A comparative cost analysis of the pathway to diagnosing lymphoma in a tertiary hospital, Western Cape, South Africa

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PART 0: A comparative cost analysis of the pathway to diagnosing lymphoma in a tertiary hospital, Western Cape, South Africa

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Declaration

I, *Dr Waarisa Fareed-Brey*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Dedication

To Muhammad, thank you for the ongoing support, I would not have been able to achieve this without you and my three beautiful children.
To my parents and family, thank you for the motivation and ongoing inspiration.
To Dr Lucy Cunnama, thank you for your patience and dedication. Your motivation and mentoring will always be remembered.
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Abstract

Cancer is one of the leading causes of death before the age of 70 in 91 countries (out of 172) with a noted increasing incidence of cancer and mortality (Bray et al., 2018). In tuberculosis (TB) endemic areas, a fine needle aspirate (FNA) is often used as the diagnostic tool of choice when trying to understand the underlying cause of lymphadenopathy (LAP), which can lead to delayed diagnosis of lymphoma (Antel et al., 2019). A significant gap exists in the lack of costing of the diagnostic pathway to diagnosing lymphoma.

The study aimed to cost the diagnostic pathways, namely FNA, core-needle biopsy (CNB), and surgical excision biopsy (SEB) using secondary data collected in 2018 (February until October) at Groote Schuur Hospital (GSH), within the tertiary level hospital outpatient clinics to informed the patient pathways. The overall purpose of the study was to inform policy-making decisions and process guidelines.

A cost analysis study was conducted using a combination of ingredients-based costing and top-down costing from a provider's perspective. Annual costs were calculated and inflated to 2021 South African Rands using the consumer price index (CPI) and converted to United States American Dollars.

More CNBs are currently being performed than SEBs at GSH, and when pathways were followed, CNB initiated pathways (US $567) were less costly compared to FNA initiated pathways (US$ 877). The cost of the CNB procedure varied with the use of a single-use biopsy gun and the multi-use Magnum BARD gun.

CNB provides an alternate choice to SEB and based on the study conducted, CNB pathways are less costly. The main cost driver for all three procedures was personnel and this could be decreased by task shifting and training of medical officers and interns.

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Abbreviations

ACL Acute lymphoblastic lymphoma
AIDS Acquired Immunodeficiency Syndrome
AML Acute myeloid leukaemia's
ART Antiretroviral therapy
CEA Cost-effective analysis
CLL Chronic lymphocytic leukaemia
CPI Consumer price index
EBV Epstein- Barr virus (EBV)
FBC Full blood counts.
FNA Fine Needle Aspirate
FNAC Fine needle aspiration cytology
GLOBOCAN Global Cancer Incidence
GSH Groote Schuur Hospital
H. Pylori Helicobacter pylori
H Haemoglobin
Hep C Hepatitis C
HIV Human Immunodeficiency Virus
HL Hodgkin's lymphoma
HREC Human Research Ethics Committee
LAP Lymphadenopathy
LDHL Lymphocyte depleted Hodgkins lymphoma
LMIC Low- and middle-income countries
LN Lymph nodes
LRHL Lymphocyte-rich Hodgkins lymphoma
MDS Myelodysplastic syndrome
n Sample population
NHL Non-Hodgkin's lymphoma
NHL Non-Hodgkin's lymphoma
NLPHL Nodular lymphocyte predominant Hodgkins Lymphoma
OPLAS Day Surgery Local Anaesthetic Service
PDE Patient Day equivalent
PLWHA People living with HIV/AIDS
SEB Surgical excisional biopsy
SSA Sub-Saharan Africa
TB Tuberculosis
ULTRA MTB/RIF Ultra
US Ultrasound
USCNB Ultrasound-guided core needle biopsy
USD United States Dollars (USD)
WCC White cell count
WHO World Health Organization

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1. Brief Literature Review

1.1 Background:

Lymphadenopathy (LAP) often causes great emotional discomfort for both patients and doctors as it has a range of differential diagnoses and can lead to either the diagnosis being missed or delayed diagnosis of malignancy (Bosch et al., 2014). In developing countries like India, Tuberculosis (TB) is considered the first differential diagnosis despite studies showing that 50% of cases of LAP are due to non-TB aetiology and malignancies account for approximately 1% of the LAP (Thakkar et al., 2016). The term LAP is used to describe lymph nodes (LN) that have become abnormal due to size, consistency, and quantity (Mohseni et al., 2014). Whilst LN less than 1cm is considered to be normal, exceptions exist and LN in the inguinal region could be considered to be normal up to 1.5cm, whilst in epitrochlear nodes, up to 0.5cm could be normal, hence LN normal size range could vary due to different anatomical regions in the human body and age as postulated by some authors (Mohseni et al., 2014). LAP is generally classified into 5 categories: malignancy, infections, autoimmune, drugs, and miscellaneous (Thakkar et al., 2016). Attentive patient history is important as in the case of varying geographical areas, the causes of LAP could vary. For instance, the most common aetiology of cervical LAP is TB in patients living in TB endemic areas like Africa (Mohseni et al., 2014). Exposure to alcohol, ultraviolet radiation, and tobacco increases the risk of suspicion of LN being head, neck, organ, and skin metastatic carcinoma, whilst in immunodeficient patients e.g. patients with human immunodeficiency virus (HIV) one would have to consider Hodgkin's Lymphoma (HL) and Kaposi's Sarcoma as differential diagnoses (Mohseni et al., 2014).

According to GOCAN 2018, cancer was one of the leading causes of death before the age of 70 in 91 out of 172 countries with an increased incidence of cancer and mortality noted (Bray et al., 2018). Lymphoma is amongst the leading top 10 cancers in the world and one of the top 10 cancers that can be cured over time (Verburgh and Antel, 2019). The leading cause of cancer mortality in patients living with HIV is lymphoma (Verburgh and Antel, 2019). Broadly categorising lymphoma, there are 3 clinical groups of lymphoma: low grade or indolent lymphoma (e.g. chronic lymphocytic leukaemia(CLL), follicular and splenic lymphoma), high grade or aggressive

lymphoma (e.g. diffuse large B cell lymphoma, HL and peripheral T cell lymphoma) and the very high grade or aggressive lymphoma (e.g. acute lymphoblastic lymphoma, Burkitt's lymphoma and plasmablastic lymphoma) (Verburgh and Antel, 2019). Despite the use of antiretroviral therapy (ART), there appears to be a marked increased risk in people living with HIV/AIDS (PLWHA) with an incidence ratio of 11.5 for non-Hodgkin's lymphoma (NHL) and an incidence ratio of 7.7 in HL (Antel et al., 2019). In sub-Saharan Africa (SSA), despite the rapid molecular TB diagnostic techniques, diagnosing extra-pulmonary TB remains a challenge, and overlapping symptoms, with lymphoma in TB endemic areas leading to PLWHA being placed on empiric TB therapy, thus delaying the diagnosis of lymphoma (Antel et al., 2019) The WHO currently recognises more than 60 types of lymphoid malignancies which are based on histological findings, thus making tissue sampling the key to diagnosis and subclassification of lymphomas (Cuenca-Jimenez et al., 2021).

1.2 Diagnostic Methods:

Fine Needle Aspiration (FNA) biopsy, surgical excisional biopsy (SEB), and core needle biopsy (CNB) are methods that can be used to obtain tissue sampling (Seviar et al., 2021) however, the WHO and many institutions and research groups recommend SEB followed by histopathological analysis as the diagnostic tool of choice for lymphoma and recognises ultrasound-guided core needle biopsy (USCNB) as an alternate diagnostic tool when the LN's are inaccessible or when the risk is high (Cuenca-Jimenez et al., 2021, Seviar et al., 2021, Johl et al., 2016)

Traditionally patients presenting with easily accessible and palpable LN's undergo FNA for cytology (FNAC), and if the diagnosis is inconclusive, the patient is referred for SEB (Allin et al., 2017). However, FNAC has poor sensitivity for the diagnosis of lymphoma and only approximately 30% of cases of acid-fast bacilli are visualised (Antel et al., 2019). Furthermore, Antel et al. (2019) have argued that FNAC could show poorly developed granulomas which are broadly misinterpreted as TB specific and, patients with overlying symptoms and ineffective FNAC in TB endemic areas could have been incorrectly diagnosed and placed on empiric TB treatment leading to delays in the diagnosis of lymphoma (Antel et al., 2019). In the last few years, TB diagnostic tools have advanced nucleic acid amplification which includes using WHO-recommended Xpert MTB/RIF, which has now been superseded by Xpert MTB/RIF

Ultra (Ultra). (Antel, 2021) Ultra was recently recommended for use on FNA biopsies, thus excluding TB and expediting referral onto CNB (Antel et al., 2019).

In a study conducted at Germany University Medical Centre in Mannheim, 101 LNs were sampled between January 2008 and June 2011, researchers showed that 49% of FNA specimens by conventional cytological analysis elicited the correct diagnosis and when accompanied by immunocytology, the ratio of a correct diagnosis increased to 72% and was statistically significant. (Metzgeroth et al.). Thus, the authors argue that FNA supported by immunocytology could be justified as the first choice for the diagnosis of LAD (12). Whilst FNA with immunocytology correctly diagnosed 20 of the 21 B lymphomas, only 1 of 4 HL was diagnosed correctly with the authors supporting the use of CNB in the uncertain diagnosis of LAP (Metzgeroth et al.).

The Amrita School of Medicine in Kochi, India, conducted a study on 86 patients who presented with cervical LAD at a tertiary level referral centre between May 2016 and September 2018 to evaluate the use of FNA and SEB (Pillai et al., 2021). Importantly all patients underwent SEB, and this tissue was examined as “histopathological results” are considered the gold standard in testing. (Pillai et al., 2021). FNA detected only 11 cases of lymphoma (58%) while after histopathology, 19 cases were confirmed in the cohort. Based on the results, 51% were diagnosed with a malignancy in the LN. (Pillai et al., 2021). Overall , the authors recommended that patients older than 45 years of age have SEB as a diagnostic tool of choice and that patients younger than 45 years of age have FNA as the initial diagnostic tool in part due to the high rates of benign LN disease. (Pillai et al., 2021). The authors recommend the use of FNA in low resource settings as it is less costly and easier to administer at the primary level of care with fewer complications than CNB which has increased the risk of damage to adjacent structures in the cervical region, especially in younger patients(Pillai et al., 2021, Oh et al., 2016).

