Next generation sequencing, an Early HTA in form of a conceptual framework for the histological/cytological diagnostics practice for advanced non-small cell lung cancer

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Abstract

Lung cancer is the second most frequent cancer site in both males and females. It remains the leading cause of cancer incidence and mortality in Norway. The most frequent classification of lung cancer is advanced Non-small cell lung cancer (NSCLC), accounting for 80-85 percent. Contributing to the most deaths, advanced NSCLC has a 5-year relative survival hovering around 20 percent. In the context of NSCLC, with a high incidence and mortality rate, it is important to evaluate the emerging innovations from personalised medicine within diagnostic and treatments practice which might lead to increased relative survival among the patient population.

The main objective of this study is to conduct an early health technology assessment (HTA). Central to this early HTA is the development of the conceptual framework which present two conceptual models that encompasses the practice of the histological/cytological genome testing for advanced NSCLC patients. These genome tests are performed either through next generation sequencing (NGS) by Roche diagnostics, NGS by ThermoFisher as a comparator, or single genome testing through Idylla as the standard diagnostic genome testing practice. The framework will also include parameter recommendations to include in the conceptual models.

With the collected information from the literature review, the consultation with experts in the field of personalised medicine and adaptation of the governmental guidelines two decision analytic models where built for this conceptual framework central to the early HTA study. The conceptual framework consists of two decision analytic models. One decision tree which models the histological/cytological diagnostic practice for the advanced NSCLC patients. The decision tree then leads into the second model, a Markov state transition model which shall model the progression free survival, overall survival and time of death for the advanced NSCLC patients.

In this study an early HTA, a conceptual framework, which include two conceptual models for the histological/cytological diagnostic practice for advanced NSCLC patients whom have been through visual diagnostics testing, was developed. Additionally, the conceptual model's central parameter information was included to make up for the conceptual framework of the early HTA. The conceptual framework can be deployed to analyse the impact that NGS by Roche Diagnostics might have on the histological/cytological diagnostic practice for advanced NSCLC patients in the Norwegian healthcare system. It can be viewed as an early contribution towards achieving the implementation of a diagnostic tool that might contribute to that advanced NSCLC patients receive more targeted treatment, which can be more cost-effective and can aid the society as a whole.

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Abbreviations

ALK	Anaplastic lymphoma kinase
AT	Additional testing
CDx	Companion Diagnostics
CGP	Comprehensive Genomic Profiling
CT	Computed Tomography
EGFR	Epidermal growth factor receptor
FISH	Fluorescence in situ hybridization
HRQoL	Health-related quality of life
KRAS	Kirsten rat sarcoma virus
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NGS	Next Generation Sequencing
NOMA	Norwegian Medicines Agency
NMB	Net monetary benefit
NSCLC	Non-small cell lung cancer
NTT	None-targeted treatment
OS	Overall survival
PET-CT	Positron emission tomography – computed tomography
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted Life-year
RR	Response rate
SoC	Standard of Care
VOI	Value-of-information
WTP	Willingness-to-pay

Introduction

In Norway, lung cancer is the second most frequent cancer site for both males and females, and remains the leading cause of cancer incidence and mortality among both sexes. It is the origin of 3200 new diagnoses and the cause of approximately 2200 deaths yearly [1-3] [4-6]. The most frequent classification is non-small cell lung cancer (NSCLC) which account for approximately 80-85 percent, contributing with the most deaths, resultingly showing the lowest relative survival [2, 4-6]. Correspondingly, this entails that the advanced NSCLC patient group might have the most to gain with improved diagnostics and the increased use of targeted treatment.

The diagnosis of advanced NSCLC patient has different technologies and practices. Some of the most relevant diagnostic measures are the computed tomography (CT), positron emission tomography (PET)-CT or histological/cytological examinations (i.e. genome testing). In the event of the oncologist suspect targeted treatment for a particular patient, the latter is to be performed [1]. These tests can be performed utilising either single genome testing, or hotspot testing with the use of next-generation sequencing (NGS) to uncover which treatment is the preferred option for each patient. Despite there being substantial research and evidence of the effect and accuracy of NGS [7-13] versus single gene testing, it is still in the early phases when looking at available conclusive evidence of this technology being cost-effective. It is therefore necessary to conduct a cost-analysis on the complex case of personalised medicine for advanced NSCLC patients and explore if the technology can be deemed cost-effective.

Hospitals are according to experts starting to implement an in-house diagnostic technology in the form of NGS-panels to aid the investigations in search for genome mutations. This is in favour of advanced NSCLC patients, where such technology is perceived to be more accurate, requires less tumour tissue and has a shorter turn-over time for providing results [10, 14, 15]. It is necessary to assess and evaluate if the introduction of in-house NGS technology is beneficial compared to single genome testing, and to other external NGS panels. Companion Diagnostics (CDx) NGS by FoundationOne is one example of this technology, it covers the whole genomic profile and provides a comprehensive diagnostic and result for the patient that is to be examined.

This study however is not aimed specifically at the genome mutations that are present, but it is meant to conceptualise the diagnostic practice for advanced NSCLC patients using

histological/cytological diagnostic practice utilising NGS. Additionally, it tries to present and promote specific targeted treatments based on either a genomic mutation is present or not.

The objective of this master thesis is to perform an Early HTA in the form of a conceptual framework of the histological/cytological diagnostic practice for advanced NSCLC patients who have undergone visual diagnostics testing to uncover possible targeted treatments. Where the scope is to compare an in-house NGS, with current single genome testing (e.g. Idylla[16]), or the intervention that is the focus of this study, NGS by Roche diagnostics[17]. To achieve this comparison, a conceptual decision model (i.e. a decision tree, leading into a Markov state transition model) of the diagnostic practice of advanced NSCLC patients is to be built, provide suggestions to targeted therapies for select genome mutations, and where to obtain essential parameter information. The study will take a Norwegian healthcare provider perspective[18]. Given the problem statement and objective, this is probably the first conceptual model for decision analytic modelling for NGS used on advanced NSCLC in a Norwegian context.

The outline of the study is as follows, in the first section the background information on advanced NSCLC, NGS, single genome testing and the relevant available information will be presented. In the second section, namely the theory section will present early health technology assessment, conceptual modelling, economic evaluation and uncertainty. The third section consists of the methods utilised, literature review and expert's opinion. The fourth section presents the results, i.e. the decision tree, Markov state transition model and parameter recommendations. In the fifth part will discuss the findings, limitations and assumptions made in the conceptual framework, and lastly the conclusion is presented in the sixth section.

1.0 Background

In this chapter information on lung cancer and advanced NSCLC, technologies assessed, the impact personalised medicine might have on the treatment and diagnosis practice for advanced NSCLC patients, the expected costs and prevalence increase in Norway will be presented.

1.1 Advanced non-small cell lung cancer

Lung cancer is the most commonly diagnosed cancer (11,6% of all cases) and the leading cause of death (18,4% of the total cancer deaths) among both sexes (behind prostate and breast cancer) and is the origin of 3200 new incidences, being the cause of approximately 2200 deaths yearly [1-6]. It remains the leading cause of cancer incidence and mortality among both sexes worldwide, 2018 [4, 5]. The most frequent classification is non-small cell lung cancer (NSCLC) which account for approximately 80-85%, with advanced NSCLC having the lowest survival [2, 4-6]. It is a severe public health issue, and contributes to enormous yearly expenditure in the Norwegian healthcare system which is attributable to the diagnostic practice, and the long-term invasive treatment regime associated with lung cancer.

Aetiology

The risk of developing lung cancer is highly associated with the rate of smoking. No other substance contributes more to the attributable risk of developing lung cancer than smoking [5, 6, 19, 20]. The remaining risk factors contributing to the development of lung cancer include environmental tobacco smoke (e.g. second-hand smoking), occupational exposure to asbestos and radon progenies, and dietary factors [5, 6, 19]. However, the risk of developing cancer is not confounded solely by smoking, genetic factors play a significant role, illustrating that hereditary components contribute with a 2-fold increase to the risk of developing lung cancer [21, 22].

Epidemiology

Lung cancer is the second most frequent cancer type among both sexes in Norway, equalling the total accumulated amount of deaths caused by breast-, prostate- and colorectal cancer [1, 2, 23]. In December 2017, 8189 individuals were living with the diagnosis [2], median age at diagnosis was 71 years and relative survival have improved exponentially for both sexes from 1978-2017 [2], where the relative 1-, 5- and 10-year survival rate in 2017 was 47%, 21% and 13.5% respectively [2].

Symptoms and diagnosis

Lung cancer can be characterised by different signs and symptoms, one of the most common being obstruction of the lungs. Early in the process of investigation it should be determined whether the tumour is limited to one particular area or if regional, distant or metastatic spreading has occurred [23-27]. Symptoms are challenging to separate between malignant and non-malignant illnesses, and for patients with symptoms from a primary lung tumour, visual diagnosis of thorax might provide strong indications of lung cancer [1].

There are different visual diagnostic tools available, among these we find: CT, PET-CT and histological/cytological examinations [1] which can contribute to predict possible targeted treatment. Magnetic resonance imaging (MRI) can provide additional information beyond that of CT and is recommended under certain conditions [1]. When targeted therapy is suspected to be the right treatment option, it is recommended to test for the following genome mutations with histological/cytological techniques; epidermal growth factor receptor (EGFR) by polymerase chain reaction, anaplastic lymphoma kinase (ALK) by immunohistochemistry or Fluorescence in situ hybridization (FISH), followed by programmed death-ligand 1 (PD-L1) if ALK and EGFR is determined negative. In some cases, Kirsten rat sarcoma virus (KRAS) and BRAF mutations might be tested for with the use of gene sequencing, followed by ROS1 with FISH [1, 28-30].

Prevention

Research has indicated that the incidence of lung cancer and its related mortality can be reduced by early detection, treatment of disease, and smoking avoidance and cessation [31-33]. Out of these preventative measures, only smoking avoidance and cessation programs have been shown to reduce lung cancer developmental risk significantly. Smokers who have terminated smoking for more than 15 years have an 80-90% risk reduction of developing lung cancer compared to individuals who did not cease to smoke [32]. Individuals who stop smoking even well into middle age avoid most of their subsequent risk for lung cancer, and stopping middle age (e.g. 30-45 year of age) reduce 90% of the risk attributable to tobacco [34].

Peto et al. [34] argue that encouraging individuals of smoking cessation should be the primary prevention agenda that should be the main focus in the attempt to reduce the risk of lung cancer. As of early 2019, a national lung cancer screening program has yet to be introduced in Norway. There also are no concrete preventative measures aimed at lung cancer apart from the occasional anti-smoking campaign [1, 35, 36], and according to the director of the Cancer Registry of Norway

[37], a national screening programme is unlikely to be implemented before there has been performed a systematic review of the smoking habits and the individuals that are at risk of developing lung cancer have been revealed. Lastly, low-dose CT scanning of the lungs has been shown to have effect in the reduction of lung cancer mortality. Proving that screening and early detection have a substantial effect on the overall survival among lung cancer patients and might affect outcomes in high-risk patients [38-41] (e.g. advanced NSCLC patients).

When prevention is not an option and lung cancer has developed it is the aim that every patient should receive the best available treatment, where it has been proven that a personalised approach will lead to an increased overall survival.

1.2 Personalised medicine

Personalised medicine can be defined as the preventative, diagnostic, treating and monitoring adapted biological relationship for any individual patient [42]. It will attempt to function as an aiding mechanism with the purpose of providing patients a more individualised and targeted healthcare experience based on their individual genome composition [43-45]. It recognises that complex diseases should no longer be considered as a single entity, and that diseases previously assessed at the same origin or pathway will require a more unique approach [44]. In Norway, personalised medicine is practiced for some diseases, predominantly for individuals whom suffer from rare disease and certain cancer forms [35, 42]. It has been invested many efforts and resources to create more personalised healthcare systems both nationally and internationally [42].

Personalised medicine is an emerging approach to patients care, and based on the patients' individual genomic profile it is better equipped to tackle predisposed conditions and guide clinical decisions, thus it has a vast potential to provide a greater number of, and more precise tools that can aid clinicians in their treatment of patients [46]. It attempts to encourage the move towards a more in-depth assessment and treatment that is more personally adapted to the individual patients need, and is a move away from a 'one-size-fits-all' (e.g. non-targeted) approach [43, 44] to a 'right treatment for the right individual' approach. This can result in an enhanced ability to better predict which medical treatment will and will not have effect for certain individuals, as well as better predict safe treatment [43], where the potential outcomes are prevented incidences, more frequently cured diseases and prolonged life [43-45].

For years, personalised medicine has been the ideal strived towards [42]. It is set to change the current reactive approach towards to a preventative approach in healthcare [44], allowing physicians to provide more tailored treatment. With regards to treatment regime, a personalised (i.e. targeted diagnostics and treatment) approach is estimated to have the greatest impact on the overall survival for advanced NSCLC patients [38, 40, 44, 46-49]. NGS makes it easier to provide a diagnosis for possible targeted treatment [8-10, 14, 15] for advanced NSCLC patients [1, 14, 40, 50-53].

The genetic information may concern hereditary factors to the DNA that might be the cause of the genome mutation, or it might be changes in the patient's genome profile which might lead to malignancies, subsequently possibly resulting in cancer development. This is particularly the case for oncology, and especially for advanced NSCLC, where some genomes are attributed to the hereditary factors and some are occurring as a direct cause of smoking or other carcinomas voluntarily consumed (e.g. smoking).

One of the new innovations and most important developments in personalised medicine is the invention of genome sequencing, which can lead to dramatically lower costs and increased speed of classifying the genome composition in an individual's DNA, this is hereby referred to as next-generation sequencing. The field of oncology have arguable the area which has the most activity in genomically-targeted treatment available at the writing of this paper, and the field is rapidly evolving where more information and evidence is synthesised and gathered in different studies. However, there is currently little available data and information of the combination therapies that is to be presented later in this chapter, but also the clinically validity of the genomic-targeted therapies and what impact it might have on the field of oncology. I.e. no cost-effectiveness study has been found in the literature for NGS on the selected genomes in this study.

