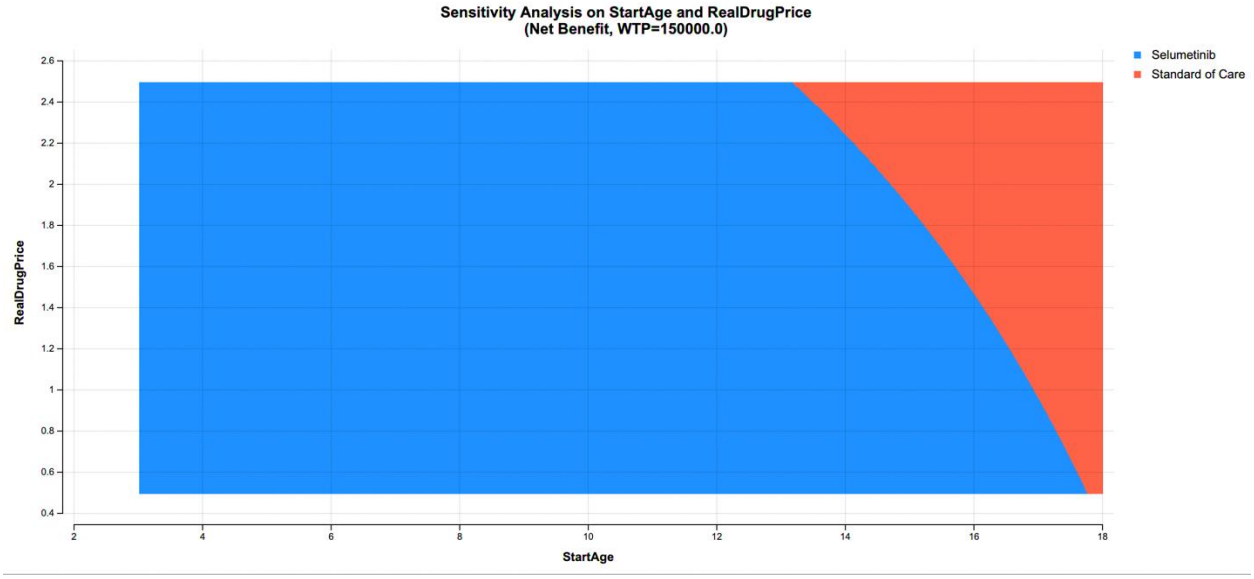
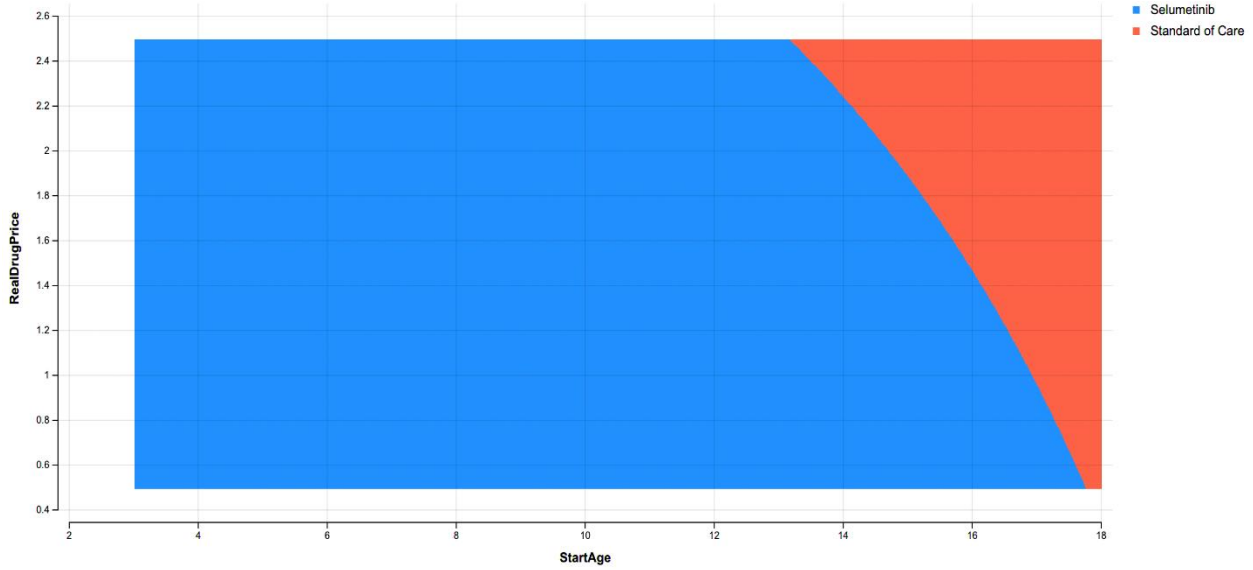


Figure 15: Two-Way Sensitivity Analysis for Strategy 3



DISCUSSION

Limitations and Delimitations

There are several assumptions made in the model. First, the study is limited to testing three different treatment strategies formulated, each with different levels of dosing requirements following a stable response. While the study strongly analyzes each of these strategies, it is reasonable that clinical evidence may dictate other strategies that are structured or parametrized differently. Accordingly, the paper does not necessarily consider cost-effectiveness of every possible treatment strategy. Nonetheless, it points strongly to the idea that Selumetinib can be cost-effective, or can be cost-prohibitive, which depends greatly on the length of treatment; and sensitive to mean diagnosis. Should a precise treatment strategy be directed by a health agency vastly different than those in this paper, the parameters and model structure can easily be adopted to facilitate cost-effectiveness evaluation.

Second, this study assumed similar hospitalization incidence of NF1 patients in the Netherlands, and this assumption may not necessarily be true. Indeed, for several other diseases, incidence and hospitalization varies by country due to differences in diet, exercise, and genetics. However, it is the best clinical evidence that currently exists. The SEER database in the US, which contains hospitalization records from 11 US states, only had records for 79 patients with NF1 which was far fewer than that in the study of the Netherlands. As a delimitation, the paper tested for sensitivity of hospitalization costs, showing a low degree in the Tornado diagram.

Third, the WTP threshold was assumed to be CAD $150,000 which may not necessarily be a precise estimate of what Canadians deem an effective use of health

dollars. However, it is approximately consistent, and lower than, the UN recommendation of effective health resources said to be at three times the national per-capita GDP, which means people are willing to pay 3 times per capita for a drug delivering 1 extra quality-adjusted-life-year gained over the SoC. As a delimitation, the paper also included cost acceptability curves at various levels of willingness to pay thresholds, up to $300,000.