A systematic review conducted by Frederiksen et al. (2015) analysed 42 publications between 1989 and 2012 and supported FNA over CNB as the supplementary investigation for subclassification of lymphoma (Seviar et al., 2021), however, Seviar et al. (2020) believed since 2015 pathologist had gained more experience using CNB and conducted a more recent literature review which included research and articles from 2015 to 2020 to assess the recent advances on CNB supported by radiological

and histopathological techniques in tissue sampling and comparing CNB to SEB (Seviar et al., 2021). CNB proved to be 79-97% diagnostically effective with an outcome of full lymphoma classification and in cases where CNB failed to make a diagnosis, it was often due to inadequate biopsy or tissue fragmentation (Seviar et al., 2021). When SEB was compared to CNB, the SEB median diagnostic yield was higher at 97.5% compared to CNB at 91.7% i.e. SEB more accurately diagnosed lymphoma (Seviar et al., 2021). CNB was more commonly used in clinical practice with lower surgical risk and, SEB was not tolerated well in patients who had poorly accessible LNs associated with more complications like bleeding, scarring, and nerve damage(Seviar et al., 2021). Additionally, more resources are required for SEB like theatre time, staff, and anaesthetic making SEB more costly (Seviar et al., 2021). Whilst CNB has significant advantages, there are limitations to its use, especially in cases with poor percutaneous visualisation (Seviar et al., 2021). Some of the drawbacks noted with CNB include the need for fully trained operators for ultrasound (US) imaging, training, and experience in CNB and potential complications which include haemorrhage, pneumothorax, nerve injury, and seeding of tumours (Seviar et al., 2021).

Over the last few years, there has been economic evaluation published on lymphoma. In 2018, Bosch et al. published a research article on a retrospective study conducted on 1779 patients and their sample included patients diagnosed with HL, large B cell, and peripheral T cell lymphomas (Bosch et al., 2018). The study compared the time interval of outpatients to inpatients and the associated cost (Bosch et al., 2018). They found the interval time to diagnosis was shorter with inpatients (12.3 days) when compared to outpatients (16.2 days, however, there was a higher mean cost associated with inpatients (Bosch et al., 2018). With the use of the micro-costing method, the mean cost was estimated at €4040 (for the year 2016) for inpatients and €1409 for outpatients and they were statically significant (Bosch et al., 2018). Whilst this may benefit patients with lymphoma, the decision-makers would have to reflect on the significant cost implications given the resource limitations, especially in LMIC. Other economic evaluations included the cost of life expectancy in patients with lymphoma (Wang et al., 2018), various cost-effective treatment options for lymphoma using Rituximab (Bonafede et al., 2018, Papaioannou et al., 2,012), and the cost of frontline treatment failure (Bonafede et al., 2018). There is a gap in the economic

evaluation and cost analysis of diagnostic tools or pathways used in clinical practice to diagnose lymphoma.

1.3 Justification:

Based on the brief literature review conducted, patients presenting with LAP often invoke concern for the patient and treating providers (Bosch et al., 2014). Whilst the standardised method recommended by WHO and many other institutions for investigating LAD is SEB (Seviar et al., 2021), over recent years there has been increasing use of USCNB to investigate LAD as it has shown to have a higher diagnostic yield than FNA yet slightly lower than SEB (with SEB diagnostic yield of 97.5%). (Seviar et al., 2021). Despite the slightly lower diagnostic yield USCNB with a diagnostic yield of (91.7%) requires fewer resources and is accurate for sub-classification of lymphomas (Seviar et al., 2021). In TB endemic areas, like SSA, FNA is often used as the diagnostic tool of choice, leading to delayed diagnosis of lymphoma (Antel et al., 2019). Antel et al. found that the longest delay in diagnosis was due to the health practitioner's high index of TB suspicion delaying LN biopsy (Antel et al., 2019). This delay has led to patients presenting late with advanced stages of lymphoma which is associated with high mortality (Antel et al., 2019). In a randomised clinical trial published in 2017, 376 patients were randomised into two arms, one arm consisting of USCNB and the other SEB. USCNB was found to be €171 (year of conversion was not included) per biopsy in Italy, compared to SEB which cost €10,393 for major surgery and €3056 for minor surgery. SEB was also associated with more complications and longer waiting times (Pugliese et al., 2017).

Whilst there is some literature on various options of diagnostic methods for LAD, diagnosis of lymphoma and economic evaluations on treatment options (Bonafede et al., 2018, Papaioannou et al., 2012), a significant gap exists in the cost comparison between diagnostic pathways to rapidly exclude TB in TB endemic areas and improve time to lymphoma diagnosis. Antel (2021) recently recommended an evolving clinically novel pathway for the rapid diagnosis of lymphomas in a TB endemic setting, however, costing of the algorithm has not yet been conducted (Antel, 2021). The pathway looks at excluding TB adenitis and rapidly moving on to LN biopsy, thus expediting the exclusion diagnosis of TB and decreasing the days to lymphoma diagnosis (Antel,

2021) thus, preventing the late presentation of lymphoma and reducing mortality (Antel et al., 2019).

This cost comparison study will be conducted to address the literature gap on costing diagnostic pathways to rapidly diagnosing lymphoma. Antel's (2021) recommended novel pathway will be divided into subsections based on clinical assessment of the LN. The cost will be estimated and compared to the standard pathway cost estimate. The pathways have been recommended in TB endemic areas and will be of value to many countries with similar contexts. The outcomes of this cost study could aid decision-makers with budget planning and policy decisions.

2. Aims and Objectives:

2.1 Aims

This study aims to provide a cost of the two pathways, namely the novel and standard pathway options, based on the algorithm proposed by Antel (2021), using data collected in 2016 to diagnose lymphoma at Groote Schuur Hospital (GSH) with the purpose to inform policy-making decisions and process guidelines.

Hypothesis: The novel pathway (using CNB or SEB) to diagnose lymphoma is more costly when compared to the standard pathway to diagnose lymphoma.

This dissertation hypothesises that both interventions, USCNB and SEB, provide an accurate diagnosis but, in a resource-limited setting like GSH tertiary hospital outpatient clinic, the least costly pathway should be determined and recommended as the best pathway to maximise resources and reduce the days to diagnosis and access to treatment.

2.2 Objectives:

1. To estimate the cost of standard pathway

2. To estimate the cost of the novel pathway using FNA plus Ultra and CNB

3. To estimate the cost of the novel pathway when using SEB

4. Cost comparison between the novel pathway and standard pathway

5. Policy recommendations based on the partial economic evaluation of the different pathways

2.3 Conceptual Framework

The standard pathway (Figure 1) will be costed based on the unit per cost of investigation and empiric treatment. The novel pathway will be split into sub-pathways based on clinical assessment of the LN (as described below in Figure 2 and Table 1). These sub-pathways should be costed per unit cost of the diagnostic tool as per Table 1, to compare the total costs.

Current Standard Pathway in the City of Cape Town

Patients presenting with enlarged LN in TB endemic areas with overlapping symptoms for lymphoma (fever, weight loss, and night sweats) are often investigated for TB, however, cytology has limited effectiveness in diagnosing lymphoma (Antel, 2021). These patients are often placed on empiric TB treatment without a conclusive TB test and are incorrectly assured (Antel, 2021). It is only when patients who fail to respond to empirical TB treatment are referred for follow-biopsy, that the realisation is met that this led to delayed diagnosis or incorrect reporting of death (Antel, 2021).

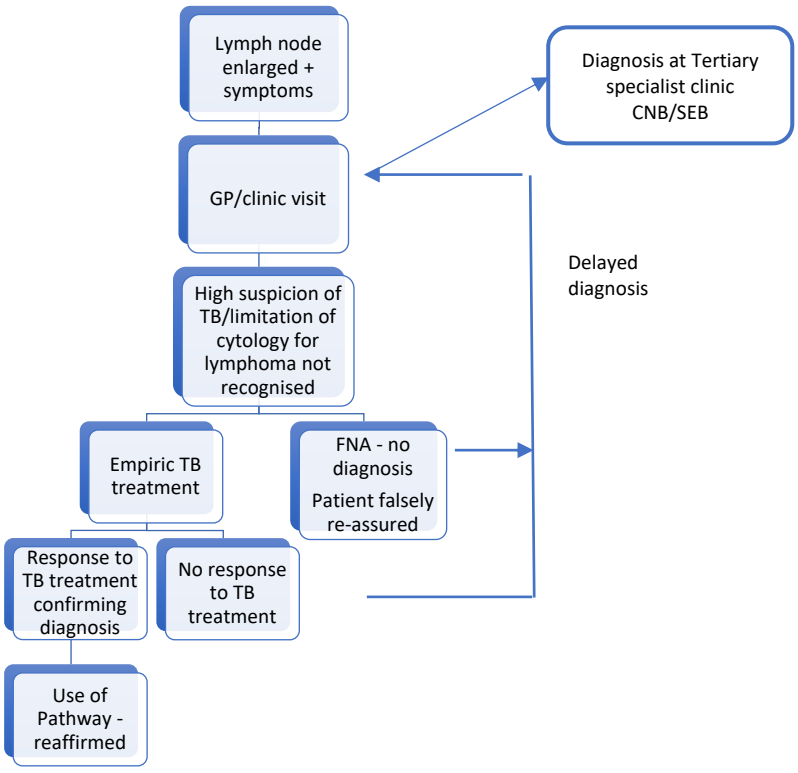

Figure 1: Standard pathway: Diagnostic processes used to diagnose lymphoma, adapted from Antel (2021)

Novel Pathway

In the novel pathway, the clinician recognises the cytology limitation early on and makes an accurate diagnosis using molecular methods to exclude or diagnose TB with tissue sampling as presented in the diagram below which leads to an expedited diagnosis of lymphoma (Antel, 2021).