Even though a personalised approach is the ideal options for oncology patients, the diagnostics of cancer might take many different forms. Where, depending on the cancer type, if lung cancer is suspected after being examined by a general practitioner one can be referred to further assessment with possible CT/mammography, followed with a histological/cytological diagnostic procedure which consist of a biopsy of the uncovered tumour [1] to assess which genome composition the tumour has. The results of the histological/cytological diagnostic practice can better predict if a patient should be in line of receiving targeted treatment, or if the patient will not reach positively to certain treatments, where it can then aid the physician in

avoiding treatment which has no proven effect [35, 36]. For advanced NSCLC, the histological/cytological tests are performed to uncover the following genome mutations ALK, EGFR and PD-L1, and in special cases subsequent tests can be performed on. BRAF, KRAS and ROS1 when EGFR, ALK and PD-L1 has been proven negative.

These genomes are found in the national guidelines [1], and are according to experts' opinion and Foundation Medicine presented with the possibility of having either an approved targeted therapy available in the market, or in ongoing clinical trials.

Experts say this practice is currently undergoing changes, with some hospitals implementing and adapting NGS-based diagnostic procedures with the usage of an oncogenic technology produced by ThermoFisher, namely Ion Torrent with an Oncomine panel the most frequent [54]. However, even though some are undergoing a change towards an NGS based diagnostic practice, others are still using single genome testing. The NGS-based panel delivered by ThermoFisher is similar to that presented by Foundation Medicine, offering a more limited genome panel and does not offer tumour mutational burden (TMB) output, nor does it does provide an as extensive report and recommendation as FoundationOne CDx CGP [17]. It will act as the comparator for FoundationOne CDx in this conceptual framework against the single genome testing approach [1, 17, 36].

1.3 Next-generation sequencing (FoundationOne CDx)

CDx NGS FoundationOne, owned by Foundation Medicine Roche Diagnostics, is an innovation in the field of personalised medicine. It is the first FDA-approved broad companion diagnostic (CDx) clinically and analytically validated for all solid tumours. It is an end-to-end comprehensive genomic profiling (CGP) technology, extracting patient samples, validated high-throughput hybrid capture-based NGS, identifying genomic alterations known to be rearranged or altered in cancers, and the delivery of biological report exhaustively referenced by continually scientific publications [17].

Apart from some incidences, personalised medicine and NGS is yet to be fully implemented in the normal pathway when investigating patients and in the development of the treatment regime for cancer patients [35, 36]. The test is designed to provide physicians with clinically actionable information, both to consider appropriate therapies for patients and understand results with evidence of resistance, based on the individual genomic profile for each patient's cancer. Every

test result includes microsatellite instability (MSI) and tumour mutational burden (TMB) to help inform immunotherapy decisions [17].

NGS by FMI has higher proven efficacy than single genome testing, and in the event of positive ROS1, BRAF or KRAS it acts as a self-confirming test for true negative ALK and EGFR mutations and vice versa. With NGS testing it is not necessary to uncover true negatives or false positives with NGS as these mutations rarely occur simultaneously. This is however necessary with single genome testing, and with additional single genome tests performed the cost and turnaround time might increase, thus leading to higher expenses and longer waiting time for the patients where time might be crucial for the survival of the patient.

The main purpose of CGP is to provide a clear answer and aid the treating physician, providing a full analysis of the patient's genomic profile which can contribute to the setting of an accurate diagnosis for the patient. With the results follow a comprehensive report with a description of the genomic profile of the patient and if applicable a list of potential treatment for that specific patient [17].

In contrast to the hotspot NGS panels used in clinical practice (ThermoFisher), FoundationOne CDx is a full-service end-to-end solution that utilizes CGP of 324 genes and provides information on complex biomarkers (TMB/MSI) as well as decision support [17]. Its service covers i) extraction of patient sample (e.g. tumour tissue sample), ii) high-throughput hybrid capture-based NGS sequencers identifying genomic alterations known to be rearranged or altered in cancer, and iii) and the delivery of a clinical and biological report exhaustively referenced by continually updated scientific publications [17]. In the FoundationOne CDx service, there are four key steps involved (see figure 1).

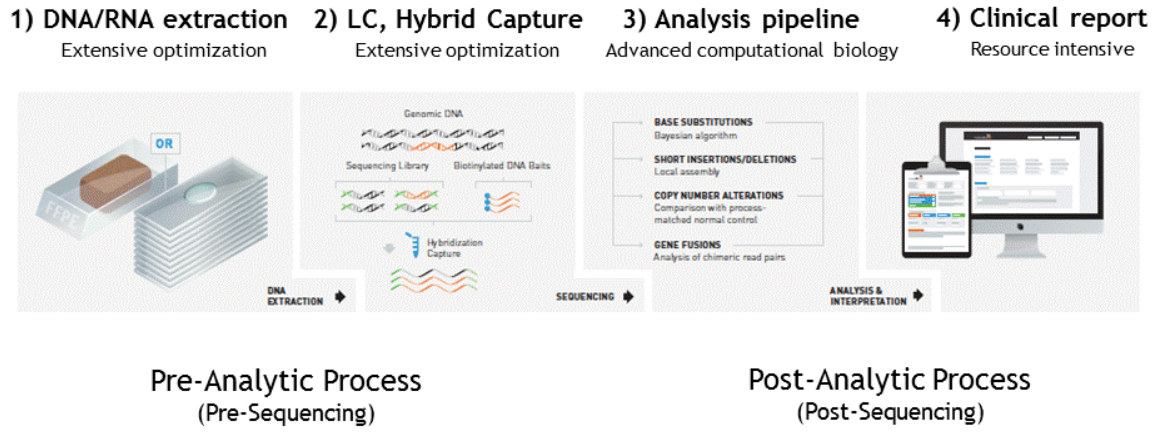

Figure 1: FoundationOne CDx cancer genomic profiling test work flow (Source: Roche, Foundation Medicine [28])

The pre-analytical phase includes control and preparation of the tumour sample where the admissibility is assessed according to criteria including a surface area of ≥25mm^2, sample volume ≥1 mm^3, nucleated cellularity ≥80% or ≥30,000 cells, and tumour content ≥20%, requires ≥50 ng of dsDNA harvested from somatic tumour cells [17]. After this a library will be created for analysis by the sequencer, the DNA is cut into small strands and a specific barcode (Molecular Index Barcode [MIB]) is assigned to each sequence. When this is done, the analytical phase begins, which consists of a hybrid capture on the Illumina HiSeq4000™ sequencer which codes the DNA in its entirety and reads the results for the analysis with a specificity of ≥99% of the exons. Thereafter follows the post-analytical phase involving two major steps, the data analysis and the interpretation and generation of a report [17].

Tumour mutational burden

In this study a distinction between the NGS technologies that are to be assessed will be made, based on the "limited" NGS Ion Torrent, Oncomine panel from ThermoFisher and the intervention in genomic profiling that is NGS by FoundationOne CDx (i.e. Roche diagnostics). The mere point of differentiation between the technologies is TMB, which has the potential to be a predictor of how patient might respond to certain immunotherapies, however this indebt discussion of the importance of TMB is not in the scope of this study.

1.4 ThermoFisher Scientific next-generation sequencing

The targeted sequencing approach introduces a PCR-based sequencing enrichment step using Ion AmpliSeg technology [54]. It is a high-throughput methodology that enables rapid sequencing o the base pairs in DNA or RNA samples [54]. Supporting a broad range of applications, including gene expression profiling, chromosome counting, detection of epigenetic changes, and molecular analysis, it is driving the discovery and enabling the future of personalised medicine [54]. Next to NGS by Roche Diagnostics, NGS by ThermoFisher is the comparator NGS of this early HTA. It has similar efficacy and validity, but with a less extensive genome panel [54].

1.5 Single genome testing (current practice)

The Norwegian decision authorities have not laid down strict recommendations for the use of specific technology to perform single genome testing. And seeing that there are multiple examples of single genome testing technology (e.g. these Thera screen, vysis, and Idylla) [10, 55-57], in which results presented show findings that NGS has similar or improved validity and efficacy in uncovering certain genome mutations. However, according to expert's assessment

and analysis of which instruments hospital utilise in the event of an NGS is not present, Idylla by Biocartis [16, 58] is the most frequently used technology (hereafter referred to as single genome testing) and is to be the selected single genome testing comparator.

1.6 Future of cancer in Norway

The forecasts conducted by Oslo Economics [59], Statistics Norway (SSB) [60] and the Norwegian Institute of Public Health (FHI) [61] indicate that with the estimated increase in population growth and the expected aging population [60], the relative incidence of cancer is expected to decrease, but the total incidences of cancer are projected to increase.

Thus, illustrating that given the relative incidence is decreasing, and the total incidences are increasing, the cost of cancer is estimated to increase in years to come, and when taking these forecasts into consideration, new innovations within both treatment and diagnostics might increase the short-term costs, but they also might contribute to cut the long-term costs associated with lung cancer [59, 62]. However, with the increased costs and the emerging innovations within the field of healthcare, an increase in survival and health-related quality of life (HRQoL) is expected to follow.

Reports developed by Oslo Economics indicate that the total healthcare expenditures for cancer in Norway in 2014 reached 14,5 billion NOK [62], and projections estimate that the total cancer cost might reach 23-24 billion NOK by 2022 [59], with a projected continuous rise to 30 billion NOK by 2035. The origin of which is related to rising hourly wages, increased use of technological innovation (e.g. diagnostic tools and pharmaceuticals), personalised approach, drugs with a higher proven efficacy at a higher cost.

In 2014, the accumulated costs for lung cancer for the Norwegian healthcare sector reached just above 1,3 billion NOK [62]. In the following years, we see that the estimated prognosis for lung cancer are somewhat conservative with a predicted increase of 15,6% between 2017-2035, going from 1,8 to 2,16 billion NOK. However, the cost estimates show a slight stagnation [59], and will be influenced by a number of factors, such as personal salary, diagnosis, treatment and follow-up costs, meaning these estimates might not be completely accurate.

1.6.1 Cost of cancer diagnostics

There is high uncertainty surrounding the health care expenditure associated with personalised medicine [42]. However, personalised medicine has the potential of reducing financial and time expenditure, and will in the short-term induce higher costs, but in the long run it might lead to cost savings with more effective diagnostics, and the avoidance of long investigations or treatments which have proven little or no effect [42, 43, 45].

In 2015 HELFO reimbursed 788 million NOK to private and public visual diagnostic laboratories divided by a total of 3,7 million assessments, where the estimated actual costs were 3,7 billion NOK [62]. There is no definite diagnostics-related statistics, and it is therefore not certain which costs are directly related to lung cancer diagnostics. However, the accumulated societal cost related to performing visual diagnostics were approximately 27 million NOK in 2015. And for laboratory tests on cancer in 2015 at private and public institutions are estimated to 5,6 billion NOK [62], of these Oslo Economics' estimates conclude that a total of 41,17 million NOK would account for the costs directly associated with lung cancer.

1.7 Relevant literature

The relevant literature in the field of personalised medicine for NGS technology versus single genome technology in histological/cytological diagnostic practice is scarce. The relevant literature uncovered at the initiation of this study was presented in this introduction. This information aids the development and synthesizing of the conceptual model for the diagnostics practice of advanced NSCLC with the use if NGS (FoundationOne CDx).

There has been performed cost-effectiveness analyses on NGS comparing different scenarios, but assessment has been done for NGS on advanced NSCLC [55, 63-69]. No studies have been able to identify or assess the clinical cost-effectiveness of NGS [70]. Cost-effectiveness analysis have been performed on advanced NSCLC comparing different treatment regimes, and some evidence comparing NGS and single gene testing in clinical studies was uncovered. Some compare and analyse a limited number of genes using both technologies, and some use gene sequencing as the main estimate to test for gene alterations and link these alterations with increased survival due to more precise (i.e. personal) treatments provided [14]. No cost-effectiveness analysis on NGS vs single genome testing with a third comparator (in-house NGS) related to advanced NSCLC has been performed.

As for clinical data available, the Barlesi study [14] performed in France over the course of one year was a nationwide screening programme for NSCLC patients involving 17662 patients measuring the frequency of molecular alterations in six routinely screened genes. It obtained molecular results and patients' clinical outcomes including progression-free survival (PFS) and overall survival (OS) comparing the presence of a genetic alteration with the absence of a genetic alteration. Approximately 50 percent of tumours screened in the study exhibited a genetic alteration, which lead to the use of targeted therapy. It showed that the presence of a genetic alteration was associated with improved median first-line progression-free survival (PFS, 10.0 versus 7.1 months), second-line progression-free survival (PFS, 3.4 versus 3.0 months) and overall survival (OS 16.5 versus 11.8 months) compared with absence of a genetic alteration

A meta-analysis from the US [52] has been conducted on phase 1 studies involving 13203 patients with cancer looking at the association of biomarker-based treatment strategies showing that when a biomarker-based approach was used it was associated with significantly improved response rate (RR) and PFS. Another meta-analysis [12] performed on phase 2 studies involving 32149 patients with cancer showed that a personalised approach compared with a non-personalised approach consistently and independently correlated with higher RR and prolonged PFS and median OS. There is limited cost data available, apart from one meta-analysis collecting micro-cost data, no applied cost-effectiveness analysis and only a few budget impact analyses in the scope of NSCLC was uncovered [70]. However, there has been presented clinical effect data through clinical trials proving the efficacy of different NGS panels vs single gene testing which could be utilised when conducting the full economic evaluation of the diagnostic practices that is to be conceptualised in this study.