Fourth, the study assumed QALY was a unit of measure for quality-adjusted life years. Another measure, Disability Adjusted Life Years (DALYs) are primarily concerned with weights based on disabilities, as represented through an index, with an index weighting for various burdens. While not interchangeable, the consensus is that selection of a QALY or DALY would not materially impact weather a treatment is cost-effective or not (Feng, Kim, Cohen, Neumann and Ollendorf, 2020); and QALYs are much more commonly used.

Lastly, this paper mapped utility values based on changes in quality of life based on a correlation with the drug effect (pain) using data from a Canadian study examining quality-of-life. While these may not model precise values given the heterogeneity of the NF1 disease, the values were tested for sensitivity and, given the standard deviations, would not likely influence the determination of cost-effectiveness of the drug.

Contributions

In specific, this paper adds to literature by providing a cost-effectiveness perspective to the design of treatment strategies for Selumetinib for patients with NF1 inoperable PN aged 3 to 18. More broadly, this research adds to the growing body of literature on pharmacoeconomic analysis within precision medicine and targeted therapies, and specifically, cost-effectiveness in precision dosing strategies. Aside from

a contracted study for the UK Health System (NICE, 2022), it is the first study to the authors' knowledge on the cost-effectiveness of this drug for this population and is one of very few pharmacoeconomic studies in neurofibromas (see also Wolkenstein et. al, 2000). This is especially important, given the many ongoing trials targeting this population (see also Copley-Merrman, 2021) and of ongoing advanced trials for further uses of Selumetinib. This paper adds to the literature on cost effectiveness for orphan drugs to rare diseases, where limited data exist in contrast to other diseases (see for instance Duckett, 2022; Ollendorf et. al, 2018); by contributing a unique application of Markov modelling in the literature of drug cost effectiveness, where utilities and costs are in part based on age, potentially useful also for many other applications of Selumetinib and for drugs currently in trial with similar characteristics (see for instance, Kun et. al, 2022).

External Validity

During the writing of this paper, one other study (NICE, ID 1590)[7] was released on the cost-effectiveness of Selumetinib, specifically, in the UK. The UK study did not make the same simplification assumptions in the calculation of utilities, instead preferring to use their own scale; and did not use a Markov model suggesting too many simplifications would be had to specify utilities or cost given their spread (in a normal Markov model, one does not use dynamic variables (i.e., based on age)). Instead, they modelled UK-specific quality of life measures using results of a Time-Trade-Off survey for the NF1 population in the UK, acknowledging heterogeneity across patients in their qualities of life. Interestingly, the ICER values are similar, with their ICER of £70,471, which converts to approximately $112,900.39 CAD, and was based on a patient receiving a maximum of 8

[7] https://www.nice.org.uk/guidance/hst20/evidence/final-evaluation-determination-committee-papers-pdf-11068867693

years following stable response to Selumetinib subject to them not receiving the drug past the age of 18. When removing their caregiver disabilities applied in their model, which are more typical of a social perspective, the ICER is £145,133 (p.469)[8] which converts to $229,280.44 CAD in 2022. Accordingly, their ICER is within only $2,000 difference from that proposed, with all other variables equal as this study, giving both studies external validity; and suggests that care giver disutility inclusion, as in the NICE paper, or exclusion as in this one, could greatly result in different ICERs, representing social and systematic perspectives, respectively.

Future Research

As discussed in this paper, utilities and cost differ on age, and hence while this study designs a model and reports an ICER for all pediatric patients, it is shown that ICERs will differ substantially for individual patients given their different tumor sizes and ages at diagnosis. This future research could use methodological assumptions contained in this paper, to develop these ICERs, which can be used to inform clinical practice on designing a cost-effective treatment duration for all patients, especially as Selumetinib is being examined for its efficacy in adults (clinicaltrials.gov, ID NCT04924608)[9].

As the primary contribution of this study, beyond the evaluation of Selumetinib for those 3 to 18, is the development of a time-dependent Markov model where utilities and costs differ per *age*; and where probabilities are dependent on *either* age (i.e. death) or treatment stage (i.e. PFS). Other time-dependent Markov models use a base age, and while using age-dependent probabilities, generally do not see costs or utilities varying

[8] https://www.nice.org.uk/guidance/hst20/evidence/evaluation-consultation-committee-papers-pdf-11068867694
[9] https://clinicaltrials.gov/ct2/show/NCT04924608

with age. This is a unique contribution, however, would serve Pharmacoeconomics well as more drugs are being released for younger patients where similar effects may be found. Some examples include applications of signal transduction inhibitors such as cetuximab, docetaxel, sulforaphane, panitumumab, pazopanib, sunitinib, sorafenib, trastuzuam, under clinical trial. Further research should explore use of the age-and-time-dependent Markov model in these contexts, to determine more fruitfully its potential usefulness.

CONCLUSION

This study finds that, when compared to the standard of care alone, Selumetinib, plus the standard of care, is cost-effective at $150,000/QALY rate in 70.94% of iterations when dosed for a maximum of one year following a stable response, and from the systematic Canadian health care perspective for the currently approved patients aged 3 to 18 who have inoperable NFI PN. In this scenario, Selumetinib results in an ICER representing an increase of approximately 7 QALYs for a net cost of $532,916.29. When treatment duration is changed to 4 and 7 years following a response (for a minimum of 5 and 8 years of total treatment, respectively), the ICER rises quickly beyond any reasonable cost-effective threshold when considering distributions of each unknown variable. This suggests that, by contracting tumor sizes by 20% and stabilizing them during their highest growth spur, from 3 to 18, Selumetinib treatment has a sincere life-long impact; however its effect on averting further tumor growth for patients older than 7, does not contribute as much to additional QALYs.

Deterministic sensitivity analyses found that the ICER is most sensitive to the mean age at diagnosis, and the real cost of Selumetinib. Two-way sensitivity analysis suggests that, should the cost of the drug rise much higher in real terms, the drug would still be cost-effective, even if rising by 2.5 times the current price, though is constrained by having the mean age of diagnosis not greatly changing from 10 (in base case) to older teens.

Some major considerations should nonetheless be considered before implementation of Selumetinib in the treatment of NF1 PN. First, a treatment plan would be recommended to define minimum and maximum boundaries on Selumetinib treatment.