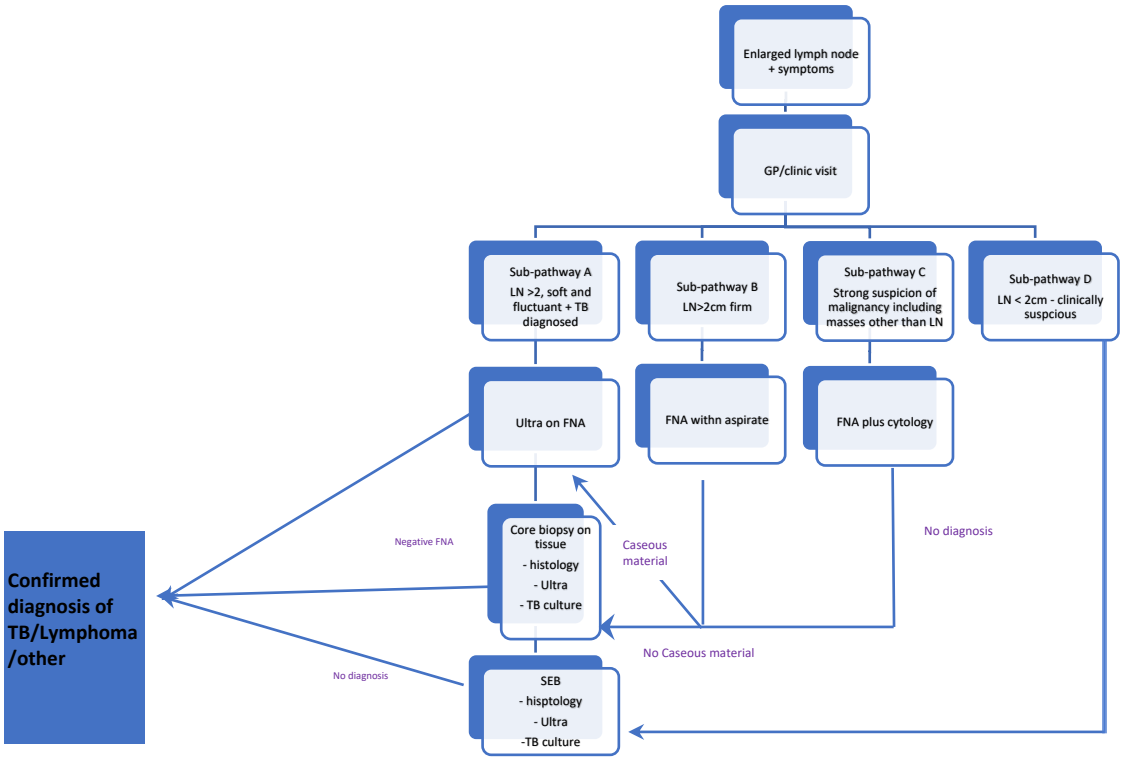

Figure 2: *Novel Pathway: Diagnostic processes used to diagnose lymphoma, adapted from Antel (2021)*

Table 1: Standard and novel pathways complete with four novel sub-pathways	
Standard Pathway	***Novel Pathway***
Estimated cost of consultation at GP Estimated cost at Clinic Cost of TB empiric treatment: to estimate the cost of the empiric treatment per month Total Cost of FNA with cytology The total cost of standard pathway	Estimated cost of consultation at GP Estimated cost at Clinic Sub-pathway A: LN > 2cm soft and fluctuant or with TB diagnosis: Total cost FNAC Unit cost of Ultra on LN Total cost CNB plus histology plus, Ultra plus, TB culture Total cost SEB plus histology plus, Ultra plus, TB culture Estimated total cost of sub-pathway A Sub-pathway B: LN>2cm Firm Unit cost of FNA without Ultra Total cost FNAC (repeat) Unit cost of Ultra on LN Total cost CNB plus histology plus, Ultra plus, TB culture Total cost SEB plus histology plus, Ultra plus, TB culture Estimated total cost of sub-pathway B Sub-pathway C: Malignancy suspected Total cost FNAC Total cost CNB plus histology plus, Ultra plus, TB culture Total Cost SEB plus histology plus, Ultra plus, TB culture Estimated total cost of sub-pathway C Sub-pathway D: LN < 2cm clinically suspicious Total Cost SEB plus histology plus, Ultra plus, TB culture Estimated total cost of sub-pathway D Estimated cost of sub-pathway with clinic/GP consultation
Compare the estimated total cost of the standard pathway with each novel sub-pathway	

The cost comparison of both pathways will provide information on the least costly diagnostic method to diagnose lymphoma. Policy recommendations will be based on the cost and expedited diagnostic methods to diagnose lymphoma.

3. Methodology

3.1 Study Design

Economic evaluations are designed to inform providers, patients, or society on the best evidence-based research and strategies to allocate resources efficiently and improve health outcomes (Hoomans and Severens, 2014). All methods of economic evaluation require the analysis of cost which enables decision-makers to make informed decisions around budget, however, its use is limited without the economic benefit (Hoomans and Severens, 2014). Resource-limited settings which require difficult decision decision-making involves competing alternatives by comparing the cost and consequences of the intervention. This enables policymakers and decision-makers to make informed decisions, thus rendering the implementation of cost-effective and efficient healthcare (Drummond et al., 2015).

A cost analysis study will be conducted using a combination of ingredient-based costing (bottom-up) and top-down costing from a health care provider perspective. A simple cost-effective analysis (CEA) will be conducted utilising specificity and sensitivity data from existing literature. Cost centre reports will be used to evaluate the financial costs. Cross-sectional data collected in 2016 for a full 12-month period (January 2016-December 2016) at the Outpatient Day Surgery Local Anaesthetic Service (OPSLAS) at GSH with Human Research Ethics Committee (HREC) approval will be used to analyse the different pathways utilised once this protocol is approved by HREC. Dr. T.T.C. Potwela collected this data in 2020 as part of his master's in medicine, however, there will not be an overlap in our analyses as the purpose and objectives are significantly different. The cost of resources will be represented in South African Rands and United States Dollars for 2016.

3.2. Study Population and Sampling

The pathway data that will be utilised was collected in the City of Cape Town, Western Cape, South Africa at the GSH, OPLAS clinic. GSH serves as a tertiary hospital receiving patients from three surrounding district hospitals (Victoria, New Somerset Hospital and Mitchell's Plain Hospital) and surrounding hospitals and clinics. The OPLAS clinic at GSH books patients referred with LAD, lipomas, and breast lumps for excision on a Google booking list at the Department of Surgery.

Patients were identified using a Google booking list at the Department of Surgery and all patients having excisional biopsies at the OPLAS in 2016 were retrospectively included in the sample. The booking list included patients attending for non-specific lumps including LAP, breast lumps and lipomas.

3.3 Inclusion and Exclusion Criteria

Inclusion Criteria

Patients diagnosed with LAP that was referred or diagnosed and subsequently attended OPLAS were booked for SEB during 2016.

Exclusion Criteria

- Patients that were booked for SEB and did not attend.
- Patients that presented for lipoma excision at OPLAS.
- Patients that presented with breast lumps at OPLAS for investigation and diagnosis.

3.4. Recruitment and Enrolment

Patients were identified using the Department of Surgery, Google booking form for attendance at the OPLAS clinic. Using secondary data, patients' records were retrospectively studied.

3.5 Research Procedure and Data Collection

This study will commence once HREC approval is received. The cost centre reports together with expenditure records for the fiscal year 2015/2016 for OPLAS will be requested from the GSH and relevant Heads of Department. National Health Laboratory (NHLS) pricelists will be utilised for 2016 to cost the unit price for the diagnostic tools in South African Rands and will be converted to US dollars (based on the annual conversion rate). In instances where the PDOH is unable to provide costs, market values will be used. Volunteers and donated resource values will be evaluated in terms of PDOH costs, or market-related values if unavailable.

Additional information may be required from the Red Cap database in the event of missing data or if additional data is required. Observation of procedures and informal discussion will be held with clinicians to gather relevant information.

The cost measures will include the unit cost per diagnostic tool including the consumables cost estimate of each pathway. The market cost will be utilised for the cost for each expenditure line-item will be included (i.e., we will not use guideline costing). The total cost of the standard pathway will include the cost of the empiric TB medication. The treatment medication for lymphoma will be excluded. The novel pathway costing elements will include consumables for SEB and CNB, infrastructure and human resources.

We intend to review and analyse data on patients' outcomes after diagnosis based on the pathway followed.

3.6. Sample Size

The sample size was based on the total number of patients who had a surgical excision biopsy for LAP at the OPLAS clinic during the 2016 calendar year, who met the inclusion criteria (patients diagnosed with LAP at GSH or referred from a peripheral hospital or clinic and booked at the OPLAS clinic) for the study conducted in 2020 by Dr T.T.C. Potwela.

4. Data Analysis Method

4.1 Cost analysis

The use of resources in the health sector has a cost implication and from a provider perspective, it is essential to analyse the costs and compare the cost between interventions to maximise the use of resources and achieve the best outcome (Drummond et al., 2015). Financial cost in costing is the monetary value of expenses whilst economic costs are choices that are expressed in alternative choices and opportunity costs (benefits that are sacrificed) (Sohn et al., 2009). For the cost analysis, two key elements will be used for each pathway, quantities of the resource used and prices. Table 2 goes into more detail on what these inputs will cover and how they will be measured.

Capital cost in the study refers to major assets utilised or purchased for the pathway which will include buildings, medical and information technology (IT) equipment, and furniture that was purchased at a single point in time. (Drummond et al., 2015). The capital cost will be amortised e.g. for the cost of the building, the percentage of the building used for consultation and diagnostic procedure estimated and the annual cost equivalent will be calculated and divided by the number of patients attended in the year (Drummond et al., 2015).

The recurrent cost will include the costs captured over less than an annum and will vary depending on the number of patients (scale) and the number of diagnostic tools utilised (scope) (Hendriks et al., 2014). Overhead cost is a term that describes the resources that are shared with other departments within the health system and will be allocated as described in Table 2. (Hendriks et al., 2014).