In personalised medicine, genomic information may contribute to the molecular understanding of disease [71], to optimize preventive health care strategies, and to fit the best drug therapies to the patient's individual characteristics. The evidence synthesis in the era of genomic (i.e. personal) medicine is extremely challenging due to a number of reasons.

1.7.1. Relevant genome mutations

Seeing that the genetic profile of an individual patients plays a big role in which treatment he might reach to, it is important to identify and present the possible genome mutations that have targeted treatment available. All genome mutations are by defection allocating an individual whom exhibit that mutation to a specific subgroup. Therefore, some assumptions have to be made based on these subgroups. For the selected genomes in this study there are presented subsequent available targeted treatment, that said this is not the focus but an attempt to follow the whole pathway a possible patient might experience in the event of either targeted and non-targeted therapies for the selected genome mutations EGFR, ALK, PD-L1, KRAS, BRAF and ROS1 for first-line and second-line treatment will be presented [1]. In the event a second-line targeted treatment is not available, standard chemo-therapy is to be assumed provided. In the case of the patient being allocated to non-targeted treatment, the non-targeted chemotherapy Nivolumab can act as a treatment strategy [72, 73].

EGFR, ALK, PD-L1, KRAS, BRAF and ROS1 mutations have either targeted therapies or ongoing clinical trials for targeted therapy approved by the Norwegian Directorate of Health [1], currently being tested with the use of single genome testing. A mutation in EGFR occurs in 15 percent of NSCLC patients, not only limited to smokers [10, 11, 30, 74, 75], and with the presence of an EGFR mutations confirms and strongly predicts for sensitivity to EGFR tyrosine kinase inhibitors (TKIs). ALK rearrangements involving anaplastic lymphoma kinase (ALK) tyrosine kinase are present in 4 percent of NCSLS patients, and with the presence of ALK rearrangement this strongly predicts for sensitivity to ALK TKIs, e.g. crizotinib [7, 30, 76-78]. Every NSCLC patient shall be tested for PD-L1, if the tumour cells exhibit >50% PD-L1 impression, and EGFR and ALK has been proven negative, immunotherapy is to be considered in first-line treatment. ROS1, a receptor for tyrosine kinase acts as a driver oncogene occurs in 1-2 percent of NSCLC patients. [8, 79, 80]. KRAS mutation occurs in 30% of adenocarcinoma, is predicted through gene sequencing (e.g. NGS), it is associated with resistance against TKI treatment and it can be used to reduce doubt in false negative EGFR mutation [8, 79, 80].

BRAF mutation is a downstream signalling mediator of KRAS patients that activates the mitogen-activated protein kinase (MAPK), it is observed in 1-3 percent of NSCLC patients, usually associated with smoking [81]. Below a short description of each of the genome mutations to be included in this study will be provided, and the select drug for each present mutation, this is summarised in figure 2.

EGFR

A mutation in EGFR occurs in 15 percent of NSCLC patients, not only limited to smokers [1, 11, 82, 83]. With the presence of an EGFR mutations confirms and strongly predicts for sensitivity to EGFR TKIs. As the recommended guidelines, and the uncovered studies present, the most common targeted therapy for EGFR mutations in NSCLC is Erlotinib (optionally, gefitinib based on price) in first-line treatment until progression, and Osimertinib for second-line treatment.

ALK

ALK rearrangements involving ALK TKI are present in 4 percent of NCSLS patients, and with the presence of ALK rearrangement this strongly predicts for sensitivity to ALK TKIs [1, 7, 30, 76]. The most frequently provided targeted therapy for ALK rearrangements is Crizotinib for first-line treatment until progression, and Ceritinib is the second-line treatment option based on recommendations from decision authorities.

PD-L1

Every NSCLC patient shall be tested for PD-L1, if the tumour cells exhibit >50% PD-L1 impression, and EGFR and ALK has been proven negative, immunotherapy is to be considered in first-line treatment [1, 84] with pembrolizumab every third week for up to two years, or until progression. After that, non-targeted therapy may be provided in the case of progression.

ROS1

ROS1, a receptor for tyrosine kinase acts as a driver oncogene occurs in 1-2 percent of NSCLC patients, and in same line as BRAF, it can act as a confirmation of true negative ALK and EGFR tests. ROS1 tyrosine kinase is highly sensitive to crizotinib due to homology between ALK and ROS1 [8, 79, 80, 85-87] and is therefore recommended in first-line treatment until progression.

KRAS

KRAS mutation occurs in 30% of adenocarcinoma, is predicted through gene sequencing (e.g. NGS), it is associated with resistance against TKI treatment and it can be used to reduce doubt in false negative EGFR mutation [8, 10, 79, 80, 88].

BRAF

BRAF mutation is a downstream signalling mediator of KRAS patients that activates the mitogen-activated protein kinase (MAPK), where it is observed in 1-3 percent of NSCLC patients, usually associated with smoking. BRAF also acts as a confirmation of true negative ALK and EGFR mutations. Chemotherapy in first-line treatment is recommended, with debrafenid plus trametinib as a combination therapy [10, 81, 89], this is also recommended for subsequent lines of treatment after progression in first-line.

EGFR	1st line	Erlotinib
	2nd line	Osimertinib
ALK	1st line	Crizotinib
	2nd line	Ceritinib
PD-L1	1st line	Pembroluzimab
	2nd line	
ROS1	1st line	Crizotinib
	2nd line	
KRAS	1st line	Cetuximab
	2nd line	
BRAF	1st line	Debrafinib
	2nd line	

Figure 2: Genome mutations included, and their corresponding 1st and 2nd line treatment matched.

It is important to note that the combination of these therapies does not have clinical effect associated with them, but are laid forth in this manner based on the governmental guidelines, expert's opinion and literature review of what might be an acceptable treatment pathway. The side-effects, or how these therapies or EGFR and ALK will interact without any severe side effects is not considered in this study, but is merely presented to provide some targeted treatment recommendations for advanced NSCLC patients that is built on expert's opinion and governmental guidelines,

2.0 Theoretical framework

In this section theory of conceptual modelling, early health technology assessment (early HTA) and economic evaluation will be presented. Central to this study is the construction of the conceptual models. Other important factors consist of presentation of fundamental parameter information, and discussion of how relevant parameter information can be collected.

2.1 Early health technology assessment for personalised medicine

Early health technology assessment plays an important role in the development of health economic evidence in the early stages of clinical research, and is progressively used to support evidence synthesise for new healthcare interventions [90].

Early HTA is employed to inform product development, early economic modelling and pricing and market assess of new pharmaceuticals and healthcare interventions [90-93]. The most commonly used form for early HTA is the employment of early health economic modelling [90] and may either include a decision tree or a Markov state-transition model to compare two treatments or treatment groups, or one can utilise both model types simultaneously [90-93]. It may be deployed to inform decisions on the commercial viability of new medical technologies for companies that is in the early research and development (R&D) phases on the likelihood of a product being successful or not. Hence, it attempts to assess the potential cost-effectiveness of new and future technologies before its implementation in real world practice, and prior to a full economic evaluation either utilising clinical trial data or other similar studies to populate the model, where the clinical data would be adapted to the scope of the problem statement.

Where standardised randomised controlled trials cannot be performed, decision modelling is a useful approach, and stratification of patients into relatively large subgroups seems sufficient as there is no regulatory incentive to further personalise these models beyond the scope of traditional decision trees and Markov state transition models [71, 91]. Albeit that it is challenging to address time-dependent behaviour in Markov state-transition models, it seems that this is possible to overcome given the right classifications and that the uncertainties are disclosed in an appropriate manner. And with the combination of both a decision tree and Markov model problems of greater complexity can be modelled.

Normally, the individual nature in the field of personalised medicine makes the target population challenging to define, and due to speedy discovery of new biomarkers it poses challenges for evidence generation. This also leads to biological heterogeneity and additional subgroups in the population. This does however make personalised medicine a prime field for early HTA.

Even though this study is located within the field of personalised medicine where it is based on individual treatment practices, a specific population group has been defined as thoroughly as possible, namely patients which has been diagnosed with advanced NSCLC (i.e. stage >IV) through visual diagnostics (e.g. CT, PET-CT or MR). Furthermore, the patient group is limited by the genome mutations presented in figure 2 [90, 94], where no one patient will exhibit more than one genome mutations, this is referred to as the subgroups. Additionally, to being a predictor for targeted therapy, the specific genome mutation exhibited may help forecast the expected survival for the patients as some genome mutations are known to react better to certain treatment than other mutations, which might lead to differentiated overall survival and experience health-related quality of life.

2.2 Conceptual modelling

Conceptual models have been utilised by economic evaluations for years. It is the abstraction of the clinical pathway and treatment regime a patient is to follow in an economic evaluation. Conceptual modelling is probably the most important aspect of a simulation study, it might also be perceived as the most challenging and least understood process. It is the act of hypothesising a process or problem statement that is to be modelled through a simulation, and it refers to the early stages of a simulation study, in this study it refers to an early HTA. Even though it is frequently used and is a central part of economic evaluations, there is limited information about how to go about the design of developing conceptual models [95]. The main parts of conceptualisation are however about the problem formulation, feasibility assessment of simulation, system and objectives definition, model formulation, model representation and programming, where all of these parts can be revisited on multiple occasions throughout the conceptualisation process.

The conceptual model can be based and inspired by studies of similar origin or designations, it can be built up by a combination of randomised controlled trials, previous studies on cost-effectiveness of similar character, this to incorporate different perspectives and angles where a

combination of different information sources will better reflect real-world practice. In the events of randomised controlled trials are unavailable, the conceptualisation process is for an early HTA. The conceptual model may therefore be built on literature reviews and experts' opinion to best capture the practice and the possible pathway for the patient population as accurately as possible.

Decision makers need confidence in the model results as well as information of how accurately the model predicts the health and cost outcomes of interest, and account for this information when deciding how to utilise the model results [96]. The confidence decision makers have in a model can be impacted in two central ways. Firstly, transparency which includes clear description of the model structure, equations, parameter values and assumptions to enable easy understanding and interpretation. The second is validation, which means to which extent an expert in a respective field can confirm that a model include certain assumptions and application reflects current research and real-world evidence [96, 97].

2.3 Economic evaluation

The recurring question that arises in healthcare decision making is how to divide and allocate already scarce resources when a new alternative course of action is to be considered reimbursed by the decision authorities [94]. Without proper information the decision makers cannot make an informed decision, and the most advantageous decision might be neglected. Economic evaluation seeks to inform the range of very different but unavoidable decision in healthcare, these decisions are in some cases pragmatic and inevitably necessary to make [94]. Economic evaluation in health is a necessary and important aspect of decision-making due to already scarce resources, as well as the need to make structured deliberations in an organised and systematic manner.

For decisions to be as accurate as possible, the information put into the economic evaluations need to, as precisely as possible, reflect the real-world information available, hence evidence applied generally come from clinical studies, (e.g. randomized clinical trials), paired with available cost data. When clinical data is not available for the purpose of an economic evaluation, one can employ data second hand from already published literature. In that way one can synthesise the effect measures based on real world data [94, 97, 98] from similar studies, or a group of studies to get rid of uncertainty surrounding the choices and technologies that are to be assessed. This is the approach that is the most relevant for this study, since there are no

clinical trials conducted on comparing different NGS technologies against the current practice of single gene testing, nor is there fully defined cost data available in the Norwegian context, thus making it a prime example for an economic evaluation, which in this case is limited to an Early HTA in the form of a conceptual framework.

Clinical trials can be a central part of decision making by providing clinical evidence to the table that aids decision making, but they rarely tell the whole picture. Therefore, looking solely at the data and results from clinical trials might be misleading since they do not consider the full impact of the allocation of the available budget for the patient group, nor the effectiveness of the intervention put against a comparator [97]. Making it relevant for advanced NSCLC, where the clinical difference for the patient is the detection of a genome alteration and seeing that NSCLC is one of the diseases with most prospective genome mutation present, it has multiple different pathways and endpoints available and might be to extensive to perform a full clinical trial on, hence decision analytical modelling is a necessary tool to assess the clinical outcomes of the different treatment options based on genome mutations for advanced NSCLC.

Decision analytic modelling allows for variability and uncertainty associated with all decisions [97]. In healthcare, decision analysis has been defined as a systematic approach to decision making under uncertainty [99]. Decision analysis has additionally been used in terms of informing clinical decisions at population and individual levels [94, 97]. Furthermore, it is useful as it provides framework for combining various types of evidence, such as effectiveness evidence, resource use in terms of costs or consumables, and health effects measures [94].

Given the need in most health care systems to make resource allocation decisions across a whole range of disease areas, cost-effectiveness analysis (CEA), a form of economic evaluation, based on a single ('generic') measure of health is increasingly used [97], the most frequently used measure is the quality-adjusted life-year (QALY). On the basis that healthcare programmes and interventions aim to impact on individuals' length of life and HRQoL, the QALY seeks to reflect these two aspects in a single measure and, remains the only generic measure of health used on a large scale [97].This corresponds with what Drummond et al. [94] propose, utilization of QALY as the preferred measure of health gain, this is also in accordance with the Norwegian medicine agency (NOMA) guidelines for measuring effect [18].
Simplified decision rules are centred on the calculation of the incremental cost-effectiveness ratio (ICER) as the main cost-effectiveness measure. The ICER is the output measure of the

results provided in cost analysis', and is the additional cost per extra unit of effect (e.g. QALY, Life years) from the more effective treatment [97], presented by the following formula [94, 97]:

$$ICER = \frac{\Delta\, EXP\ cost}{\Delta\, EXP\ effect} = \frac{Cost\ of\ Intervention - Cost\ of\ comparator}{Effect\ of\ Intervention - Effect\ of\ comparator}$$

The ICER can be seen as either cost-effective or not [97] and is compared with the willingness-to-pay (WTP) threshold for the value for an additional unit of effect, or compared with the interventions in question. Based on this, the preferred option can be established and a decision made [97].