As this paper suggests, it is not necessarily cost effective to begin treatment at ages 16, 17 and 18 in some strategies, as the marginal utilities are not outweighed by their lifetime impact. This paper is limited to determining cost effectiveness and not necessarily cost efficiency or optimality. Given the smaller growth rates in later teens compared to younger patients, once the tumor is contracted and stabilized for one year, the health utilities would not necessarily change much thereafter.

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APPENDIX A: FIGURES

Figure 1: Costs – Utilities 1

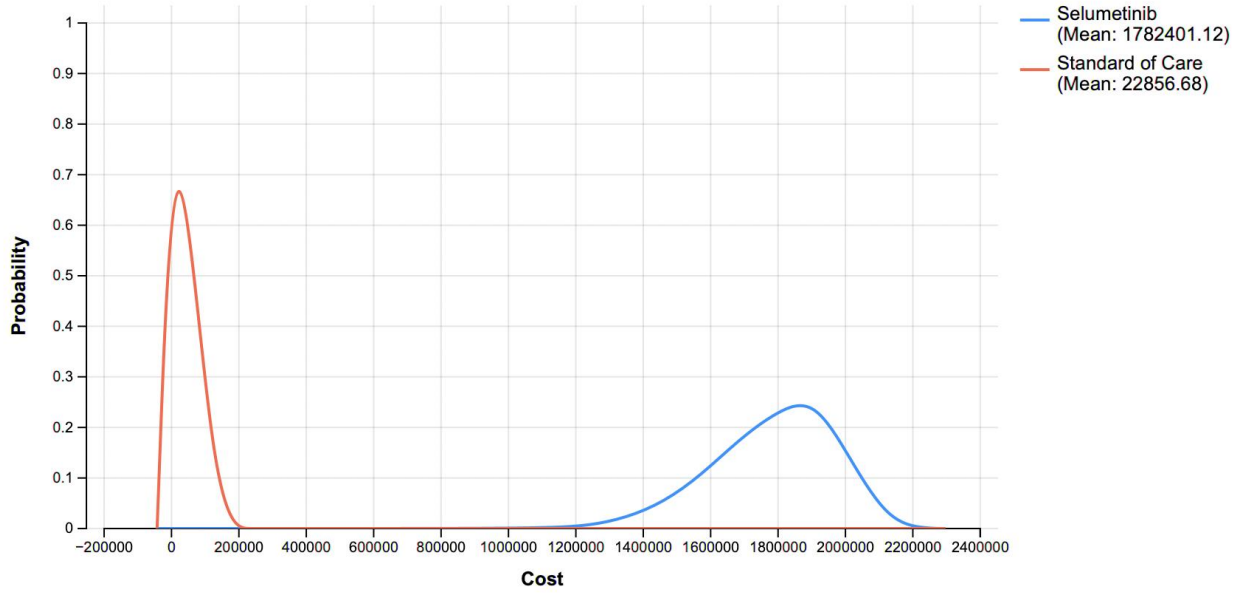


Figure 2: Utilities – Strategy 1

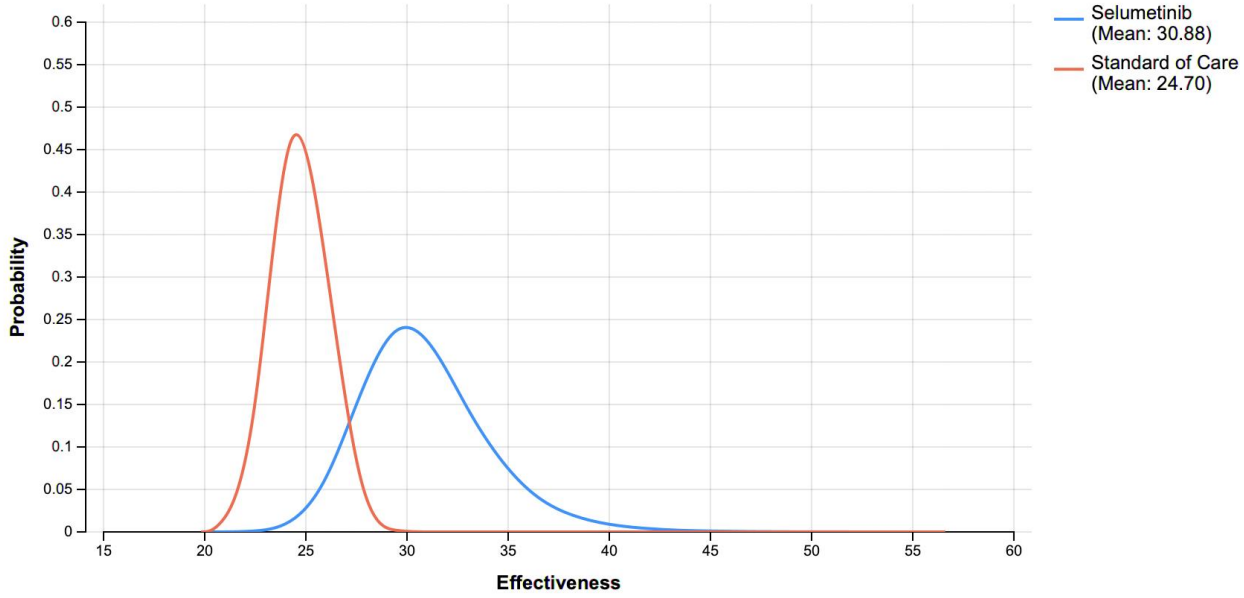


Figure 3: Costs – Strategy 2