In the case of volunteer personnel, the cost will be calculated on PDOH/DOH salaries for unskilled labour or market wage for an unskilled per hour (Drummond et al., 2015).

Table 2: Standard Pathway

	Table 2: Methods used for identified inputs				
Cost Type	Cost identified	Method of costing	Measurement		
Capital cost	Category	Top-down/bottom up	Quantity	Valuation method	Data Source
Building	Consultation room, waiting room	Bottom-up	Percentage of building used for consultation, waiting room, and diagnostic tests will be measured in m^2 against the percentage off total building calculated	The capital cost will be annuitized at 3%. The annual cost calculated will be divided by the number of the patients had attended in 2016.	Provincial DOH (PDOH)/Department of public works
Equipment	Medical equipment, IT equipment.	Top-down method	Replacement cost divided by the number of diagnostic tests	Replacement value in 2016	Provincial DOH (PDOH)
Furniture	Desk, chairs, examination bed, bed step, cupboard	Top-down method	Replacement cost divided by the number of diagnostic tests	Replacement value in 2016	Provincial DOH (PDOH)
Recurrent cost	Category	Top-down/bottom up	Quantity	Valuation method	Data source
Personnel	Administration clerks, cleaners, clinicians (i.e., doctors, nurses)	Bottom-up method	The proportion of time spent on consultation and diagnostic tools in these pathways obtained via an interview process with personnel/use of timesheets and	Volunteer time: market-related wage rate per hour Permanent staff: the gross salary per month including benefits	Provincial DOH (PDOH)
Medication	Local anaesthetic, TB medication	Bottom-up method	Unit of drug dispensed and multiplied by utilisation by patient	Cost per unit utilised per patient per month /per diagnostic test	Provincial DOH (PDOH)
Consumables	FNA: needle, syringe, sterile surgical pack, specimen slides, fixation spray alcohol for cleaning, sterile dressing	Bottom-up method	Unit of consumable utilised per diagnostic test, quantity utilised will be obtained through observing the diagnostic test or through the interview	Cost per unit per diagnostic test multiplied by quantity per pathway	Provincial DOH (PDOH)

	pack, gloves, aprons,				
Laboratory test	Cytology	Bottom-up method	Unit of laboratory per diagnostic test	Cost per unit of laboratory test multiplied by the quantity used per pathway	Provincial DOH (PDOH), NHLS
Overhead costs	Water, electricity, rates, waste, telephone, disposal, stationery, maintenance of building and equipment	Top-down method	The proportion of time utilised for consultation and diagnostic tools per day and shared as per time allocated	Cost per day multiplied by the proportion of time utilised per day	Provincial DOH (PDOH)

Novel Pathway

The novel pathway table with sub-pathways has been included in the appendices (appendix 3,4,5,6) and varies to include pathway-specific resources. However, the methods between the two pathways do not vary.

5. Expected results and implications of the research

The expectation is that the novel pathway should lead to the expedited diagnosis of lymphoma and exclusion of TB. The financial cost of the novel pathway may be more than the standard pathway; however, the earlier diagnosis would result in the patient being diagnosed earlier and placed on treatment earlier thus reducing mortality and the financial burden on the public sector.

6. Possible difficulties and solutions

The cost comparison study will be utilising secondary data which may be incomplete or may have missing data. In the event of key data not being collected or further information is required, additional approval will be sought from HREC. Additionally, cost-centre information line items or aggregate costs may not be complete.

7. Ethical considerations

The protocol will be submitted to HREC, and the SPHFM Department Research Committee (DRC) for approval before commencing. The protocol will be shared with the Provincial Department of Health (PDoH) and is required for access to the OPLAS cost centre.

8. Potential Risk and Benefits

The cost comparison analysis study does not include any human subjects. Data will be de-identified before being received. To this end, subjects whose information is included in this study, will not directly benefit from the cost analysis study, however, the study will initiate important discussions which could improve future rapid diagnosis of lymphoma. Patients who are rapidly diagnosed with lymphoma will benefit from early treatment inventions. Policy makers and decision-makers will benefit from cost analysis and understanding cost and benefits attached to each pathway. Thus, leading to possible policy changes that could impact the planning and budgeting process in the future. This study can form the basis for future evaluation studies.

9. Confidentiality

Data will be de-identified with the use of unique identifiers to maintain confidentiality and anonymity. No personal identification will be included in any publications. All data will be stored electronically and will only be accessed via passwords. Financial information will be kept confidential and only approved information will be published.

10. What happens at the end of the Study?

The study is being conducted for Masters in Public Health dissertation and will be submitted to the Postgraduate Office for external examination upon completion. As part of the submission, a manuscript for a specific journal will be drafted for possible

submission. The outcomes will be disseminated to the GSH Head of Surgery and PDOH for consideration and policy amendment.

11. Timeline

Table 3

Event	August 2021	September 2021	October 2021	November 2021
Finalise protocol and submit to DRC and HREC	X			
Approval of HREC, DRC, PDOH		X		
Collection of data, data cleaning and analysis			X	
Write up the structured literature review		X		
Write up study including journal manuscript, and policy brief				X
Submission of dissertation				X

12. Budget

The study will be self-funded for the Masters in Public Health dissertation specialising in Health Economics. The resources required will be the time of the researcher and the supervisor appointed by the Health Economics Unit and Division. At the time of the protocol being written up, no additional costs have been envisaged.

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14. Appendices

Appendix 1: Standard and Novel pathway

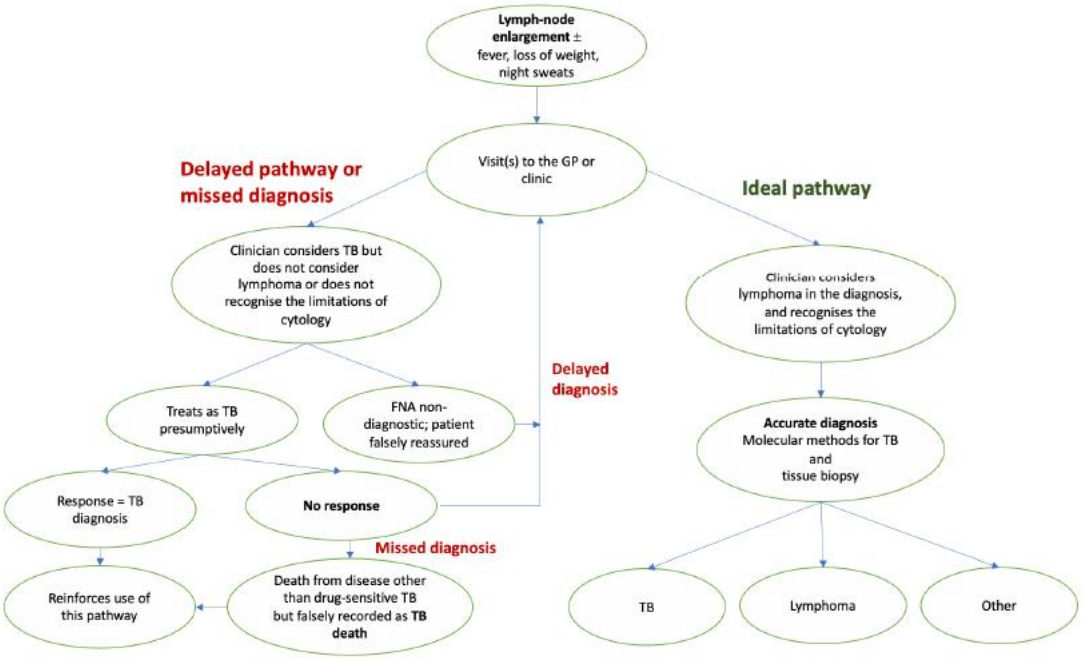

Figure A1: Standard and novel pathways to diagnosis of lymphoma, reproduced directly from Antel 2021(Antel, 2021)

Appendix 2: Adapted pathway

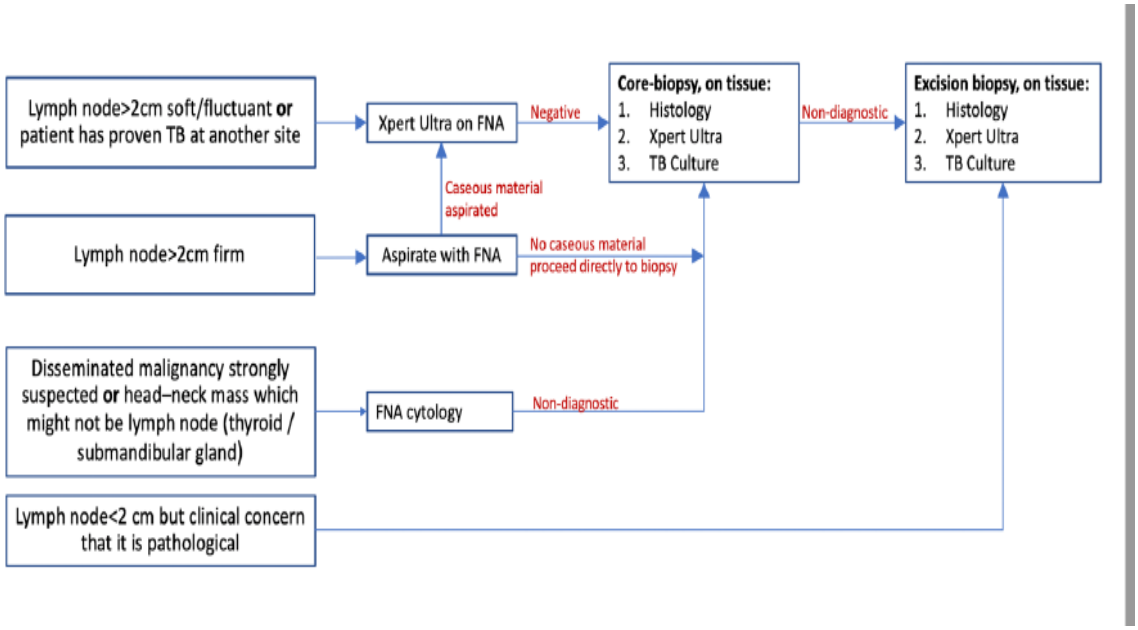

Figure A2: Standard and novel pathways to diagnosis of lymphoma, reproduced directly from Antel 2021(Antel, 2021)