The results of the ICER can be placed in the cost-effectiveness plane, as presented in Figure 3, showing the difference in effectiveness. The horizontal x-axis represents the difference in effect, and the vertical y-axis represents the difference in costs [97]. The plane can be defined as four separate quadrants, labelled with the point of a compass to enhance simplicity. A new treatment is said to be 'dominant' (e.g. less costly and more effective) towards the comparator, if it is located in the south-east (SE) quadrant, and vice versa of the comparator being dominant if the plot is located in the north-west (NW) quadrant [97].

Given these circumstances, a clear preference is to implement the less costly and more effective treatment. However, more frequently than not a treatment is more effective, but also costlier and the plot of the treatment is located in the north-east (NE) quadrant and a trade-off is necessary where a decision must be made if the additional health benefit of the more effective treatment is worth the additional costs [97]. The straight line that passes through the origin (ΔC/ΔE) represents the willingness-to-pay threshold for the decision maker. If the ICER of the new therapy (ΔC/ΔE) is lower than this line, it is perceived to be more cost-effective, than the threshold ratio and the treatment should be adopted [97]. If the ICER is located in the south-west (SW) quadrants it is perceived to be completely dominated, being both costlier and less effective than the comparator, in this case it cannot be implemented due to the sheer lack of favourable outcome exhibited [97].

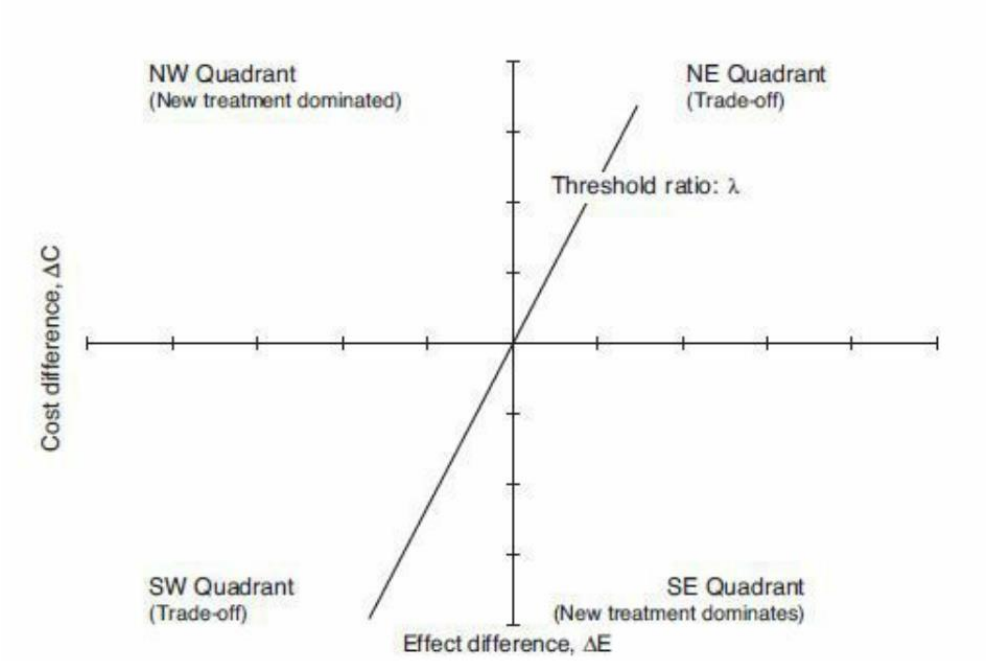

Figure 3: Cost-effectiveness plane, illustrating the different quadrants and the CE-threshold ratio: λ (Source: Briggs et al. [92]).

2.4 Uncertainty

The comparison of two drugs for one indication, including their subsequent effect and cost-effectiveness, is known to be challenging [71, 94, 97, 99]. A natural occurrence in cost-analysis is uncertainty surrounding the input and output of the analysis itself. In this study we look at one disease, however multiple indications are to be examined. This due to the nature of personalised medicine with the individual genome composition of each patient. This heterogeneity needs to be tackled through some sort of analysis, and assumptions and limitations needs to be made as a result of how this study is built of. Therefore, a number of uncertainty analysis is necessary to tackle the limited available data, the disease in question, the different genomes and subsequent targeted treatment or non-targeted treatment that are possible of experiencing.

The uncertainty that occur is costly, and there is always a risk that any decision made is wrong. When an incorrect decision is made, society will suffer the loss as a consequence. Hence, in decision theoretical approach, value is ascribed to the reduction of uncertainty such that the decision may include the option to acquire more information.

Decision models are commonly used to evaluate the cost-effectiveness of health interventions, populated with input parameters collected and estimated from and with the use of different

sources, however the true value of these parameters is not always known with certainty, which may lead to suboptimal and inaccurate decisions [97, 100, 101]. The uncertainty that arises can come from a number of sources, and not solely from implemented parameters but also from probabilities included, potential bias or relevance of evidence and the assumptions required in extrapolation of effect and cost over time. Assumptions are one of the central properties of economic evaluation and no model is founded on perfect evidence, therefore it is essential to demonstrate the uncertainty that arises in the available evidence and how it will affect the results of the analysis.

Every model that simulate real-world events comes with variability, uncertainty (parameter and decision), and heterogeneity. In personalised health care (i.e. medicine), it is crucial to manage this heterogeneity in terms of their genome composition, values and preferences. Stratification of the patients based on their genome profile is a sub optimal solution given the unique characteristics they each exhibit and it needs to be tackled. Thus, variability in the population indicate that patients will inevitably differ from one another, either it be the HRQoL or clinical events they experience. This form of variability cannot be altered with additional data collection [97], nevertheless one can account for individual development when taking into consideration the assumption of individuals being variable in nature, thus taking the variability into account in the development and elaborate further on this when performing the analysis. In this framework the patient might not only differ in HRQoL estimates, but overall survival due to the individual genome mutations that might be experienced and subsequent treatment which has shown to impact the health outcome the advanced NSCLC patient might experience.

Input parameter uncertainty is estimated for population cohorts on the basis of imperfect information, thus the collection of additional evidence can reduce the uncertainty of the input parameters. Decision uncertainty implies that the joint implications of parameter uncertainty in a model result in a distribution of possible cost-effectiveness relating to the options under comparison. Here, the distribution might indicate that the correct decision has been made based on the probabilities estimated [97]. Lastly, heterogeneity relates to the extent in which it is possible to explain a proportion of the interpatient variability in a particular measurement on the basis of one or more patient characteristics [97].

Probabilities indicate the likelihood of an event occurring in the future, affecting health outcome and expenditure of an intervention. It can be generalised to represent a strength or weakness of belief which is based on their previous knowledge and experience [97]. Hence, in

this framework it represents how much time passes until an event occurs, namely the time spent in a certain health state and how long a patient suffering from advanced NSCLC might stay in remission after immunotherapy, or before the patient will progress further in the illness development, or the probability of experiencing an adverse event given the treatment offered. This will also determine how long a patient might stay in 1st line treatment, 2nd line treatment and progressed thus affecting the estimated PFS and OS and time until death occurs, or potential censoring.

Due to one of the fundamental properties of personalised medicine being individualised treatment, it is crucial to handle this uncertainty. Different analyses can be performed to account for the uncertainty that follows decision and assumptions made and restrictions and limitations adapted. A sensitivity analysis is meant to reflect and capture this uncertainty that arise from the available data sources, assumptions and limitations offered by the cost and effect parameters to provide the output in the economic evaluation [97]. Another method to include is the value-of-information (VOI) analysis [90], generally used to estimate the value of (future) interventions and to identify preferences for new medical products while estimating unknown probabilities as well as unknown effect sizes. Where the outcome can be that additional research into the field, or additional information is needed to gather a decision on the reimbursement of the potential interventions.

Another method in the simulation that might be utilised is probabilistic sensitivity analysis (PSA) by assigning specific distributions, e.g. beta and Dirichlet for probability, and gamma for cost parameter groups to check the effect of variation in parameter values on the cost effectiveness results [97]. With the results from the PSA, it is possible to create the plot for the cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC) due to the large sample simulations provided to help inform decision makers of which intervention is most likely to be being cost-effective [97].

3.0 Methods

The method used to develop the conceptual framework will be presented in this section. The two methods utilised is literature review and collaboration with experts in the field of personalised medicine.

3.1 Model conceptualisation

According to best practice by ISPOR-SMDM presented by Roberts et al. [102] and recommendations by Briggs et al. [97] the development of a conceptual framework consists of two distinct parts. It begins with the conceptualisation of the problem statement where it is gained knowledge of the specific disease and health care intervention such as histological/cytological diagnostic practice for advanced NSCLC patients, and their specific clinical and economic characteristics. Afterwards, the information and knowledge are to be transferred to represent the specific research problem and capture the central components of the research problem. Hence, the second part is the conceptualisation of the model itself, where it needs to adequately reflect the research problem handled in the first part.

The purpose of conceptual modelling is to provide a framework for the problem situation and objectives. It provides a clear means of communication between all relevant stakeholders [95]. Furthermore, it is about abstracting a model from the real-world procedure or proposed system to represent a simplification of the problem statement where it adequately captures all the central components of the, in this case, histological/cytological diagnostic practice for advanced NSCLC patients. The simplifications made and abstraction of the problem statement reflected in the model makes it possible to reproduce the complex clinical real-world practice of the diagnostic practice. However, seeing that there is limited available clinical trial data on personalised medicine for advanced NSCLC with the use of NGS in the diagnostic practice, some assumptions has to be made. And due to the different subgroups (i.e. individual genomes), some complexity arises because clinical trials cannot be explicitly design for particular subgroups, as they are not known initially. Treatments are selected based on the presence or absence of genome mutations and thus additional tests, thus making it nearly impossible to mirror this real-world evidence perfectly in a conceptual model, therefore it takes a great deal of simplification to conceptualise the complexity to reflect this in a sufficient manner. Challenges of this conceptual model is therefore to abstract the appropriate simplification of the problem [95], as well capture the central components of the histological/cytological diagnostic

practice and subsequent targeted treatments and non-targeted treatments for advanced NSCLC patients and the assumptions made [97].

No model is perfect, this is aligned with the limitation of perfect available information, it is therefore important to rationalise choices made in terms of information inclusion, assumptions and limitations presented [4, 94], as this will affect model credibility and interpretation. Essential to every decision analytic model is which parameters to include, how they are to be linked as well as how these parameters should be represented in form of evidence. This can be crucial for the end results.

Greater complexity might be necessary in some settings, e.g. policy models that include a magnitude of outcomes, and selection of the correct model level complexity is among the most challenging decisions a modeller face. Therefore, it is important to make the distinction between making a model as simple as possible, and making it simpler [103] seeing that model simplicity is desirable for transparency, ease of analysis, validation and description. These factors can be affected in the event of a model being too simple, subsequently resulting in that the expected outcome is not reflected in a sufficient manner, hence misrepresentation in the model development could lead to ambiguous and inaccurate results of the analysis [95, 97].

In this study, during the first part of the conceptualisation process, a knowledge base was gained on the specific disease (e.g. advanced NSCLC), the current diagnostic procedure (e.g. single genome testing), the intervention (NGS, FoundationOne CDx) that is meant to be evaluated, and comparator (in-house NGS by ThermoFisher). The target population, intervention and current practice, possible targeted treatments, health outcomes are to be defined. Costs are suggested expressed in monetary units, and health outcomes is to be expressed in QALYs, and the relevant time horizon of the analysis is a recommended life-time horizon. The second part consists of developing the two interconnected decision models with the specific characteristics and attributes that meet the requirements of part one (i.e. the problem statement) [95-97, 102].
The decision tree is to capture the diagnostic pathways, i.e. the genome mutations that a patient might experience of not experience and subsequent treatments, the Markov state transition model is to model the health outcomes for the first-line, second-line treatment in terms of overall survival for the advanced NSCLC patients.

3.2 Information elicitation

To make well-informed choices to develop a credible and valid conceptual model for the diagnostics practice of advanced NSCLC patients, consultation with clinical and diagnostic experts was performed to gain clinical and economic opinion of how to conceptualise the model. This was performed via meetings and correspondence by email. Throughout the development of the conceptual model, two different versions of the decision tree and Markov model were presented to, and revised with the help of experts' opinion. The final conceptual model (i.e. the second version) was developed based on a combination between expert's feedback and literature review.

The conceptual framework was developed through literature review and with the consultation with expert's and with the relevant evidence and information presented in the introduction. During the consultation with experts, choices were made on which real world considerations and literature uncovered are relevant and to be applied to the decision problem and subsequently added to the conceptual model. This was performed to acquire stronger face validity to the model as to reassure that the conceptual model followed the current practice, intervention and comparator appropriately. Through the literature review, relevant studies, research and information was gathered to populate and aid the conceptual development.

In figure 4, a flow-chart of how the model conceptualising process was conducted is illustrated, it goes through the steps performed from problem statement, to finalised conceptual model.