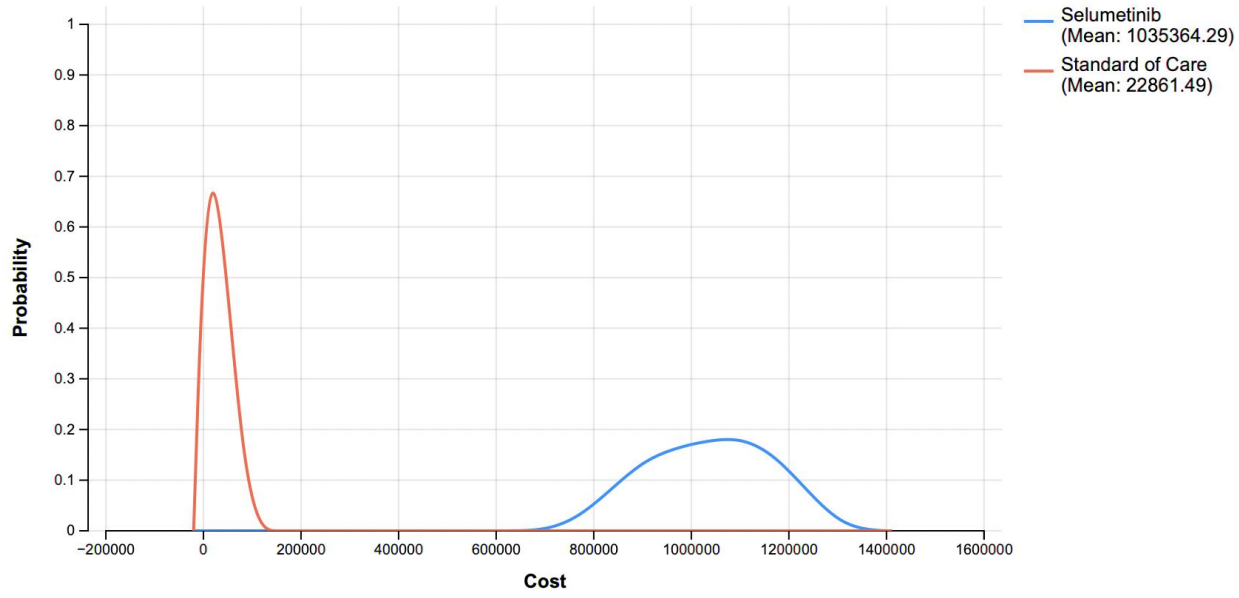


Figure 4: Utilities – Strategy 2

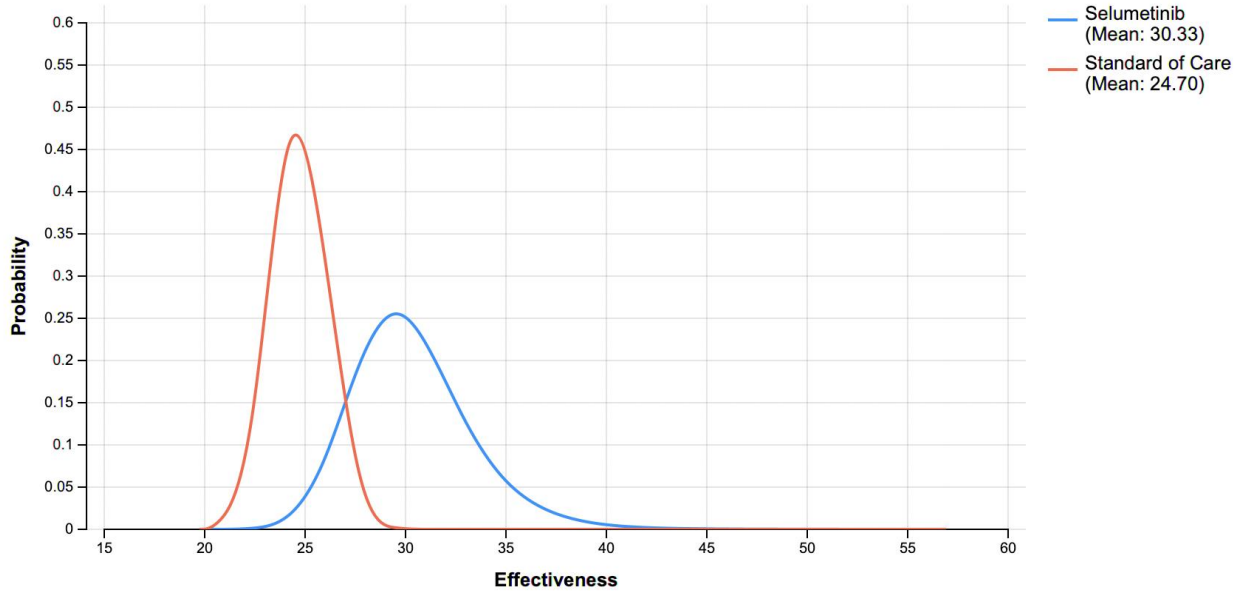


Figure 5: Costs – Strategy 3

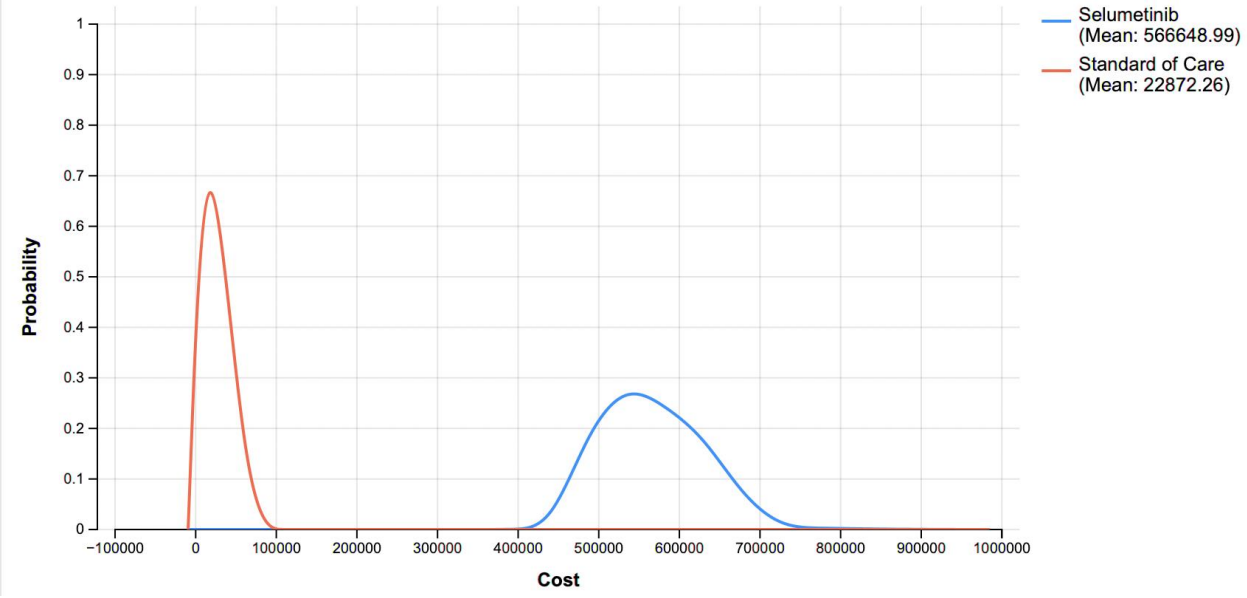


Figure 6: Utilities – Strategy 3

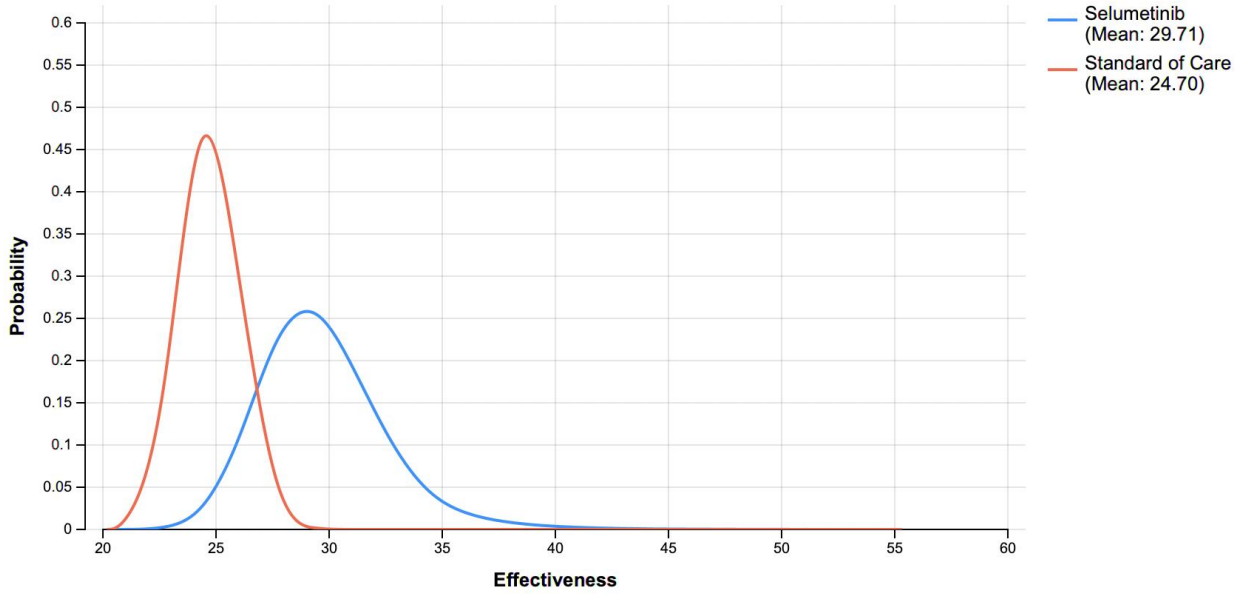


Figure 7: % of Iterations Cost-Effective: Strategy 1

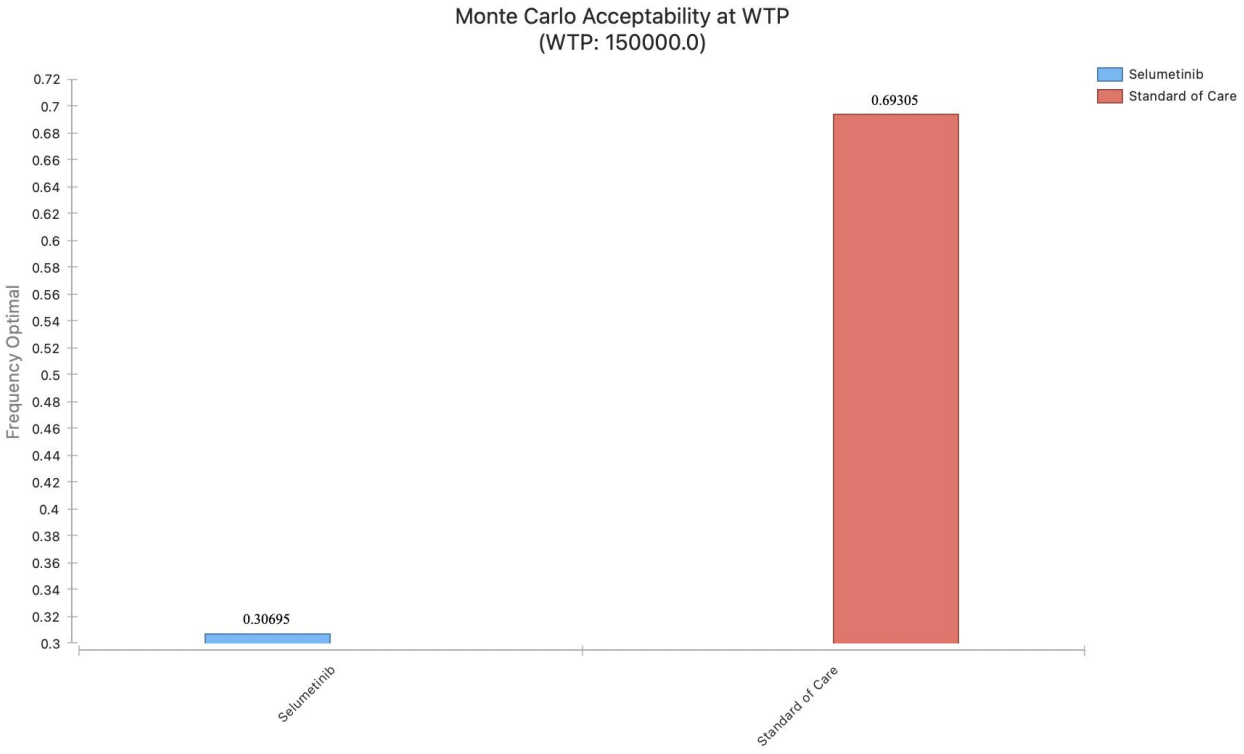