Appendix 3: Table A1: Sub pathway A

Cost Type	Cost identified	Method of costing	Measurement		
Capital cost	Category	Top-down or bottom-up	Quantity	Valuation method	Data Source
Building	Consultation room, waiting room, theatre	Bottom-up	Percentage of building used for consultation, waiting room, and diagnostic test will be measured in m^2 against the percentage of a total building calculated	The capital cost will be annuitized at 3%. The annual cost calculated will be divided by the number of the patients had attended in 2016.	Provincial DOH (PDOH)/Department of public works
Equipment	Ultrasound machine, theatre equipment, medical equipment	Top-down method	Replacement cost divided by the number of diagnostic tests	Replacement value in 2016	Provincial DOH (PDOH)
Furniture	Desk, chairs, examination bed, bed step, cupboard	Top-down method	Replacement cost divided by the number of diagnostic tests	Replacement value in 2016	Provincial DOH (PDOH)
Recurrent cost	Category	Top-down/bottom up	Quantity	Valuation method	Data source
Personnel	Administration clerks, cleaners, clinicians (i.e., doctors, nurses)	Bottom-up method	The proportion of time spent on consultation and diagnostic tools in these	Volunteer time: market-related wage rate per hour Permanent staff: the	Provincial DOH (PDOH)

			pathways obtained via an interview process with personnel/use of timesheets and	gross salary per month including benefits	
Medication	Local anaesthetic,	Bottom-up method	Unit of drug dispensed and multiplied by utilisation by patient	Cost per unit utilised per patient per month /per diagnostic test	Provincial DOH (PDOH)
Consumables	FNA: needle, syringe, sterile surgical pack, specimen slides, fixation spray alcohol for cleaning, sterile dressing pack, gloves, aprons, CNB-ultrasound: probe covers, ultrasound gel, sterile surgical pack, sterile dressing pack, core needle, needle, syringe, specimen bottle, gloves, aprons,	Bottom-up method	Unit of consumable utilised per diagnostic test, quantity utilised will be obtained through observing the diagnostic test or through the interview	Cost per unit per diagnostic test multiplied by quantity per pathway	Provincial DOH (PDOH)

	SEB: needle, syringe, specimen bottle, suture material, dressing pack, sterile surgical pack, sterile dressing pack, gloves, aprons,				
Laboratory tests	FNA Ultra CNB - histology, TB culture, Ultra SEB- histology, TB culture, Ultra	Bottom-up method	Unit of laboratory per diagnostic test	Cost per unit of laboratory test multiplied by the quantity used per pathway	Provincial DOH (PDOH)
Overhead cost	Water, electricity, rates, waste, telephone, disposal, stationery, maintenance of building and equipment	Top-down method	The proportion of time utilised for consultation, theatre and diagnostic tools per day and shared as per time allocated	Cost per day multiplied by the proportion of time utilised per day	Provincial DOH (PDOH)

Appendix 4: Table A2: Sub pathway B

Cost Type	Cost identified	Method of costing	Measurement	
Capital cost	Category	Top-down or bottom-up	Quantity	Valuation method
Building	Consultation room, waiting room, theatre	Bottom-up	Percentage of building used for consultation, waiting room and diagnostic test will be measured in m^2 against the percentage of total building calculated	The capital cost will be annuitized at 3%. The annual cost calculated will be divided by the number of the patients having attended in 2016.
Equipment	Ultrasound machine, theatre equipment, medical equipment	Top-down method	Replacement cost divided by the number of diagnostic tests	Replacement value in 2016
Furniture	Desk, chairs, examination bed, bed step, cupboard	Top-down method	Replacement cost divided by the number of diagnostic tests	Replacement value in 2016
Recurrent cost	Category	Top down/bottom up	Quantity	Valuation method
Personnel	Administration clerks, cleaners, clinicians (i.e., doctors, nurses)	Bottom-up method	The proportion of time spent on consultation and diagnostic tools in these pathways obtained via an interview process with personnel/use of timesheets and	Volunteer time: market-related wage rate per hour Permanent staff: the gross salary per month including benefits
Medication	Local anaesthetic,	Bottom-up method	Unit of drug dispensed and multiplied by utilisation by patient	Cost per unit utilised per patient per month /per diagnostic test

Consumables	FNA cytology needle, syringe, sterile surgical pack, specimen slides, fixation spray alcohol for cleaning, sterile dressing pack, gloves, aprons, FNA Ultra-needle, syringe, sterile surgical pack, specimen slides, fixation spray alcohol for cleaning, sterile dressing pack, gloves, aprons, CNB, ultrasound probe covers, ultrasound gel, sterile surgical pack, sterile dressing pack, core needle, needle, syringe, specimen bottle, gloves, aprons, SEB-needle, syringe, specimen bottle, suture material, dressing pack, sterile surgical pack, sterile dressing pack, gloves, aprons,	Bottom-up method	Unit of consumable utilised per diagnostic test, quantity utilised will be obtained through observing the diagnostic test or through interview	Cost per unit per diagnostic test multiplied by quantity per pathway

Laboratory tests	FNA-cytology FNA Ultra CNB -histology, TB culture, Ultra SEB- histology, TB culture, Ultra	Bottom-up method	Unit of laboratory per diagnostic test	Cost per unit of laboratory test multiplied by the quantity used per pathway
Overhead cost	Water, electricity, rates, waste, telephone, disposal, stationery, maintenance of building and equipment	Top-down method	The proportion of time utilised for consultation, theatre and diagnostic tools per day and shared as per time allocated	Cost per day multiplied by the proportion of time utilised per day

Appendix 5: Table A3: Sub pathway C

Cost Type	Cost identified	Method of costing	Measurement	
Capital cost	Category	Top-down or bottom up	Quantity	Valuation method
Building	Consultation room, waiting room, theatre	Bottom-up	Percentage of building used for consultation, waiting room and diagnostic test will be measured in m^2 against the percentage of total building calculated	The capital cost will be annuitized at 3%. The annual cost calculated will be divided by the number of the patients having attended in 2016.
Equipment	Ultrasound machine, theatre equipment, medical equipment	Top-down method	Replacement cost divided by the number of diagnostic tests	Replacement value in 2016
Furniture	Desk, chairs, examination bed, bed step, cupboard	Top-down method	Replacement cost divided by the number of diagnostic tests	Replacement value in 2016
Recurrent cost	Category	Top down/bottom up	Quantity	Valuation method
Personnel	Administration clerks, cleaners, clinicians (i.e., doctors, nurses)	Bottom-up method	The proportion of time spent on consultation and diagnostic tools in these pathways obtained via an interview process with personnel/use	Volunteer time: market-related wage rate per hour Permanent staff: the gross salary per month including benefits

			of timesheets and	
Medication	Local anaesthetic,	Bottom-up method	Unit of drug dispensed and multiplied by utilisation by patient	Cost per unit utilised per patient per month /per diagnostic test
Consumables	FNA cytology needle, syringe, sterile surgical pack, specimen slides, fixation spray alcohol for cleaning, sterile dressing pack, gloves, aprons, FNA Ultra-needle, syringe, sterile surgical pack, specimen slides, fixation spray alcohol for cleaning, sterile dressing pack, gloves, aprons, CNB, ultrasound probe covers, ultrasound gel, sterile surgical pack, sterile dressing pack, core needle, needle, syringe, specimen bottle, gloves, aprons, SEB-needle, syringe, specimen bottle, suture	Bottom-up method	Unit of consumable utilised per diagnostic test, quantity utilised will be obtained through observing the diagnostic test or through interview	Cost per unit per diagnostic test multiplied by quantity per pathway

	material, dressing pack, sterile surgical pack, sterile dressing pack, gloves, aprons,			
Laboratory tests	FNA-cytology FNA Ultra CNB -histology, TB culture, Ultra SEB- histology, TB culture, Ultra	Bottom-up method	Unit of laboratory per diagnostic test	Cost per unit of laboratory test multiplied by the quantity used per pathway
Overhead cost	Water, electricity, rates, waste, telephone, disposal, stationery, maintenance of building and equipment	Top-down method	The proportion of time utilised for consultation, theatre and diagnostic tools per day and shared as per time allocated	Cost per day multiplied by the proportion of time utilised per day

Appendix 6: Table A4: Sub pathway D

Cost Type	Cost identified	Method of costing	Measurement	
Capital cost	Category	Top-down or bottom up	Quantity	Valuation method
Building	Consultation room, waiting room, theatre	Bottom-up	Percentage of building used for consultation, waiting room and diagnostic test will be measured in m^2 against the percentage of total building calculated	The capital cost will be annuitized at 3%. The annual cost calculated will be divided by the number of the patients having attended in 2016.
Equipment	IT equipment, ultrasound machine, theatre equipment, medical equipment	Top-down method	Replacement cost divided by the number of diagnostic tests	Replacement value in 2016
Furniture	Desk, chairs, examination bed, bed step, cupboard	Top-down method	Replacement cost divided by the number of diagnostic tests	Replacement value in 2016
Recurrent cost	Category	Top down/bottom up	Quantity	Valuation method
Personnel	Administration clerks, cleaners, clinicians (i.e., doctors, nurses)	Bottom-up method	The proportion of time spent on consultation and diagnostic tools in these pathways obtained via an interview process with personnel/use	Volunteer time: market-related wage rate per hour Permanent staff: the gross salary per month including benefits

			of timesheets and	
Medication	Local anaesthetic,	Bottom-up method	Unit of drug dispensed and multiplied by utilisation by patient	Cost per unit utilised per patient per month /per diagnostic test
Consumables	SEB-needle, syringe, specimen bottle, suture material, dressing pack, sterile surgical pack, sterile dressing pack, gloves, aprons	Bottom-up method	Unit of consumable utilised per diagnostic test, quantity utilised will be obtained through observing the diagnostic test or through interview	Cost per unit per diagnostic test multiplied by quantity per pathway
Laboratory tests	SEB-histology, TB culture, cytology Ultra	Bottom-up method	Unit of laboratory per diagnostic test	Cost per unit of laboratory test multiplied by the quantity used per pathway
Overhead cost	Water, electricity, rates, waste, telephone, disposal, stationery, maintenance of building and equipment	Top-down method	The proportion of time utilised for consultation, theatre and diagnostic tools per day and shared as per time allocated	Cost per day multiplied by the proportion of time utilised per day

PART B: STRUCTURED REVIEW

A comparative cost analysis of two pathways to diagnosing lymphoma in a tertiary hospital, Western Cape, South Africa

1. Introduction

We will be conducting a cost comparative analysis, of a recommended evidence-based pathway to expedite the process to diagnose lymphoma in a TB endemic area. This study will use an algorithm proposed by K. Antel (2019), during previous work conducted at Groote Schuur Hospital, involving two pathways, novel versus the standard pathway to diagnose lymphoma.