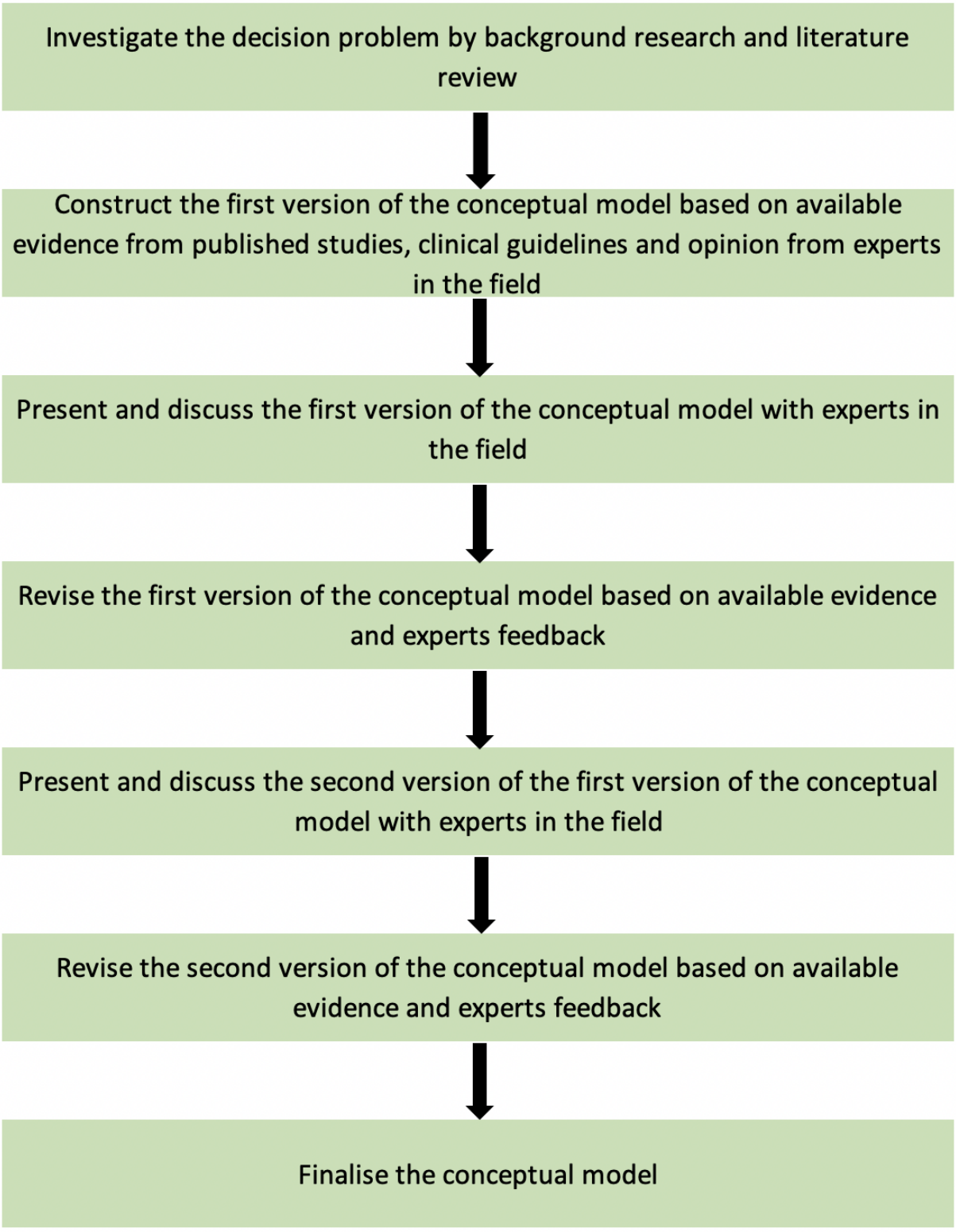

Figure 4: Flow-chart of the development and construction process of the conceptual model.

4.0 Results

In this section, the conceptual models will be presented, as well as the recommendations of relevant parameter information that may be included in later research.

4.1 The conceptual models

The conceptual model for the histological/cytological diagnostic practice of advanced NSCLC attempts to present the possible genome mutations that each individual patient might exhibit, furthermore it will present possible treatments based on the presence of absence of genome mutations utilising either NGS FoundationOne CDx (including TMB) or current diagnostic practice of single gene testing and the comparator (in-house NGS panels). As mentioned the quantifiable difference between the NGS panels is the measurement of TMB, the fact that the test is conducted in-house at a hospital and the estimated difference in costs between the two NGS panels.

The model consists of two parts, first a decision tree presents the possible pathways, i.e. diagnostic practice, if genome mutation is detected or not and possible treatment, (e.g. targeted or non-targeted). Secondly, the decision tree leads into a time dependent Markov state-transition model which simulates the possible health outcomes given the absence or presence of genome mutations and subsequent targeted or non-targeted first-line and second-line treatments.

The target population consist of patients who have been diagnosed with advanced NSCLC who have been through visual diagnostic screening (e.g. CT, PET-CT & MRI), and are suspected eligible candidates to receive targeted treatment. Following the identification of eligible patients, they are to go through histological/cytological diagnostic testing using either NGS or single genome testing to uncover possible genetic mutations in biopsy of the tumour, and subsequently allocated to either targeted therapy if either of the following genome mutations are present; EGFR, ALK, PD-L1, ROS1, BRAF and KRAS and [1] or non-targeted therapy if none are present.

The first version of the decision tree capturing the histological/cytological diagnostic practice is linked with the first version of the Markov state transition model. This practice is extended to the second versions, where they are tangibly linked to one another. Both the decision tree,

and the Markov model was revised once (i.e. two models were developed). The revision was performed to create the optimal model for capturing the diagnostic and treatment practice.

4.1.1 The decision tree

It is known that a targeted treatment lead to increased survival for patients that exhibit a genome mutation [14]. It is also known that certain mutations have a greater survival than others. This is in contrast to when a patient does not experience a genome mutation for the patient group advanced NSCLC. Hence, both the presence and the specific genome mutation exhibited may dictate the estimated overall survival an advanced NSCLC patient might expect to experience [7, 8, 10-15, 52, 68, 104, 105].

The occurrence of multiple genome mutations is not frequently observed, it is in this framework assumed that a patient will only exhibit one genome mutation at a time, hence the occurrence of multiple genome mutation cannot be experienced, this to limit the uncertainty and handle the variability in the population group further.

As mentioned in the background chapter, every genome has a different probability of occurring in any given patient. Therefore, in the decision tree for the single genome arm, the genome mutation with the highest probability of occurring would be the first to be tested for with similar trend followed for the subsequent genomes, where it for example EGFR would be tested for first, thereafter ALK and so on. For the NGS arms every genome is assumed tested for simultaneously. However only one genome mutations can be experienced at any given time and the likelihood of any genome occurring is to be modelled and used as the probability of each genome being present, this goes for both NGS arms and the single genome arm. For example, of EGFR is present, then no other mutation can be present, and if EGFR is negative, ALK has the next highest probability of occurring, this practice is followed if until all genomes are negative, where a non-targeted chemotherapy is to be provided for the respective patient.

The practice presented above, combined with the information presented in the background chapter is replicated and adapted into the first version of the decision tree, illustrated in figure 5 below. It captures the histological/cytological diagnostic practice after performed visual diagnostics to examine whether targeted treatment might be the correct approach for advanced NSCLC patient or if the patient is to be allocated to non-targeted treatment for the select genome mutations.

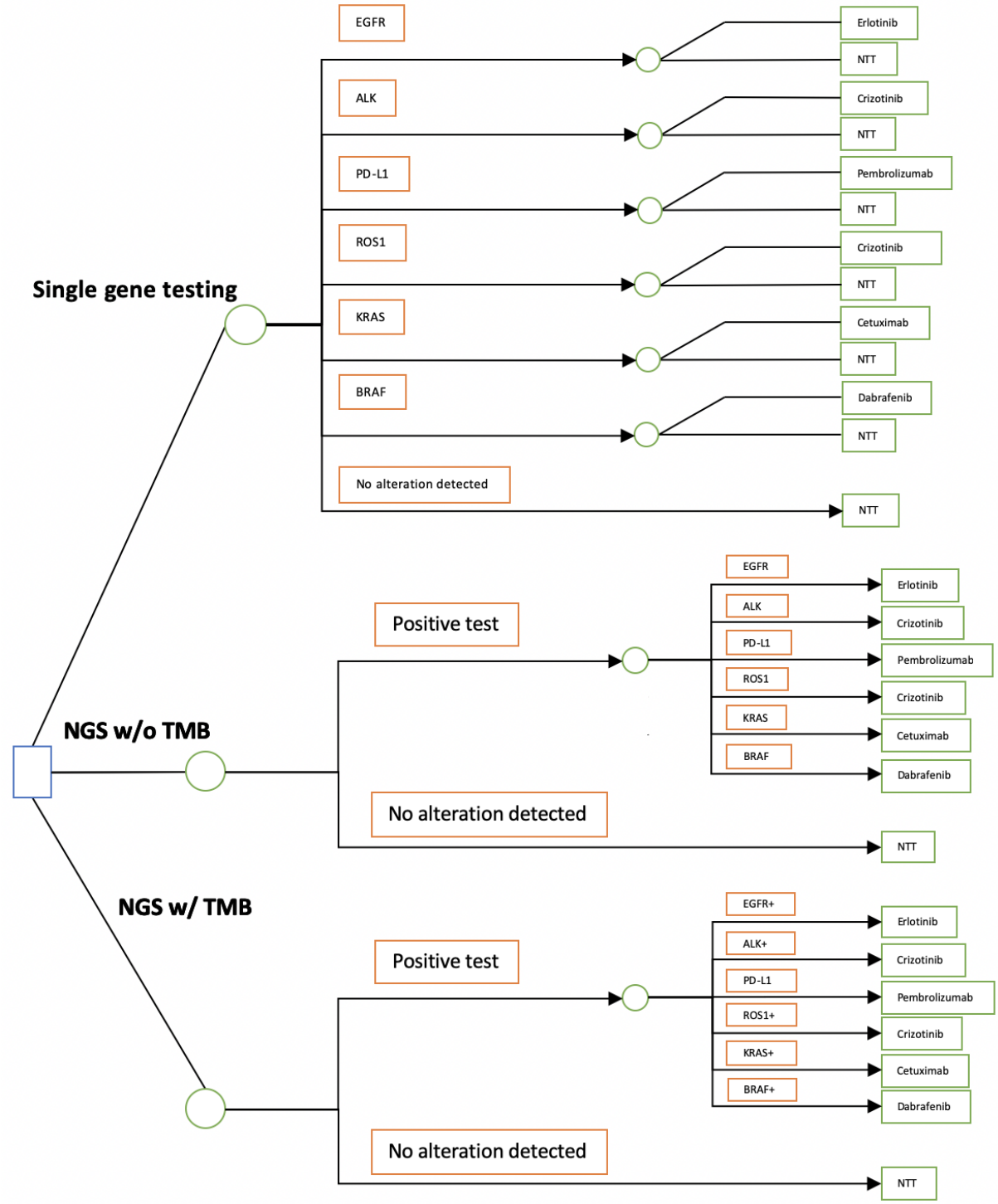

Figure 5: First version of the decision tree, capturing the first part of the diagnostic and treatment outcome (+ indicating inclusion of TMB in the results), with single gene testing, NGS w/o TMB (in-house NGS) and NGS w/tmb (FoundationOne CDx).

First version of the decision tree

In the first version, two general clinical endpoints of the histological/cytological NSCLC patients' diagnostics practice can be experienced, either the scenario of a patient exhibiting a genome mutation, where he or she will be allocated to the targeted treatment associated with that specific mutation, see figure 2. Or the patient might reach the endpoint non-targeted treatment denoted 'NTT' (i.e. non-targeted chemotherapy), in which the patient does not experience a genome mutation and will be allocated to a non-targeted treatment regime.

In the initial decision node there is a selection between three opportunities leading into the chance nodes, these being 'single gene testing', where a single genome mutation is tested at a time, the comparator 'NGS without TMB' (in-house NGS) tests all genes simultaneously, this is similar for the intervention 'NGS with TMB' (FoundationOne CDx). Every pathway has a specific endpoint, which denotes if a genome mutation is detected or not, this is similar for all the different pathways presented. For all decision arms, every patient can experience the same genome mutations (figure 2), and the distinction is the probability of testing positive or negative and the diagnostic technology does not dictate if the patient can experience a mutation or not, it merely predicts the likelihood and probability of occurrence.

For the 'single gene testing' decision arm it is assumed that one gene test is to be performed at a time, where one can only test positive for one of the specific genes. As mentioned, every genome mutation occurs at a different rate and subsequent probability of occurrence. The genome mutations are ordered in the likelihood of testing positive, EGFR being the most likely, ALK second most likely, and so on. The most probable outcome is conversely, 'no alteration detected'. However, all pathways of the decision arm can exhibit either the presence of a genome mutation, which is dependent on the genome mutation exhibited where a targeted treatment is the endpoint, or there might be no genome mutation present, in which a non-targeted treatment is the endpoint.

The decision arms for 'NGS w/o TMB' and 'NGS w/ TMB' are identical in structure, and exhibit a simpler construction than the one presented for the 'single gene testing'-decision arm. Here the quantifiable difference is the measurement of TMB, the fact that the test is conducted in-house at a hospital and that the cost is different for both the NGS panels. The practice is in itself limited to two different decision arms, these being 'positive test' and 'no alteration detected. In the first decision arm, if a patient test positive for one genome mutation, it is

assumed that he may not test positive for another, thus that endpoint is to be followed. Therefore, for NGS if a first genome is negative (e.g. EGFR), then the estimated probability of the following genome mutations to be positive is used (e.g. ALK), and in the case of the second mutation being negative, a similar practice is to be followed until one is found to be positive given the probabilities exhibited. In the event that a genome mutation is present, the patient experiencing the specific mutation shall receive the corresponding treatment, this is illustrated in figure 2. In the case where no genome mutation is detected in the upper arm, the patient will be allocated to a non-targeted treatment regime (i.e. non-targeted chemotherapy). For the lower arm of the NGS decision arms, it is assumed that no genome mutation is present, and the patient may be allocated to non-targeted therapy (i.e. non-targeted chemotherapy).

The first version of the decision tree developed was a simple version to provide an overview of the different diagnostic pathways possible for the genome mutations and it was anticipated that the model needed some revision. Therefore, after further review, communication with experts, presentation of, and description of the model the decision tree was adjusted accordingly.

Second version of the decision tree

When all relevant options were considered, with the help of expert's feedback, additional literature uncovered and additional examination of the governmental guidelines. The development of the second version of the decision tree could be commenced. The second and revised version of the decision tree is presented in the figures *(6-8)*, this naturally became slightly more complex with additional transitions and became somewhat cumbersome to interpret.