Figure 8: % of Iterations Cost-Effective: Strategy 2

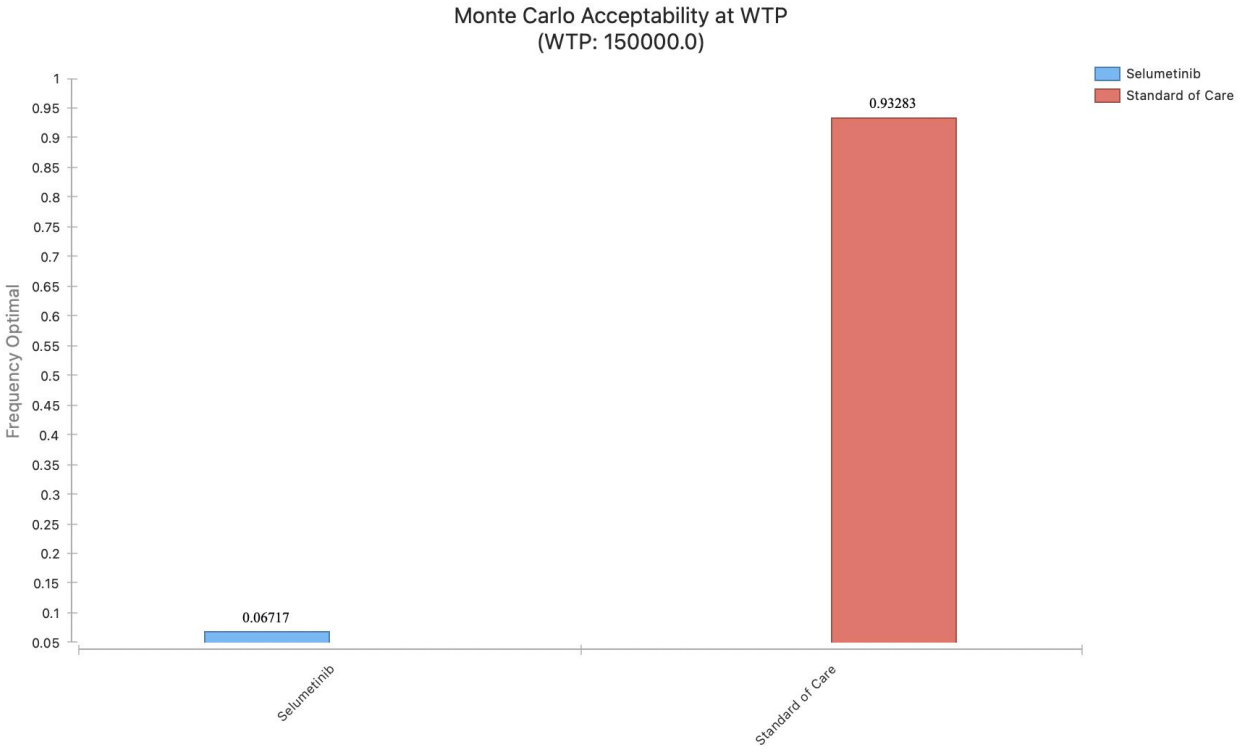


Figure 9: % of Iterations Cost Effective – Strategy 3

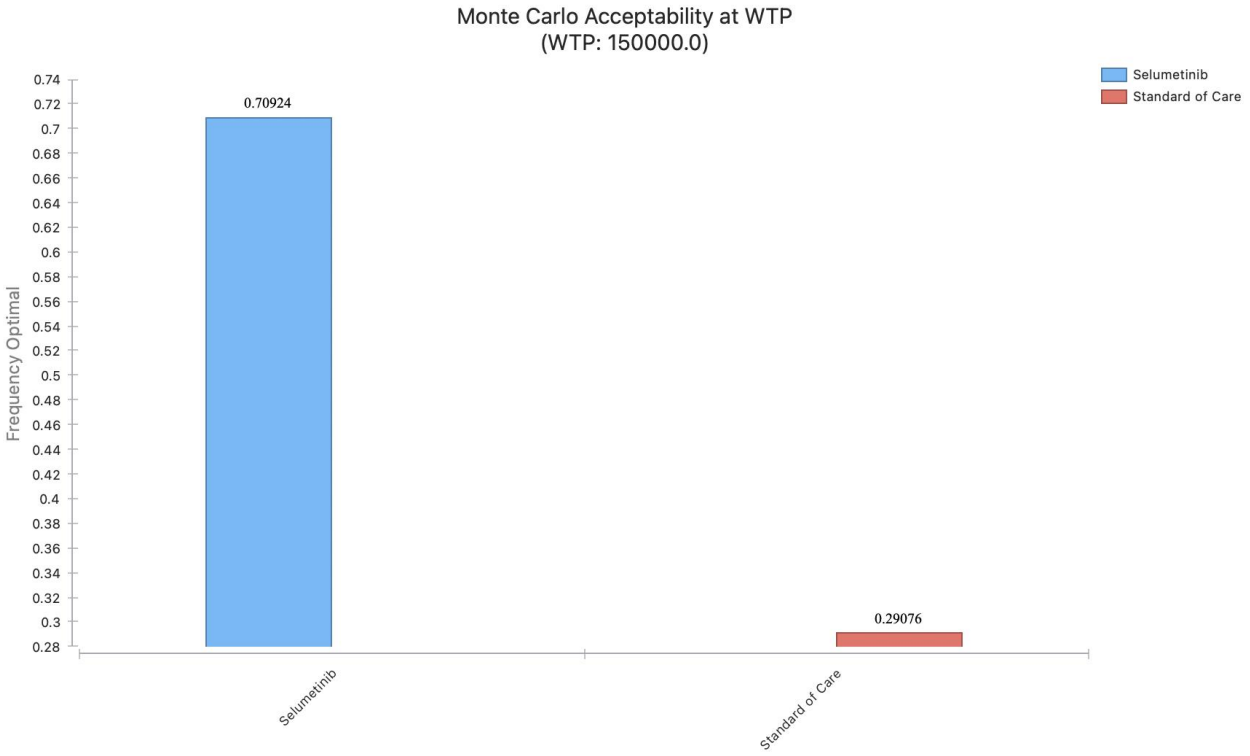


Figure 10: Distribution of Mean Age of Diagnosis in Monte-Carlo Simulation

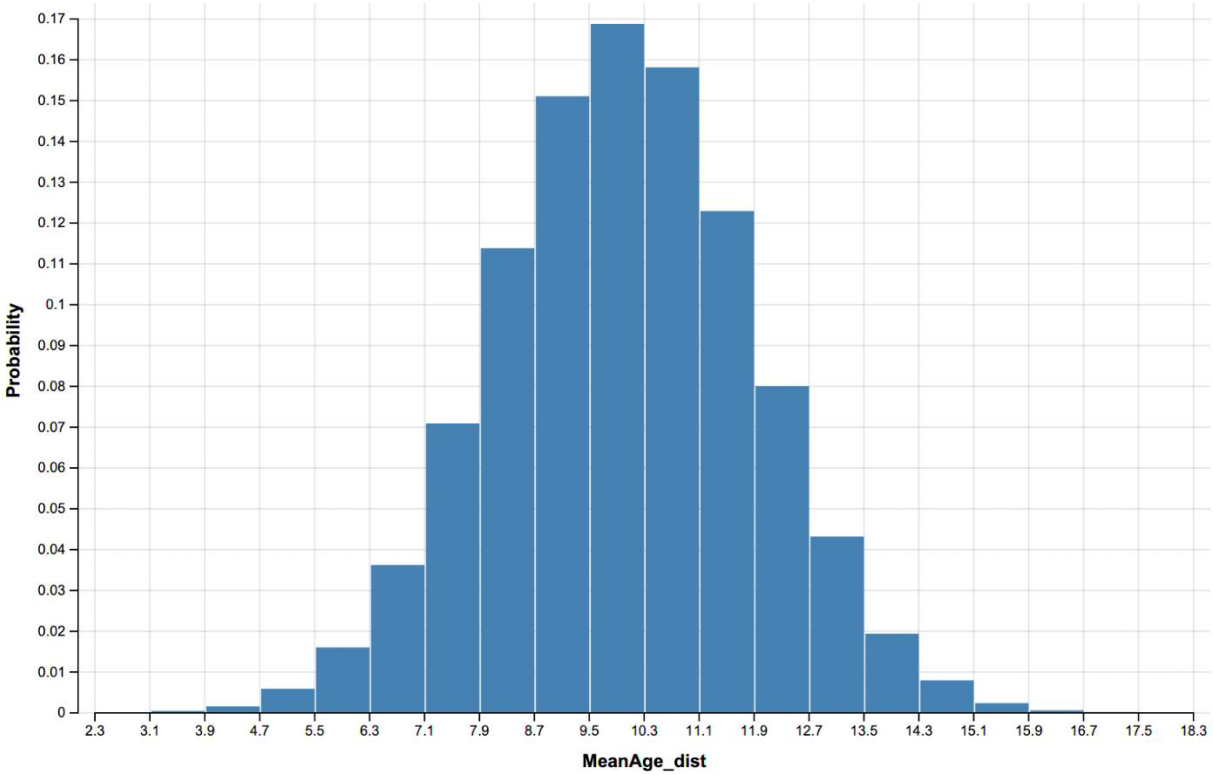


Figure 11: Survival Curve – Strategy 1

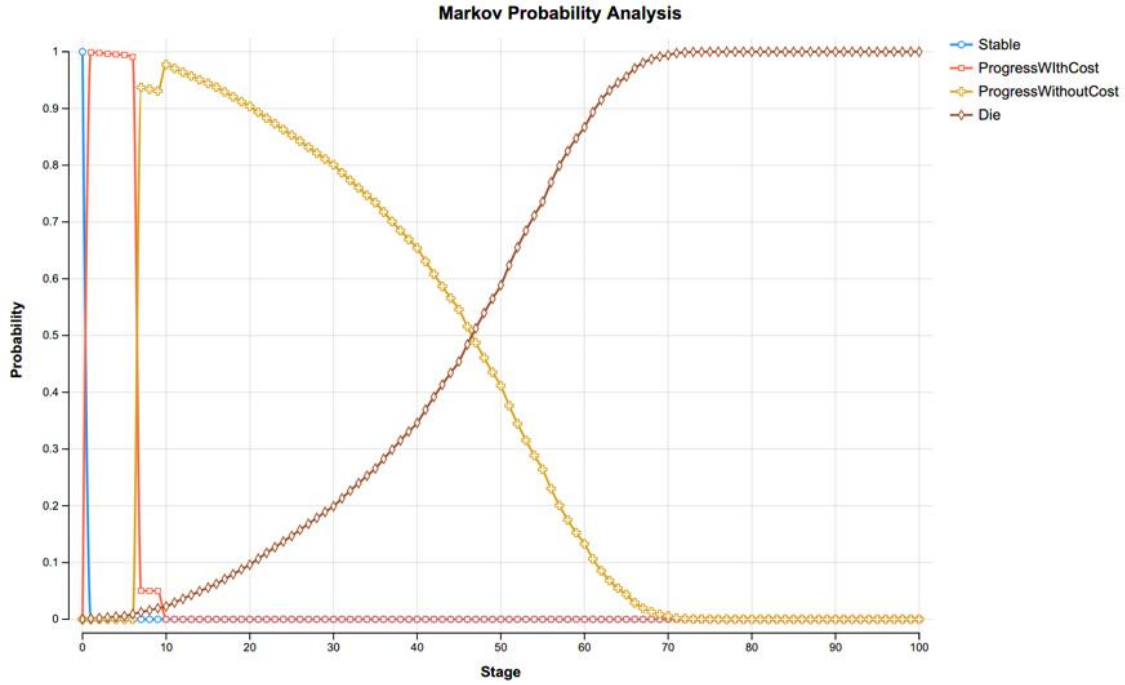