To inform this analysis this literature review will seek to provide a summary of information on the following:

-An overview on lymphadenopathy (LAP) and lymphoma

-A lymphoma diagnosis within the South African Context

-Economic evaluation including costing

-Justification of the research

The literature review first provides an overview on lymphadenopathy and lymphoma including prevalence, incidence, and presentation of the malignancy. The following section describes the different methods of diagnosing lymphoma, with a literature review on each procedure used to diagnose lymphoma, including advantages and risks associated with each pathway that is followed. Economic evaluation is further detailed and a justification of the research describes the reasons for the research and the benefit of providing economic evidence for health care interventions.

The literature search was based on keywords from the initial research questions and additional synonyms were added based on the systematic reviews retrieved. A table was drawn up to document the keywords and applied filters were recorded. The advanced search option was used to identify the relevant literature on PRIMO, PUBMED, and Cochrane databases. Other databases used included Google Scholar, EBSCO, and Scopus. The search terms utilised included the terms cost analysis, economic evaluation, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, core needle biopsy, excision biopsy, fine needle aspirate, FNA, fine needle biopsy with cytology, lymphadenopathy, surgical excision biopsy, lymph node removal, tuberculosis, TB, human immunodeficiency, HIV, COVID-19, SARS CoV-2, and South

Africa. The search was restricted by language to English, for the most up-to-date literature, the timeline included literature published from 2011 to 2021.

1.1 Lymphadenopathy

LAP is a term that is used to describe enlarged lymph nodes (LN) which are generally greater than 1cm, however, in certain areas of the human body like supraclavicular, epitrochlear, popliteal and the iliac region, palpable LNs greater than 5mm are considered to be abnormal (Gaddey and Riegel, 2016). LAP is classified into two categories, namely local (restricted to one area) and generalised LAP (two or more regions involved with enlarged LN and the cause is associated with the area of lymph drainage (Gaddey and Riegel, 2016). In most instances LAP is self-limiting and non-malignant however, a good history and clinical assessment is a key to obtaining a good differential diagnosis (Gaddey and Riegel, 2016). In a primary healthcare setting, unexplained LAP has an incidence of 0.6%, of which only 1.1% is associated with malignancy, however, an increasing incidence of unexplained LAP is seen with increasing age, as patients over the age of 40 years have an incidence of 4% compared to an incidence of 0.4% in patients under the age of 40 years (Gaddey and Riegel, 2016). LAP can be caused by malignancies, infections, autoimmune, iatrogenic and miscellaneous (Gaddey and Riegel, 2016). Malignancies include leukaemia, lymphomas, Kaposi's sarcoma, metastases, and skin neoplasms and these patients often present with fever, night sweats, and weight loss (Gaddey and Riegel, 2016).
Mycobacterium Tuberculosis (TB) is a common infectious disease affecting populations globally and one of the ten most common causes of death worldwide (Tahtabasi and Sahiner, 2021). TB is an acid-fast bacillus and the probability of inhaling an infectious droplet and developing clinical TB over a lifetime is less than 10% (Meghji and Giddings, 2015). There is an estimated incidence of 10.0 million cases of TB annually across the world (Tahtabasi and Sahiner, 2021) with the prevalence varying according to geographical location, drug resistance, and immunosuppression, making patients infected with the human immunodeficiency virus twenty times more susceptible to developing TB (Meghji and Giddings, 2015). The world average of TB cases is estimated at 130 per 100 000, with sub-Saharan

Africa (SSA) accounting for 29% of the TB cases (Tahtabasi and Sahiner, 2021).TB usually manifests in the lungs and can affect almost any organ in the body, with extrapulmonary TB constituting 15-20% of all TB infections and frequently involves LNs (Tahtabasi and Sahiner, 2021). Patients infected with TB have a delayed onset of symptoms and are often asymptomatic with only a minority of patients presenting with weight loss, malaise and night sweats, and LAP (Meghji and Giddings, 2015) which overlap with symptoms of malignancy and as noted constructing a diagnosis may be difficult. In India and some developing countries, due to the high prevalence of TB, in patients presenting with enlarged LN's, TB is considered the first differential diagnosis even though studies have shown that more than 50% of cases presenting with LAP are non-TB cases and tissue sampling with histopathology and microbiological examination is the only way to exclude TB (Thakkar et al., 2016). The World Health Organization (WHO) recommended the use of the rapid nucleic acid amplification test Xpert MTB/RIF (Xpert) for the diagnosis of extrapulmonary TB which now includes LN tissue (Antel et al., 2020)In unexplained LAP, HIV and lymphoma should be excluded as in some types of lymphoma, like follicular lymphoma, disease progression can be delayed with current treatment options (Thakkar et al., 2016) hence, making the need for early diagnosis vital to reduce morbidity and mortality.

2. Lymphomas and Classification

Lymphoma is amongst the ten most common worldwide malignancies which can be cured long-term (Verburgh and Antel, 2019). In the unclear diagnosis of LNs, lymphomas are one of the most common malignant diagnoses with incidence predicted to increase over the next few decades (Kühnl et al., 2018), especially with the increasing incidence of lymphoma in patients infected with HIV (Antel et al., 2019).

Since the early eighties, the acquired immunodeficiency syndrome (AIDS) epidemic has been associated with lymphoma as the responsible agent for defining the syndrome before the discovery of HIV (Re et al., 2019). Patients living with HIV (PLWH) have a higher risk of both non-Hodgkin's lymphoma (NHL) and Hodgkin's

lymphoma (HL) (Re et al., 2019). In PLHV, diffuse large cell lymphoma, Burkitt's lymphoma (BL), and primary central nervous cell lymphoma are recognised as AIDS-defining illnesses and without the use of antiretroviral therapy (ART) many PLWH cannot tolerate chemotherapy and die (Re et al., 2019). Even though the risk for lymphoma is higher in PLWH than in the general population, with the use of ART the risk has decreased significantly (Re et al., 2019). Despite there being established evidence that PLWH have an increased risk of developing lymphoma, there was no evidence to support the theory that HIV infection itself causes cell transformation, however recently it was hypothesised that HIV may play an indirect role in lymphomagenesis (Re et al., 2019).

Lymphomas are a group of diverse lymphoid malignancies which may behave differently clinically and in response to treatment (Jiang et al., 2017). Lymphomas are cancers of the lymphoid cells originating usually in more mature B and T cells (Verburgh and Antel, 2019). The WHO classification of lymphoid malignancies has been developed from cells of origin, i.e. precursor cells and mature cells, and the malignancies arising from mature cells are further sub-divided into malignancies arising from B and T cells (Jiang et al., 2017). Lymphomas are divided into NHL and HL based on the origin of cell histology.

In 2018, NHL ranked as the 10th and 12th most common cancer in the world amongst men and women respectively with an estimated incidence of 509 590 and 248 724 deaths (Miranda-Filho et al., 2019). A larger proportion of NHL arises from B cells (86% of all NHL) due to the malignant transformation of both mature and immature B lymphocytes, with a smaller proportion arising from T and natural killer cells (Miranda-Filho et al., 2019). NHL has a higher incidence in the older age groups with a peak incidence rate in the 75 and above age group (Miranda-Filho et al., 2019). The NHL subtypes vary geographically and survival rates for five years are estimated to be at 80% in high-income countries depending on age and subtype, however significantly lower in middle and low-income countries (Miranda-Filho et al., 2019). The aetiology of NHL is multifactorial with genetic determinants and an association with certain lifestyles including occupational exposures and obesity (Miranda-Filho et al., 2019). Some infections have been associated with an increased risk of NHL which include Epstein- Barr virus (EBV), Hepatitis C (Hep C), Helicobacter pylori (H. pylori),

and HIV (Miranda-Filho et al., 2019). PLWH are more susceptible to NHL when they have high viral loads and low CD4 counts (Puvaneswaran and Shoba, 2012). Whilst the risk of NHL is higher amongst HIV-infected patients, due to immunosuppression, the risk has been shown to decline with the use of ART as described above (Miranda-Filho et al., 2019). Even though the classification of NHL is complicated, information on the clinical elements and genetic abnormalities is important for accurate diagnosis. (Miranda-Filho et al., 2019).

HL is one of the most frequent types of lymphoma diagnosed in the world, with an incidence of 3 per 100 000 persons annually (Küppers et al., 2012). Whilst HL mainly affects the peripheral LNs, it can involve organs like the liver, lung, and bone marrow. (Küppers et al., 2012). HL is further subclassified into nodular sclerosis, mixed cellularity, lymphocyte rich (LRHL), lymphocyte depleted (LDHL), and nodular lymphocyte-predominant HL (NLPHL) based on the histological picture and phenotype of the cell (Küppers et al., 2012). Nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted HL are collectively known as classical HL with a >80% cure rate. The malignant cells are known as Hodgkin and Reed-Sternberg cells, which are classically large cells that are mono-, bi- or multinucleated cells (Küppers et al., 2012, Verburgh and Antel, 2019). LRHL accounts for 3-5% of HL and typically presents in stage I or II of the disease, having a better prognosis when compared he classical HL (Jiang et al., 2017). In 40% of cases, EBV infects the tumour cells which has pathogenetic significance (Küppers et al., 2012).