For easier interpretation, the second version of the decision tree will be presented in three sections, where each pathway will be presented separately, in figure 6 ('single gene testing'), figure 7 (NGS w/o TMB') and figure 8 ('NGS w/ TMB'). The full-scale version can be found in Appendix 1. Furthermore, in the second version of the decision tree, mainly for the decision arm 'single gene testing', an additional pathway/endpoint option 'additional testing' denoted 'AT' has been applied. This was included done to model the transition be and due to the changes made in the decision arm, where in this version for single genome testing the tests are performed in a sequential order, and in the event of a negative first test, the patient can either receive non-targeted treatment (chemotherapy) or additional tests might be performed to see if other genomes are present in the tumour of the individual patient.

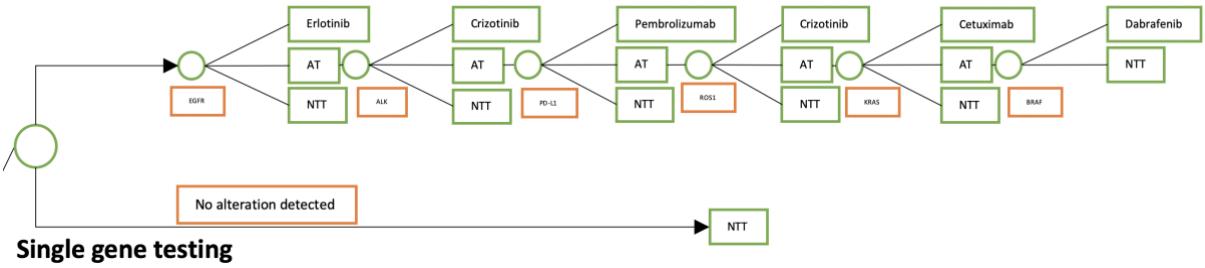

Figure 6: Second version of decision tree (i.e. 'single gene testing' pathway) illustrating the possible pathways that the NSCLC patient might take under the histological/cytological tests when performing one genome mutation at a time.

In Figure 6, the second version of the decision tree, the decision arm for 'single gene testing' is presented. Here two different pathways can be followed. However, compared to the first version, the practice of each individual genome test has been put in a sequential order for the upper branch, instead of being put in a descending order. The first genome mutation tested is EGFR, illustrating three possibilities where it can either test positive where erlotinib is to be provided. If the test is negative, the patient can continue with further testing where additional genome mutation will be examined, or it can be allocated to non-targeted treatment. The possible options are identical for the ALK-genome, it can either test positive, where crizotinib is provided, it can test negative and be allocated to non-targeted treatment, or it might continue further into the model where subsequent genome mutations will be tested. Following negative EGFR and ALK test results, PD-L1 is to be tested, following an identical process as the two mentioned before, where if a positive test is found the patient will be provided with the targeted immunotherapy treatment pembrolizumab, it can test negative where subsequent tests will be performed or it will be allocated to non-targeted treatment. Provided the three previous tests have been negative, the patient will be tested for ROS1, with the possible where the patient can either be allocated to targeted therapy (i.e. crizotinib) if tested positive, or test negative where a non-targeted therapy is provided, or it might lead into additional tests. Hereafter assuming the patient continued further into the model, KRAS is to be tested for, where if found positive cetuximab is provided, if not a non-targeted treatment may be provided or additional testing can be done where the patient progressed further into the model. Following a negative KRAS, the BRAF will be the genome mutations that is tested for, where it can if tested positive be provided with dabrafenib (i.e. targeted treatment) or it might test negative where lastly non-targeted therapy will be the treatment provided for said patient. In the second decision arm, no genome alteration is detected and the patient will be allocated to non-targeted treatment.

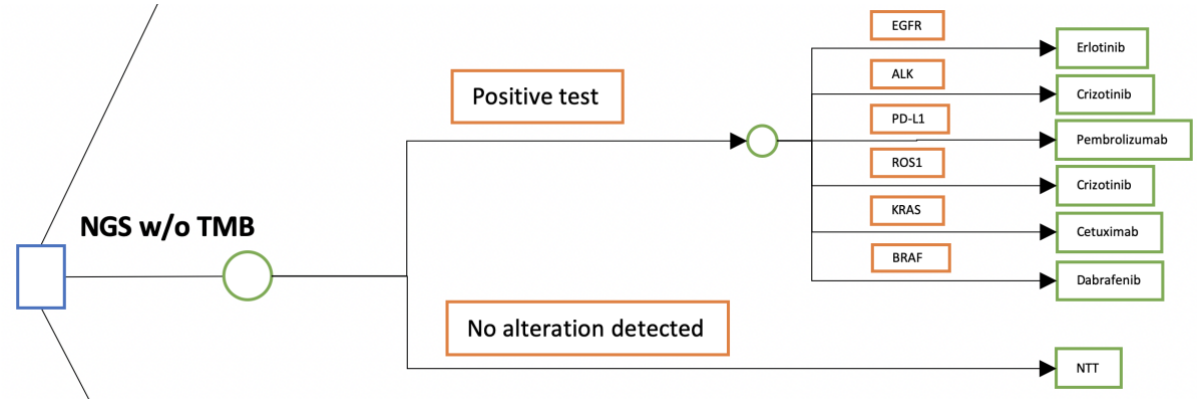

Figure 7: Second version of decision tree (i.e. NGS w/o TMB), illustrating the possible pathways that the advanced NSCLC patient might take under the histological/cytological tests when performing genome mutation tests at a time.

In figure 7, the pathway of 'NGS w/o TMB' is presented. Illustrating a similar structure as the decision arm in the first version where the two options are denoted 'positive test' or 'no alteration detected'. Where if no alteration is detected, a non-targeted therapy is assumed provided.

The practice is in itself limited to two different decision arms, these being 'positive test' and 'no alteration detected. In the first decision arm, if a patient test positive for one genome mutation, it is assumed that he may not test positive for another, thus that endpoint is to be followed. Therefore, for NGS if a first genome is negative (e.g. EGFR), then the estimated probability of the following genome mutations to be positive is used (e.g. ALK), and in the case of the second mutation being negative, a similar practice is to be followed until one is found to be positive given the probabilities exhibited. In the event that a genome mutation is present, the patient experiencing the specific mutation shall receive the corresponding treatment, this is illustrated in figure 2. In the case where no genome mutation is detected in the upper arm, the patient will be allocated to a non-targeted treatment regime (i.e. non-targeted chemotherapy). For the lower arm of the NGS decision arms, it is assumed that no genome mutation is present, and the patient may be allocated to non-targeted therapy (i.e. non-targeted chemotherapy).

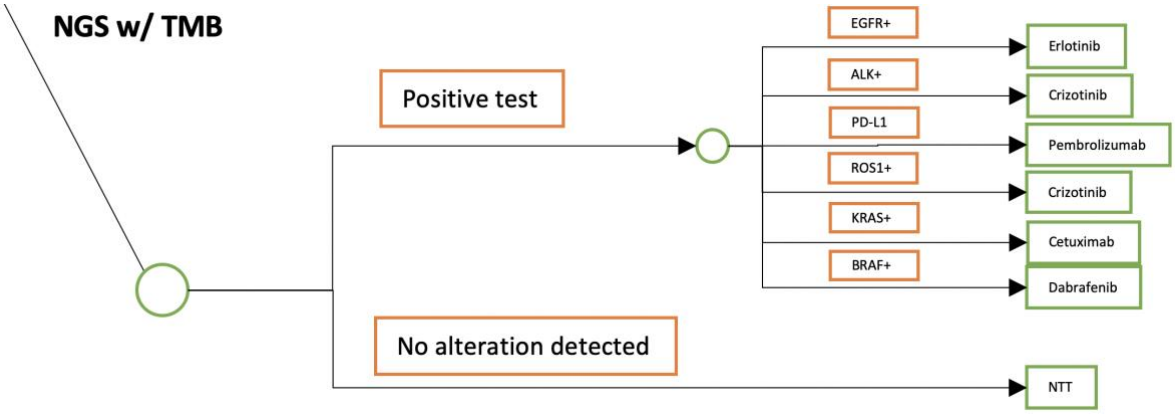

Figure 8: Second version of decision tree (i.e. NGS w/ TMB), illustrating the possible pathways that the NSCLC patient might take under the histological/cytological tests when performing genome mutation tests at a time.

In figure 8, showing the second version of the decision tree, the pathway of 'NGS w/ TMB' is presented. As a mere mirror to the decision arm illustrated in figure 7 'NGS w/o TMB' is the decision arm presented in figure 8, where the quantifiable difference is the measurement of TMB, denoted with '+' after each genome, and the fact that the test is conducted in-house at a hospital and that the cost is different for both the NGS panels.

Similar with the practice for 'NGS w/o TMB', the decision arm for 'NGS w/ TMB', the practice is in itself limited to two different decision arms, these being 'positive test' and 'no alteration detected. In the first decision arm, if a patient test positive for one genome mutation, it is assumed that he may not test positive for another, thus that endpoint is to be followed. Therefore, for NGS if a first genome is negative (e.g. EGFR), then the estimated probability of the following genome mutations to be positive is used (e.g. ALK), and in the case of the second mutation being negative, a similar practice is to be followed until one is found to be positive given the probabilities exhibited. In the event that a genome mutation is present, the patient experiencing the specific mutation shall receive the corresponding treatment, this is illustrated in figure 2. In the case where no genome mutation is detected in the upper arm, the patient will be allocated to a non-targeted treatment regime (i.e. non-targeted chemotherapy). For the lower arm of the NGS decision arms, it is assumed that no genome mutation is present, and the patient may be allocated to non-targeted therapy (i.e. non-targeted chemotherapy).

4.1.2 The Markov model

According to governmental guidelines [1], the patients are to be timely diagnosed and re-assessed throughout the treatment regime, and is expected to transition between different disease states, therefore it is important to capture this structurally.

The second part of the NSCLC histological/cytological diagnostic practice is hence captured by the following Markov state-transition model. The model contains a set of transitions between mutually exclusive health states over a series of time periods (i.e. cycles) [97]. At first one specific Markov model was developed based on previous cost-effectiveness analysis of advanced NSCLC treatment where an adaptation was made based on single genome mutation indications, hence the probable outcomes and based on standard treatment regime. This practice is illustrated in figure 7.

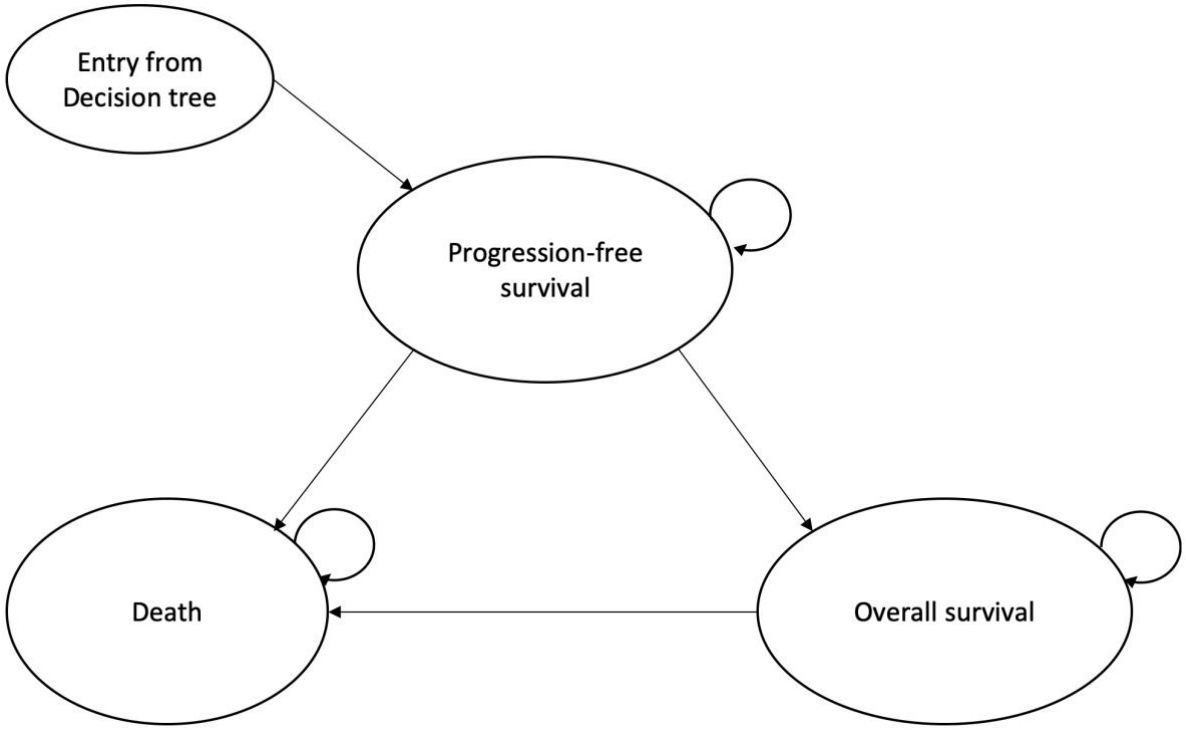

Figure 9: The first version of the Markov model capturing patient survival, including the mutually exclusive health states Progression-free survival, Overall Survival and Death based on the pathway from the decision tree, where the following transition probabilities and estimated effect measures follow individual patients throughout the course of the model simulation.

The Markov model presented in figure 9 captures the possible clinical consequences during a life time horizon for the advanced NSCLC patients. Depending on the outcome from the histological/cytological diagnostic practice modelled in the decision tree, the patient can either follow a targeted treatment regime. This is as mentioned dependent on the genome mutations that each individual patient may or may not exhibit and subsequent treatments presented in figure 2. The purpose of the decision trees is to model the diagnostics pathway and prospective treatment for the advanced NSCLC patient, therefore all patients are assumed to enter into the Markov model with unique treatments labelled to them. In the first version it is assumed that all patients that reach the Markov model can experience three mutually exclusive health states.