Figure 12: Survival Curve – Strategy 1

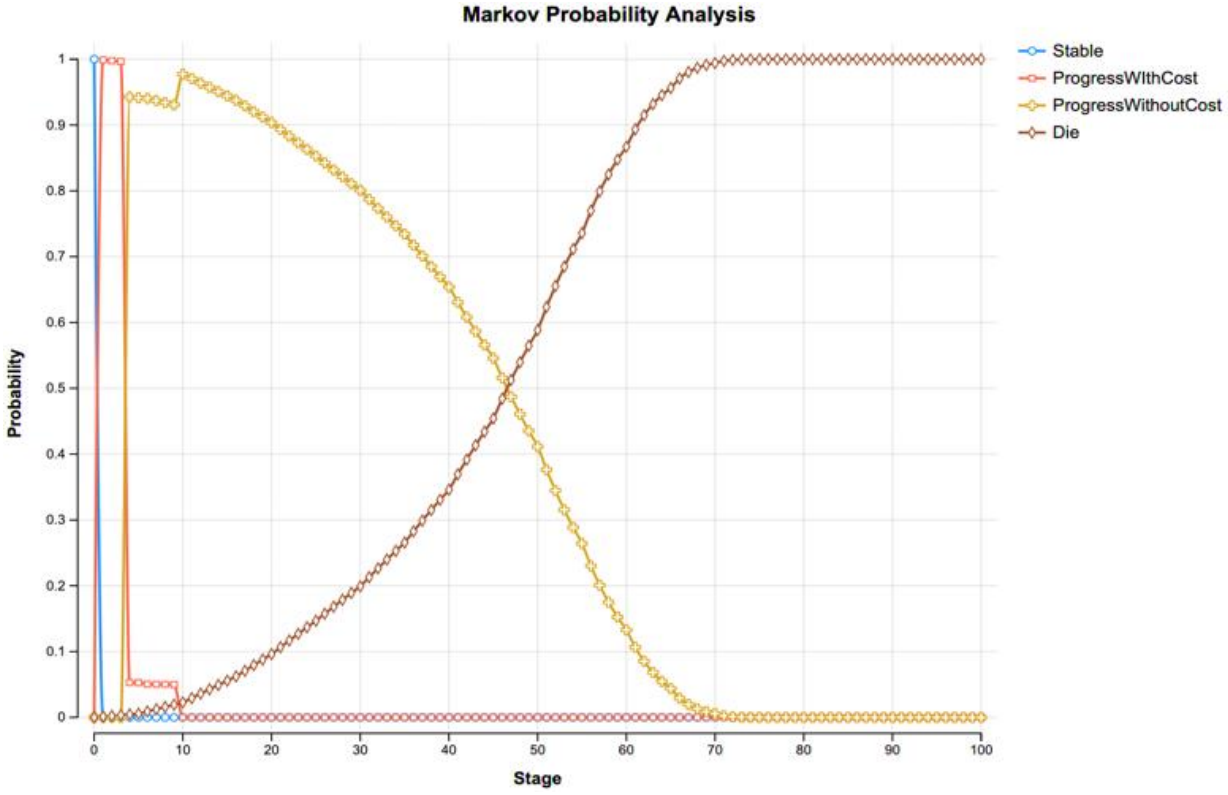
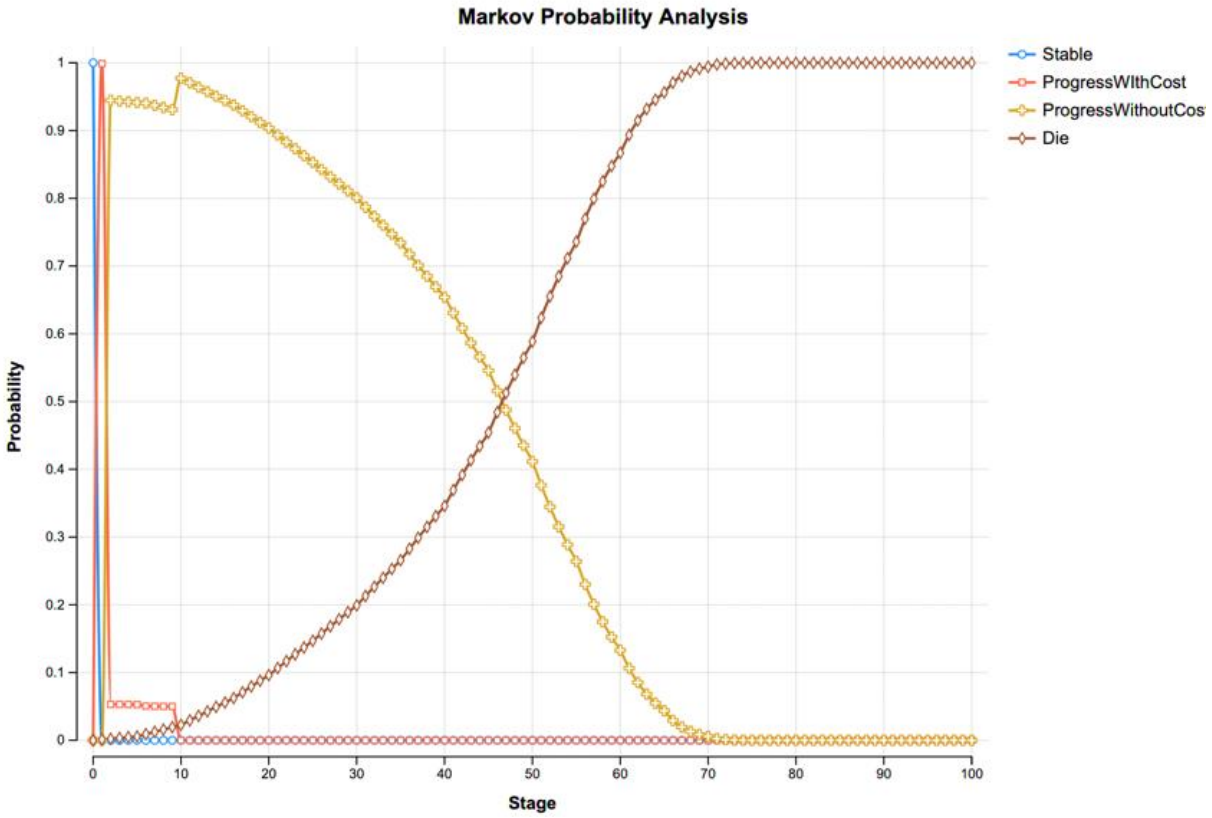


Figure 13: Survival Curve – Strategy 1



APPENDIX B: TABLES

Table 1: Population Eligible in Canada for Selumetinib

Population of Canada, 0 to 19		38,010,000	8002681	Canadian Census, 2021
Estimated Population, 2 to 18			6,002,011	Divided population of 0-19, by the 20 ages it represents, and multiplied by 16 (18-2)
Rate of NF1 in Canada	1 in 6000	0.0001666		scielosp.org/article/medicc/2014.v16n3-4/22-26
Total NF1		6335		Estimated based on Rate* Population 2-18
Total NF1 Pediatric			1000.33	Estimated based on Rate*Estimated Population 2-18
Total NF1 Inoperable PN	0.25	0	**250**	Estimated based on 50% Plexiform NF1, and 50% of those being inoperable