In 2016, the WHO lymphoma classification was reviewed and included significant changes to the diagnosis, prognosis, and management of the disease with expert opinion believing that the lymphoma classification needs to be reactive to the developing field of new clinical, pathological, and molecular understanding of lymphoma (Jiang et al., 2017).

3. The South African Context of Lymphoma

Malignancy is quickly becoming a public health crisis and a priority in low- and middle-income countries (LMIC) with the prediction that 70% of the 24 million people predicted to have cancer by 2050 will reside in LMIC (Kingham et al., 2013). The

healthcare systems of SSA are being challenged by the increasing burden of cancer patients and a lack of adequate resources (Kingham et al., 2013). Patients with AIDS have an increased risk of Kaposi's sarcoma (KS), lymphomas, and cervical cancer, and treatment of these patients with chemotherapy is of no benefit without ART.

South Africa (SA) has been the epicentre of TB and HIV infections, which posed several difficulties in the diagnosis of lymphoma (Antel et al., 2020). It is estimated that there are 5,6 million PLWH in SA who are co-infected with TB (Puvaneswaran and Shoba, 2012).

In the retrospective study conducted on 560 LN biopsy reports at Chris Hani Baragwanath Hospital (CHBH) in Johannesburg, SA, between 1 January 2020 and 31 December 2012, the majority of women (55% of the total cohort), 90%, were part of the African Black racial group with a mean age of 40 years had LN biopsies and the main reason for LN biopsy was uncertain diagnosis (Reddy et al., 2015). The study further highlighted a strong correlation between HIV incidence (49 % of the sample were HIV positive) and the incidence of aggressive B cell lymphoma and HL (Reddy et al., 2015). Given the SA context of TB prevalence, the other common reasons for LN investigations were suspicion of TB and malignancy (Reddy et al., 2015).

In TB endemic areas like SA where there is an increasing incidence of lymphoma, lymphoma should be considered in cases where TB is not definitively confirmed (Puvaneswaran and Shoba, 2012). It has been highlighted in several African studies that 25-85% of patients with lymphoma are on empiric TB treatment at the time of diagnosing lymphoma, and have not had a TB diagnosis confirmed (Antel and Verburgh, 2019). The problem of misdiagnosis is further exacerbated in PLWH, who not only have a higher risk of TB and lymphoma but also an increased risk of other cancers like KS which may also have LN involvement (Antel and Verburgh, 2019). Despite treating PLWH with ART, the risk of developing lymphoma remains, hence lymphoma is the leading cause of HIV mortality globally based on four papers reviewed.(Antel and Verburgh, 2019).

Furthermore, in TB endemic areas such as SA, TB misdiagnosis occurs due to the lapping symptoms (for instance cough, weight loss, and night sweats), overlapping investigation findings results (like cytopenia's, pleural effusions, and hypodense lesions in the spleen), and non-conclusive cytological findings (like poorly formed

granuloma seen in both diseases) (Antel and Verburgh, 2019). Both TB and lymphoma may share the onset of immune reconstitution inflammatory syndrome which overlaps at the time of clinical presentation (Antel and Verburgh, 2019).

Due to the relationship between TB, HIV, and lymphoma, PLWH in TB endemic areas are particularly vulnerable to having their malignancy being incorrectly diagnosed as TB (Antel and Verburgh, 2019) and suffering from delayed diagnosis.

To add to the complications of diagnosing lymphoma, a new pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China and spread globally, bringing on the most serious health, economic and social crisis of the millennium (Molica et al., 2020). To reduce transmission, many countries restricted movement and implemented restrictive measures which led to anxiety in the general population (Molica et al., 2020). SARS-CoV-2 causing coronavirus diseases (COVID-19) have placed a great burden on global health systems, thus further increasing the challenges in diagnosing lymphoma (Antel et al., 2020).

Pre-pandemic delays in the diagnosis of lymphoma were highlighted in many articles from developed countries, now with the SARS-CoV-2 pandemic, this delay will likely be exacerbated with de-escalation of services and the use of virtual consultation (Antel et al., 2020) and with underdiagnosis of haematological symptoms and delays in haematological investigations (Molica et al., 2020). The delayed diagnosis of lymphoma has been associated with late presentation of the disease and poor prognosis (Antel et al., 2020) and will require rapid access pathways for the diagnosis of lymphoma to prevent further delays in diagnosis.

4. Presentation of Lymphoma

LAP is a common presentation to primary health care services and outpatients (Thakkar et al., 2016). All patients presenting with LAP should have a detailed history taken to help illicit the differential diagnosis and a complete systematic physical examination (Mohseni et al., 2014). Lymphoma can present with the variable mode of symptoms which include constitutional symptoms, LAP, superficial or deep-seated masses, and effusions clinically. In patients with HL, pain may occur with the intake of alcohol (Mohseni et al., 2014). 30 % of patients with HL and 10% of patients with

NHL may present with generalised pruritis (Mohseni et al., 2014). Supraclavicular LAP has the highest risk of malignancy (90%) in inpatients older than 40 years and a 25% risk of malignancy those under 40 years of age (Mohseni et al., 2014).
Verburgh and Antel (2019) describe five typical lymphomas 'presentation syndromes' with typical confounders.

In a study conducted in the United Kingdom, between 2001 and 2009 on a dataset of 1 000 patients, at the Royal Marden Hospital, all patients with malignant disease presented with LN or lumps greater than 1,5 cm, and of the 35 patients that presented with HL, 15 (43%) had increased levels of lactate dehydrogenase (LDH) and 5 (14%) had B symptoms. Patients with the malignant disease had more LAP involving multiple sites than non-malignant cases and lymphomas presented more often in multiple sites when compared to solid tumours (Kühnl et al., 2018).
In another study conducted between June 2012 and June 2014, at Groote Schuur Hospital, in SA with a sample of 163 patients, the majority of patients presented with peripheral LAP (64%) and 59 % presented with B symptoms at diagnosis of lymphoma (Antel et al., 2019). When HL was compared to NHL, HL was more likely to present with peripheral LAP and was statistically significant (p-value <0.01), as was having B symptoms (p-value < 0.03) and bone marrow involvement (p-value <0.01) (Antel et al., 2019). These overlapping symptoms make diagnosing lymphoma complicated and good diagnostic tools and rapid access pathways can lead to delayed diagnosis.

Table 1: Overlapping Symptoms, adapted from (Verburgh and Antel, 2019)

Signs and Symptoms	Presentation	Confounders/ Differential Diagnosis
1. B -symptoms that are the presence of systemic symptoms (triad described in presentation)(Verburgh and Antel, 2019)	Inexplicable temperature >38°C, drenching night sweats and >10% weight loss for the last six months.	Constitutional symptoms are confounded by other diseases like those that present with similar symptoms. These include HIV, TB, connective tissue disease, solid organ cancers, and endocrine conditions.
2. Significant LN	Non-painful LNs that are frequently equal in size (area) and rubber hard texture. Whilst LN present typically for >3 weeks and are > 1,5 cm in size in lymphoma, the LN can present as a smaller LN in lymphoma	Other conditions that present with peripheral LN that can confound the diagnosis of lymphoma include viral conditions like HIV, and herpes; bacterial infections like Staphylococcus aureus, TB; malignancy, and connective tissue disease. (Mohseni et al., 2014).
3. Cytopenia's	Lymphomas invade the bone marrow suppress normal cell production and commonly result in anaemias.	Other haematological confounders include acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS). The differential diagnosis for cytopenia is wide and traverses across many systematic and immunological conditions.
4. Lymphocytosis	Due to the spill of tumour cells into the bloodstream, typically after bone marrow invasion. These blood-borne cells are easily diagnosed as cancer cells.	A differential blood count is often not requested and is one of the pitfalls of diagnosing lymphoma. It is recommended that a white cell count (WCC) be included in a differential count and abnormal haemoglobins done in hospital wards (inpatients) should be followed by full blood counts (FBC), differential counts and blood film.

5. Tumour masses	The masses grow indolently in body cavities and later cause dysfunction of the organs resulting in symptoms like mediastinal masses, pleural effusions, or in the case of B cell lymphoma can cause gastrointestinal obstruction.	Histological diagnosis is the key to establishing the cause of the tumour mass and is supported by imaging. In young patients, lymphoma is the primary cause of mediastinal masses and is an important differential diagnosis of lung cancer in all ages. In TB endemic areas, patients presenting with pleural effusions are commonly commenced on empiric TB treatment, which is acceptable, however, it is recommended that they are followed up two weeks later with lymphoma being considered as the differential diagnosis.

5. Diagnosing Lymphoma: Is There an Expedited Pathway?

Delayed diagnosis of lymphoma can lead to treatment failure (Oh et al., 2016) which can have an impact on morbidity and mortality. Whilst a thorough medical history, physical examination, laboratory, and radiological examination are important in the diagnosis of lymphoma, an adequate tissue biopsy is a key to making an accurate examination (Oh et al., 2016, Tahtabasi and Sahiner, 2021).

The typical methods used to evaluate LAP highly suspicious of lymphoma or malignancy are surgical excision biopsy (SEB), core-needle biopsy (CNB), and fine need aspirate (FNA) (Tahtabasi and Sahiner, 2021). The WHO published guidelines in 2016 for classifying and diagnosing malignant lymphomas which were constructed on clinical, pathological, and genetic or molecular attributes (Heidari et al., 2021). For the evaluation of LAP, the gold standard is tissue diagnosis and the gold standard for diagnosing lymphoma is SEB based on the fact that one can obtain adequate tissue samples surgically for histology (Heidari et al., 2021). In more recent years, the preferred method for obtaining tissue samples for the exclusion of lymphoma has shifted to FNA and CNB due to the good diagnostic outcomes (Heidari et al., 2021).