They might stay in stable disease without any progression after diagnosis (denoted progression-free survival (PFS)), they might progress (denoted Overall survival (OS)), or they might die (denoted Death). The first version is kept as simple as possible due to the initial limited survival that is related to advanced NSCLC.

Patients who are in PFS might stay in PFS throughout the model simulation, transition to OS due to progressed illness, or die due to the illness. Once reached OS, a patient might stay there for the reminder of the model simulation or transition to death due to failed treatment or progressed illness. Once a patient has reached the Death state it will remain here throughout the remainder of the model simulation. The total number of patients transitioning from the decision tree can be counted as the total number of patients in the state of PFS. The length of the model is a life-time horizon, even because it is assumed that after the end of 5 years the majority of the patients will have been deceased, it is important to capture the true relative survival for the advanced NSCLC patients. The length of each cycle is estimated to three weeks, as this the general length of one chemotherapy treatment cycle, thus the full length of the analysis in which a patient can survive is estimated to be 87 cycles if the patient survival for 5 years, in the event of a patient still being alive past this threshold, more cycles may be experienced.

Throughout the model simulation it is known that patients can experience significant different PFS, OS and point of Death, this especially between patients which has the presence or absence of a genome mutation. Therefore, it is known that a personalised has an advantage for advanced NSCLC patients due to the advantage that a personalised diagnostics and treatment approach has over a non-personalised approach diagnostics and treatment approach. Therefore, whether an advanced NSCLC patient has the presence of a genome mutation or there an absence of a genome mutation can help predict and indicate the expected survival each patient might experience. Hence, patients whom is allocated to targeted treatment can anticipate an expected increased survival compared to patients who end up in pathway arm NTT (non-targeted treatment) [9, 10, 14, 15, 55, 67, 76, 79, 106].

Depending on the initial starting point, the patients transition probabilities will differ in accordance with the genome mutation they tested positive for or whether they exhibited any mutation at all. Therefore, they might see differentiated costs and HRQoL, in the different health states the patients can be placed in.

After the last revision based on experts' feedback and a literature review, it was found that the first version of the Markov model developed was perceived as too simplistic to tackle the decision problem in question. Since Markov models are cycle independent, i.e. memoryless, it does not account for the patients' disease history, hence additional health states are added to the second version of the Markov model in an attempt to capture the clinical pathway of the patients as accurate as possible and at the same time keep it as simple as possible. This is illustrated in the second Markov models developed, and presented in figure 10.

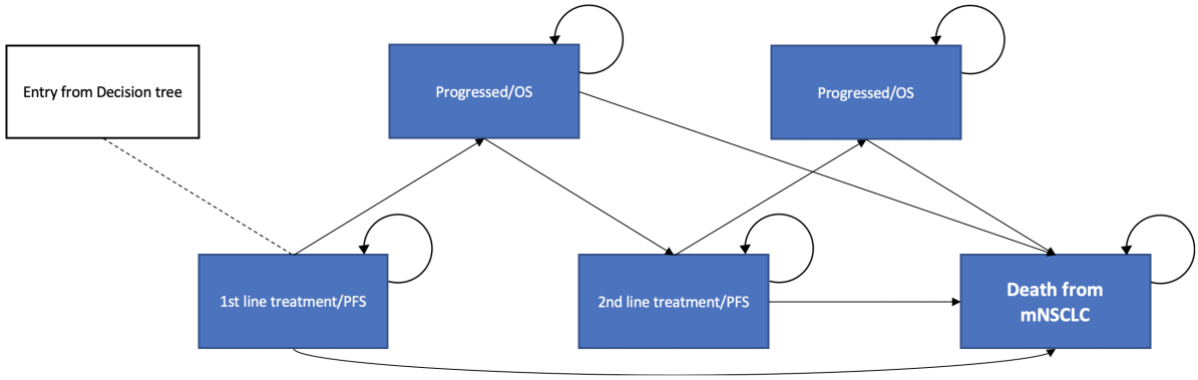

Figure 10: The second version of the Markov model (i.e. final structure) capturing patient survival, including the revised health states developed. These health states are based on the pathway from the second version of the decision tree, where the following transition probabilities and estimated effect measures follow individual patients throughout the course of the model simulation.

The entry from the decision tree leads the patients directly to 1st line treatment, where the patient is assumed to go through at least one cycle (3 weeks) of treatment, after that they can either stay in 1st line treatment, they might progress where OS is measured, or they might die from the illness. After progressed illness, the patient can be re-assessed, following a transition into 2nd line treatment, or the patient might die. In the 2nd line treatment, after going through one cycle, the patient might progress again, where OS is again measured, or the patient might die. Lastly, following the second progressed state, the patient might stay there, or the patient might die. Throughout the model, it is assumed that every state is a recurring state, where a patient can stay until the end of the model simulation, depending on their transition probabilities and their reaction to the treatment. When the health state death is reached, the patient will remain in this health state until the end of the model simulation, regardless of previous health states. In this model, 3rd line treatment is not included, this based on the rational, experience and review that a very small percentage of patients reaching this initial treatment-line due to an untimely death, and is excluded due to the limited available data on this line of treatment.

4.1.3 Uncertainty analysis

The quality of the available data affects a model's credibility significantly, so adding data that has questionable character or have high uncertainty surrounding it should not be implemented into an economic model [95]. The conceptual framework of the HTA decision model should be determined by the decision problem and research question, it should not be dictated by the available data and no compromise regarding the development of the framework should be made.

The results of decision models are generally summed in an ICER, cost-effectiveness per incremental QALY gained. Information about these cost-effectiveness ratios are critical for the decision process. However, assessment of effect and cost leading to the cost-effectiveness result is uncertain, hence any decision based on cost-effectiveness is uncertain [100, 101, 107].

Considering these uncertainties however, for this conceptual framework, like most economic evaluations, the selected output measure will be summarized with the ICER, and therefore, due to the uncertainty surrounding the conceptual model and the limited data it is essential to assess, capture and consider this in a form of uncertainty analysis [107]. This framework will suggest the utilisation of a probabilistic sensitivity analysis (PSA) [107], followed by a value-of-information (VOI) analysis to assess whether a decision can be made on the basis of current evidence or if additional research is required [108, 109]. Through these analyses, the conceptual framework will attempt to further clarify the necessity of collecting information, due to the yet early phases of the development and implementation of these health interventions as well as the natural heterogeneity that is captured in the essence of personalised medicine as a field and the patient population that is the target for this study.

The genome mutations mentioned in figure 2, and utilised in the decision tree, are the ones most frequently observed in advanced NSCLC patients. The number of genome mutations might lead to additional variability in the outcomes exhibited by the population, and might restrict and lead to unclear findings. Therefore, it is important to stratify the patients accordingly to the genome mutations they exhibit after the diagnostics practice in the Markov state transition model. It is also importance to ensure that each individual patient is allocated to the correct treatment that they qualify for in the decision tree, and that this is reflected in the Markov model.

4.2 Parameters

Prior to conducting the economic evaluation on FoundationOne CDx by implementing the conceptual models it is essential to collect data to estimate the effectiveness and costs associated with each part of the conceptual model. There are usually four categories of parameters involved in the model; state costs, state utilities in every health state in the conceptual model, transition probabilities and discount rates.

4.2.1 State cost

The data available on costs components and in general of diagnosing and treating NSCLC patients in Norway is limited. The cost per diagnosis is based on diagnostic related-groups following the regulations presented by the Norwegian authorities [1, 110, 111]. It is based on a set unit price (44,654NOK)[111], and each diagnosis is a weighted sum multiplied with the unit price per intervention. Even though the exact cost estimate is provided here, it remains challenging to estimate the true cost of diagnosis and treatment of advanced NSCLC, per patient since every hospital runs its own practice. In the context of cancer diagnosis, it is surrounded by high uncertainty with regards to the health care expenditure associated with personalised medicine. Even though the cost of laboratory tests in 2015 related to lung cancer is estimated to 41.17 million NOK[62], this is with high uncertainty. Recommendations have, however been given based on two times co-pay and two times reimbursement rate to estimate the cost for analyses for the healthcare providers, this is assumed to be similar for single genome testing and the in-house NGS. For NGS (FMI), the cost of a full genomic profile including report and following recommendations, a total of 37,000NOK excluding VAT is presented.

The cost per targeted pharmaceutical will be presented in Figure 11 below, these costs are collected from The Norwegian Medical Agencies (NOMA) database [112], and all costs are expressed in NOK. However, these costs are surrounded by some uncertainty where the rates are not adjusted for dosage per patient or per cycle is not presented.

Pharmaceutical	Dosage	Cost	Company
Erlotinib	30 tablets - 100mg	14758.11	Roche Registration GmbH
Osimertinib	30 tablets - 80mg	55212.00	AstraZeneca AB
Crizotinib	60 capsels - 250mg	45175.01	Pfizer Europe MA
Ceritinib	3x50 capsels - 150mg	47179.50	Novartis Europe Limited
Pembrolizumab	1x4ml - Concentrate 25mg / ml	29606.21	Merck
Cetuximab	1x100 ml - Fluid 5mg / ml	9020.19	Merck
Dabrafenib	28 capsels - 75mg	12988.14	Novartis Europe Limited

Figure 11: Cost per pharmaceutical, targeted treatment

4.2.2 Discounting rate

Discounting cost and effects of healthcare intervention can occur at a timely difference. For example, when using NGS by FoundationOne CDx, the additional costs are incurred short-term at the time of diagnosis, but the health effects might be incurred at a later time due to the nature of how cancer treatment takes effect and how costs are allocated. Based on general discounting theory, individuals generally prefer to receive benefits sooner and incur cost at a later point in time, this might create a discrepancy for the valuation of the health effect [113]. Most national guidelines however, take advantage of equal discount rates by a dominant margin [114], this without any justification of such, when alternative methods are available. However, since this study is performed in the Norwegian perspective, the guidelines laid forth by the Norwegian Directorate of Finance are recommended followed, the factors for health effects and costs are to be discounted at a 4 % annual rate [110].

4.2.3 Overall survival, HRQoL and transition probabilities

Currently there is no Norwegian HRQoL data available for lung cancer patients, and according to experts at the Cancer Registry of Norway, such data will commence collection within the coming few years. Therefore, when providing recommendations of where to obtain HRQoL values, there exists utilisable sources from completed studies outside of Norway. They can be obtained from survival analysis studies on advanced NSCLC where targeted treatment has been provided versus non-targeted treatment. HRQoL is a relevant and important measure included when patients are to measure and assess their perception of the treatment provided in

personalised medicine [50, 115-117]. However, when looking at clinical effectiveness of provided treatment, OS might be equally or more important due to the limited survival associated with advanced NSCLC.

When performing an economic evaluation, every researcher wants to utilise as accurate information and sources available as possible, and in the scenario in which there is an abundance of relevant information available, choices has to be made with respect to what to include the following references state research and results on OS and HRQoL for advanced NSCLC patients and their respective treatments.

However, the inclusion of a magnitude of different sources might be challenging to summarize appropriately and justify properly. It might be perceived as too cumbersome, unnecessary and might lead to more uncertain results due to the different origin of study, even though the purpose is to reflect the real-world evidence as accurately as possible. Based on this available evidence, the following studies are recommended for to be utilised in this conceptual framework [14, 80, 87]. All of the mentioned studies include necessary information regarding the genome mutations used in this study, including OS and PFS for when a targeted treatment is to be provided and when non-targeted treatment is provided for patients suffering from advanced NSCLC.

From the recommended studies presented, it is possible to obtain transition probabilities for the occurrence of an event to another, these probabilities can be extracted when performing the curve-fitting practice presented by Hoyle and Henley [98]. Even though this study will not go into the different adverse events, one can also find information to better populate the parameters from the aforementioned publications.

5.0 Discussion

The objective of this master thesis was to perform an early HTA in the form of a conceptual framework. It captures the histological/cytological diagnostic practice for genome testing in patients whom have been through visual diagnostics testing. And have proven advanced NSCLC to uncover possible targeted treatment in the respective patients. The framework consists of two distinct parts. First, the decision analytic models, a decision tree and a Markov state transition model, secondly it includes key parameter information for state cost, discount rates, overall survival and HRQoL. The framework uses the following technology to perform the histological/cytological diagnostic practice of the solid tumour of the lung: NGS technology by Roche diagnostics, a comparator in-house NGS panel (ThermoFisher) and single genome testing in the form of Idylla. Together, the analytical models and the provided information is meant to aid researchers and decision makers in the implementation of NGS by Roche Diagnostics.

The conceptual framework was developed after consulting with experts in the field, through literature review and from adaptation of governmental guidelines. It encompasses comprehensive key components and factors of the histological/cytological diagnostic practice for advanced NSCLC patients also including specific genome mutations and respective targeted treatment associated with each mutation the advanced NSCLS patients might exhibit. Utilising the conceptual models and parameter recommendations the framework may be deployed to analyse the impact NGS by Roche diagnostics might have on the histological/cytological diagnostic practice in a Norwegian setting.

The experts consulted in the development of this study include a health economist and a biophysicist and experts on personalised medicine from Roche Diagnostics Norway. Seeing that these experts work for the company that own the intervention, NGS by Roche Diagnostics, it might be thought that they act with the interest of the company in mind when consulting and providing feedback for the conceptual framework and provide information that is favourable for the intervention. However, seeing that a conclusion on whether or not the intervention is to be implemented is not a part of this study, but merely a conceptualisation of the histological/cytological diagnostic practice for an Early HTA to guide future economic evaluation, this concern can be set aside.

As mentioned, the relevant literature in the field of personalised medicine for NGS technology versus single genome testing Idylla in histological/cytological diagnostic practice for advanced NSCLC is scarce. In that context, there is limited available information on the cost and effect of the implications that the personalised approach NGS and the subsequent targeted treatment might have on advanced NSCLC, and the impact on the field of oncology [42, 118]. Nevertheless, to the best knowledge of the author, all the relevant available information was included. The relevant available information uncovered through the literature review was presented in section 1.6 of the background chapter. Therefore, with the limited available information, and since model conceptualisation is a continuous, a formal literature review was not conducted as new information was uncovered throughout the development process. This should however not impose any limitations or restrictions on the results of the study, seeing that to the best knowledge of the author, all relevant literature and information is disclosed.

The governmental guidelines [1, 18, 35, 36, 42] encompass central recommendations and suggestions of diagnosis, follow-up and treatment. In this study, some select guidelines have been adapted to elicit the possible pathways for genome mutations and their subsequent targeted treatments, alongside the expert's opinion and the uncovered literature. With the help of the uncovered information, the treatments and subgroups have been thoroughly specified and each targeted treatment (i.e. genome mutation) has been conditioned on the specific subgroup associated with it (figure 2). In the event of no genome mutation being present, the subgroup will have non-targeted chemotherapy.

Along with the limited available data and information, there has not been performed any cost-effectiveness studies on the histological/cytological diagnostics practice for advanced NSCLC and its subgroups (i.e. genome mutations) with subsequent targeted treatments and non-targeted treatments. There has however, been performed a few budget impact analyses on similar research [55, 67, 69]. These were, alongside the abovementioned information elicitation utilised to inspire the development of the conceptual framework presented in this master's thesis.

In an economic evaluation it is common to compare two drugs or two technologies on one indication. They are frequently based of off data from RCTs, and in the event of RCTs not being present one adapts data from a combination of studies. For this study there is as mentioned a scarcity of available information, and there has not been performed any RCTs, this might be due to the many biomarkers (i.e. genome mutations) and the quantity of subgroups which makes

it challenging to control for the different stages. Therefore, it is challenging to adapt and translate this methodology meant for single indication and comparison on the field personalised medicine. One reason why there is limited available data from RCTs is the challenges related to building up RCTs in the first place to reflect the true nature of personalised medicine for advanced NSCLC.

Where RCTs generally draw conclusions of population level, personalised medicine is specifically interested in the reactions that occur at the individual patient level. Complexity arises because RCTs cannot be design for the specific subgroups (.i.e. genome mutations) included. Due to the intricacy of the subgroups per genome mutations that occur a patient's reaction and the efficacy, where it is either more or less effective, of the treatment might change throughout the RCT, due to the dynamic nature of personalised medicine. An explanation for why RCTs for personalised medicine, and on advanced NSCLC, have not been performed yet might be that new innovations surface at a higher frequency than agencies are able to assess their validity and clinical impact, as well as the cost and effect that follows.

When future researchers deploy the conceptual framework, the parameter information presented might be susceptible to some bias. The cost per diagnosis is based on diagnostic related-groups following a particular format presented by the Norwegian authorities [1, 110, 111], where the set unit price as mentioned earlier equals 44,654NOK. The costs presented for NGS by Roche Diagnostics has an exact cost per test performed, equalling 37,000NOK excluding VAT. Some ambiguity does surround the cost per diagnosis, seeing that not every hospital uses the same practice, where some utilise either an NGS panel or Idylla single genome test. Furthermore, the costs per targeted pharmaceutical that are disclosed involve some uncertainty since this is the available cost estimate based on the Norwegian Medical Agencies own database[112], which is presented in figure 11. That mentioned, these cost estimates might not be the true costs that the treating physician prescribe per patient.

During the diagnostic procedure, to speed up the diagnosis and letting the patient receive treatment as soon as possible, it might not be deemed worthwhile for all advanced NSCLC patients to undergo additional testing. This is in the event of EGFR, ALK and PD-L1 having been confirmed negative for a respective patient when single genome testing is performed using Idylla[1]. Therefore, in scenarios where it might be relevant for the patient to undergo additional genomic tests, this practice is not followed and patients that might have been eligible for

targeted treatments as a result of ROS1, KRAS and BRAF mutations might get non-targeted chemotherapy with a lower efficacy and response rate. In the event that targeted treatment might be provided when positive genome mutations are detected, the patient will receive a more cost-effective treatment which might not only lead to increased survival for the respective patients, it might save the healthcare sector substantial expenditure. However, if NGS is utilised there is no need for additional tests since all genome mutations are tested simultaneously. Hence, when utilising NGS instead of Idylla, additional genome detections might be uncovered, which resultingly can lead to an increased number of targeted treatments, and subsequent increased overall survival for these patients. Even though the advanced NSCLC patient might receive more effective treatment, this can lead to added treatment costs due to the increased genome mutations for the NSCLC patients and the higher costs of these treatments.

When the future researchers deploy this conceptual framework to analyse the impact NGS might have on the histological/cytological diagnostic practice for advanced NSCLC patients, the results might lead to the implementation of NGS by Roche Diagnostics. It might lead to long-term decreased costs, not only for the treatment practice for advanced NSCLC patients due to the avoidance of treatments that has proven little to no effect, but also for the diagnostics practice in the event where multiple genomes are to be tested for when using Idylla. It might lead to a more effective diagnostics procedure for advanced NSCLC patients, since NGS by Roche diagnostic have a shorter turn-around time than Idylla when multiple genomes are to be tested. Additionally, the patient will not undergo unnecessary and prolonged diagnostic testing through NGS, thus in the event of a positive genome mutation, avoid treatment that has proven little to no effect. As a result, the patient is spared the burden of unnecessary treatment with little to no effect and can in favour can experience a higher HRQoL if NGS is utilised and a positive genome mutation is uncovered. That said, it is not clear what the results might be. It might also be that the comparator in-house NGS by ThermoFisher presented which some hospitals are said to invest in might turn out to be the cost-effective choice. After these investments are considered, and the in-house technology has been utilised over a long-term period, the comparator might be the cost-effective choice.

NGS by Roche diagnostics is predicted to be costlier per one test than single genome testing. However, if additional testing is performed utilising single genome testing (i.e. Idylla), the waiting time for the test results will increase. Thus, when the additional tests with single genome testing is utilised, the accumulated difference will decrease between Idylla and NGS

and might, according to experts, come in favour of NGS not only in diagnostic accuracy, but in overall cost per patient diagnosed. This is yet to be confirmed, although this might be what the results of an economic evaluation could conclude with.

Despite the fact that NGS by Roche diagnostics has the potential of being less costly when subsequent single genome tests are to be performed, this does not include the investment costs and the short-term costs that are to be incurred to fully implement the technology of the in-house NGS by ThermoFisher. These costs should be fully evaluated before a decision on which of the technologies are to be a part of the standard practice is made. Moreover, it does not investigate the cost of performing the different biopsies that are necessary to extract the tumour to run the histological/cytological diagnosis. When future researchers deploy this conceptual framework, it might be interesting to include the cost per healthcare personnel extracting the biopsy samples from the advanced NSCLC patients.

The cost per diagnosis and respective targeted pharmaceutical treatment is disclosed. These costs might lead to some uncertainty due to the collection of information from the NOMA database[112]. The costs are associated with the pharmacy purchase and selling price, and might not reflect the expenses the respective hospitals that treat each individual patient might undertake. These factors might make it challenging to estimate the true cost-effectiveness per subgroup with the given treatment rates, this can however be handled in the PSA.

Every economic evaluation in healthcare involves some uncertainty. Hence, when future researchers decide to arrange an economic evaluation utilising this conceptual framework it will be in their best interest to perform a probabilistic sensitivity analysis on the results to handle the uncertainty that arises from the inclusion of the information presented in this conceptual framework. In addition to the PSA it might be imperative to perform a value-of-information analysis due to the uncertainty the information presented lead. So, an analysis to estimate the impact the collection of additional information might be worth the extra effort to reassure that the results of the analysis are trustworthy.

There is limited available data and knowledge about the impact NGS and personalised medicine might have on the health care sector. This further points out the necessity of performing an economic evaluation of the technology to assess the implications it might impose on the sector. If found cost-effective it can be adopted as soon as possible to aid the patients in receiving an

accurate diagnosis, not only among advanced NSCLC patients, but for the healthcare sector so that all relevant patients might benefit from the new technology.

After performing the economic evaluation on NGS by Roche Diagnostics, and the event of it being the favourable choice, the researchers might wish to negotiate with the decision authorities for the implementation. Strategies that might be exploited is a specified payment plan. This can be done either on per genome mutation detected related to the cancer form looking for it, in a pay-for-performance scheme. They might suggest a cap on the total number of patients that can take advantage of the technology. Or they can suggest to perform a multi-criterion decision-analysis to investigate other factors than those associated with cost and effect of the respective diagnostic procedures.

5.1 Limitations

In this section, limitations and simplifications will be listed. This includes model limitations and simplifications of real-world evidence, parameter information and for the subgroups presented.

Every model is a simplification and an abstraction of real-world evidence based on several assumptions and limitations. All models are by definition imperfect and accordingly need corrections and improvements. Hence, the conceptual models developed in this master's thesis can be improved to some degree. Future researchers can explore which additional steps and improvements can be made to increase the credibility of this model by assessing the structural and methodical uncertainty. Further limitations done are based on the restrictions that naturally follow the subgroups included (i.e. individual genome mutations).

For the single genome testing in the decision tree it is assumed that one test is to be performed at any given time. This is not necessarily the true practice. In the real-world practice, multiple genome tests might be performed at any given time. In this study it is assumed that one test is performed at a time, this might restrict the diagnostic results and turnaround time for certain patients and might differentiate the real-world practice from this model. Another limitation for the decision tree is that the only difference between the two NGS panels in this conceptual framework is the cost associated with the different tests and the inclusion of TMB, additional points that could have been included is the amount of genome mutations detectable with NGS by Roche Diagnostics over the in-house NGS by ThermoFisher, the full-scale report per

patients genome composition, or the sensitivity and the possible saved costs of not investing in the technology for the in-house apparatus. Therefore, the difference mentioned in this study might not be enough to fully differentiate the technologies and further investigation between the two might be necessary.

In the Markov state transition model, it is assumed that no patients will survive past second-line treatment. In the real-world practice a finite number of patients go beyond this line, a true estimate is not found in the literature, neither could the experts consulted predict the number of patients who had or could have survived beyond second-line.

The recommended parameter information mentioned in the results chapter (e.g. state cost, discount rate, HRQoL, OS and transition probabilities) is based on relevant studies, expert's opinion and governmental guidelines. The reason for this might be how personalised medicine is built up where it cannot depend on generalised methodologies and treatment patterns, and every patient needs an individual adaptation of the treatment regime. Therefore, what is normally based of off a normative treatment method does not necessarily fit completely into the personalised method presented in this study. Furthermore, since personalised medicine fundamentally is a heterogenetic diagnostic and treatment practice adapted to the specific patient, thus making it challenging to capture in an economic model and this might not be captured well enough by the different pathways in the decision tree and health states in the Markov state transition model. Therefore, additional research into personalised oncology medicine for advanced NSCLC is welcomed by the author, where future researchers can investigate if the uncertainty and heterogeneity can be tackled differently.

It is important to note that this is a conceptual model, which attempts to investigate and abstract the histological/cytological diagnostic practice for advanced NSCLC. Therefore, until one has attempted to actually run a simulation using the conceptual framework presented in this thesis, with the clinical available data presented in the result section, it is impossible to know how the results of the conceptual models might look like. It might be challenging to run the pathways that are presented with the interlinked treatments per subgroup (i.e. genome mutation), and other methodological approaches might fit better to the problem in question.

6.0 Conclusion

Personalised medicine is becoming more relevant than ever. This is due to its potential and accuracy of diagnosis and predicted increased survival a patient might experience with a more tailored approach [14].

Innovations in the field are surfacing at a rapid pace. It is therefore important to analyse and evaluate the impact these technologies might have on current practice. For example, according to experts on personalised healthcare, and the information found in literature mentioned in this study, it is believed that NGS is better at uncovering and predicting possible genome mutations that can qualify for targeted treatment for advanced NSCLC patients.

At this time a cost-effectiveness analysis for NGS panels vs Idylla single genome testing with a comparator NGS utilised for the histological/cytological diagnostic practice following visual diagnostics testing for advanced NSCLC patients in a Norwegian setting has not yet been performed. Therefore, this might be the first conceptual framework developed for the personalised technology NGS histological/cytological diagnostic practice for advanced NSCLC patients who have been through visual diagnostics.

NGS is still in the early phases of assessment and implementation into Norwegian diagnostics practice. Therefore, the author of this study calls for additional research into the field of personalised diagnostic practice so that a full economic evaluation might be carried out and so that NGS can reach the diagnostic practice in the Norwegian healthcare system. This conceptual framework was developed to help and guide these future cost-effectiveness analyses. It can be a contribution and possibly guide future cost-analyses, thus playing an important role in the field of personalised medicine, particularly for advanced NSCLC patients.

Not only does the results of this early HTA in form of a conceptual framework allows future researchers to analyse the impact NGS by Roche diagnostics versus NGS by ThermoFisher might have on the histological/cytological diagnostic practice for advanced NSCLC patients that have been through visual diagnostics with a cost-effectiveness analysis. The conceptual framework may also be implemented elsewhere. The framework might aid and inspire other studies related to other cancer forms in the field of personalised medicine than advanced NSCLC. Some adaptation is although necessary. First, the problem statement and objective

needs to be defined, secondly, the development of the objective needs to be adapted to the decision analytic models. Lastly, the models need to be adapted to the problem statement, since the decision analytic models might not fit perfectly into a new disease area

This master's thesis can be viewed as an early contribution towards achieving the implementation of a diagnostic tool that might be better for patients with advanced NSCLC, that might be more treatment efficient for patients and more cost-effective for the society.

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Appendix 1 - Second version decision tree