Both FNA and CNB can assist in the diagnosis of LAP when the cause is unknown and there is a risk or high suspicion of malignancy. (Gaddey and Riegel, 2016)

According to Mohseni et al. (2014), FNA is considered to be a safe and simple technique proven to be accurate in the diagnosis of granulomatous LAP, metastatic cancers, reaction hyperplasia, and lymphomas amongst others. It can be quickly and easily performed as an inpatient or outpatient as it is minimally invasive and can assist in the assessment of unexplained LAP with its greatest strength being recognised for the diagnosis of recurrence of cancer (Mohseni et al., 2014, Gaddey and Riegel, 2016). In adults, FNA has good specificity between 98-100% and sensitivity between 85-95% with rare false positives (Gaddey and Riegel, 2016). The reliability of FNA has been questioned in the diagnosis of lymphoma as difficulties are often encountered with the assessment of the LN architecture (Gaddey and Riegel, 2016) hence its diagnostic abilities for lymphoma are particular is limited. Due to the narrow gauge of the needle used in FNA, the architecture is often distorted (Allin et al., 2017) Ultrasound-guided FNA (USFNA) is noted to be more precise than blind FNA as it provides more precise information as one can guide the needle into the most suspicious area (Mohseni et al., 2014).

Previously at the hospital in Lewisham in London , the investigation of lymphoma guidelines for patients presenting with easily accessible and palpable LN's recommended patients undergoing FNA for cytology (FNAC), and if the diagnosis was inconclusive, the patient was referred for SEB (Allin et al., 2017). However, FNAC has poor sensitivity for the diagnosis of lymphoma and only approximately 30% of cases of acid-fast bacilli are visualised (Antel et al., 2019). Furthermore, Antel et al. (2019) have argued that FNAC could show poorly developed granulomas which are broadly misinterpreted as TB specific and, patients with overlying symptoms and ineffective FNAC in TB endemic areas could have been incorrectly diagnosed and placed on empiric TB treatment leading to delays in the diagnosis of lymphoma (Antel et al., 2019). Without adequate evaluation of LAP and the commencement of patients on empiric treatment can lead to risks of unproductive treatment and can increase the risk of aiding drug resistance TB (Meghji and Giddings, 2015). In the last few years, TB diagnostic tools have advanced nucleic acid amplification which includes using WHO-

recommended Xpert MTB/RIF, which has now been superseded by Xpert MTB/RIF Ultra (Ultra). (Antel, 2021). Ultra was recently recommended for use on FNA biopsies, thus excluding TB and expediting referral onto CNB (Antel et al., 2019).

In the study conducted by Reddy et al. at Chris Hani Baragwanath Hospital, the use of FNA was highlighted as the diagnostic method of choice for diagnosing TB lymphadenitis. It promotes the use of SEB as a follow-up test for non-diagnostic FNA given the context of the TB endemic in SA, despite SEB traditionally being the method of choice for primary diagnosis. (Reddy et al., 2015)

Antel and Verburgh (2019) reported in their article that FNA is a 'poor test' for diagnosing lymphoma, especially in the absence of flow cytometry and immunohistochemistry (Antel and Verburgh, 2019). However, they suggest that due to its low negative predictive value the use of FNA may be valuable for the diagnosis of disseminated malignancy, but should not be used as a 'rule-out' test for lymphoma or any other cancers (Antel and Verburgh, 2019).

FNA is an inexpensive and easily performed which makes it the preferred method for evaluation for LAP (Tahtabasi and Sahiner, 2021). In a retrospective study conducted between January 2016 and February 2020 on 241 patients in Somalia, the diagnosis of lymphoma was made using FNA with radiological confirmation of atypical lymphoid cells in accordance with the FNA biopsy resulting in a 91.5% sensitivity rate (Tahtabasi and Sahiner, 2021).

CNB is another method used for diagnosing LAP with the ability to provide more tissue samples than FNA (Mohseni et al., 2014). This ultrasound-guided technique is more accurate than an FNA and could provide an accurate diagnosis without the need of a SEB having proved to be 76-100% accurate in diagnosing lymphoma (Mohseni et al., 2014). The CNB procedure is conducted with the use of an automated gun, a wide needle (14 gauge or 16 gauge), and is safe to use in patients suspected of having lymphoma with a diagnostic yield of 89% (Antel and Verburgh, 2019). The use of an automated gun has been reported to provide a clean edge with the retention of the tissues' architecture (Antel and Verburgh, 2019). CNB can be easily performed in a

consulting room with a low risk of complication, however, SEB is still recommended in patients with LN less than 15 mm (Antel and Verburgh, 2019). CNB can replace the need for the use of SEB as it is less invasive and is useful for diagnosing the cause of LAP in PLWH (Antel and Verburgh, 2019). The use of USCNB has increased due to its use in diagnosing malignant and non-malignant LAP owning to the architecture retention and the ability to conduct histochemical and immuno-histochemical tests (Altuwairgi et al., 2014). A retrospective study was conducted between January 2008 and December 2011 on 55 patients who underwent SEB, and out of the 55 cases, five patients had USCNB which showed a 100% definitive diagnosis, with four patients having extrapulmonary TB and one patient lymphoma (Altuwairgi et al., 2014).

A retrospective observational study conducted on 79 patients in Korea, between January 2007 and July 2009 comparing ultrasound-guided FNA and USCNB showed 23 out of the 62 cases that had ultrasound-guided FNA biopsy (37%) were non-diagnostic, whilst 73 of the 79 cases of USCNB (91.3%) provided adequate specimens for diagnosis (Oh et al., 2016). This suggests that USCNB can be used as a diagnostic test to diagnose lymphoma in some cases. During this study, none of the 79 cases that underwent USCNB had neurological or vascular complications and importantly there was no tumour seeding (Oh et al., 2016). This study noted the limitations of FNA in diagnosing lymphoma due to poor or inadequate tissue sampling and the disadvantages of SEB due to its invasive nature and risk of complications, further highlighting the cost and delays in diagnosis associated with the choice of SEB (Oh et al., 2016). Whilst USCNB is associated with an increased risk of seeding, the risk of tumour seeding can be due to the size of the needle, with 14G needles having a higher risk of tumour seeding than 18G needles (Oh et al., 2016).

A 17-month retrospective study was conducted on 70 patients who underwent USCNB, 63 of these patients were diagnosed on the initial diagnostic test, thus not requiring additional diagnostic tests (Allin et al., 2017). The seven non-diagnostic cases were referred for additional investigation, and overall 39 (62%) of the 70 patients were diagnosed with lymphoma, thus USCNB diagnosed 95% of the lymphoma cases (Allin et al., 2017) building a case to support the use of USCNB as part of the initial investigation for the evaluation of LAP.

Whilst CNB has significant advantages, there are limitations to its use especially in cases with poor percutaneous visualisation (Seviar et al., 2021). Some of the drawbacks noted with CNB include the need for fully trained operators for ultrasound (US) imaging, training, and experience in CNB and potential complications which include haemorrhage, pneumothorax, nerve injury, and seeding of tumours (Seviar et al., 2021).

Groneck et al (2016) published a study in the European Journal of Haematology in which CNB was performed for 138 patients who presented with LAP or subcutaneous tumours, in which they varied the needle gauge according to the lesion size (14G, 16G, 18G). Of the samples obtained 132 (95.6 %) were adequate, with 4.4% requiring follow-up SEB (Groneck et al., 2016). The complication rate of the CNBs performed was 2,2% and included all self-limiting complications - LN fistula, transient hypoesthesia of the trigeminal nerve, and 8cm haematoma in a thrombocytopenic patient (Groneck et al., 2016). The CNB resulted in 24 lymphomas being primarily diagnosed, however, 54 patients (39%) required a secondary biopsy, of which the nine cases from the 54 differed from the CNB diagnosis with five false-negative results in patients with HL and two cases of false positives of grade one follicular lymphoma, with the case being diagnosed as a reactive LN and one case being classified as inadequate material for diagnosis (Groneck et al., 2016). Based on the outcome of the study, the size of the needles did not significantly impact the results, and larger needles were not associated with higher complication rates (Groneck et al., 2016) CNB was recommended as a fast, effective way to diagnose lymphoma with the caveat that benign lesions should be followed up with SEB when there is a high suspicion or clinical presentation of malignancy (Groneck et al., 2016)

Despite the reported accuracy of CNB, SEB continues to be recognized as the gold standard for the diagnosis of lymphoma (Mohseni et al., 2014) with CNB being reserved for malignancies that are deep-seated in tissue (Groneck et al., 2016). The European Society for Medical Oncology (ESMO) among other institutes endorses SEB as the gold standard for lymphoma and reserves the use of CNB for LNs which are inaccessible or for patients w high risk for surgery (Chatani et al., 2020). SEB remains the gold standard for the diagnosis of lymphoma as it provides more information and maintains the histological structure required for diagnosis, however it is attached to

a significant cost requiring surgical time and expertise associated with anaesthetic and surgical risk even though they are low (Thakkar et al., 2016). In certain patients, SEB may not be the choice of diagnostic test due risk of wound infection, large scars, and general anaesthesia (Groneck et al., 2016). SEB requires hospitalisation of at least one day, it is invasive, painful and the required resources may not be available in peripheral hospitals (Altuwairgi et al., 2014) thus delaying diagnosis of patients with LAP. The referral pathway for SEB to surgical departments and the planning requirement for operations can delay the diagnosis of malignancies for weeks (Groneck et al., 2016). An interdisciplinary team is required for SEB, whilst to perform a USCNB, a single person and low material expense is required (Groneck et al., 2016). When SEB was compared with the use of FNA, SEB was reported to be twice as sensitive as FNA, when FNA was supported by traditional diagnostic histology and culture for the diagnosis of TB LAP, with a p-value <0,005 showing statistical significance (Thakkar et al., 2016).

In the study retrospective study conducted by Chatani et al. over five years on 263 CNB cases and 108 SEB cases, the waiting time for CNB was shorter than for CNB (p value< 0.01) and re-biopsy rate was higher in cases who underwent CNB (p-value = 0.02) (Chatani et al., 2020). SEB provides a more accurate diagnosis (93.4%) when compared to the CNB group which achieved 89% diagnostic accuracy (Chatani et al., 2020) however the complication rate was higher with the SEB group (6.5%) and lower in the CNB group (4.9%).

Numerous challenges exist when diagnosing lymphoma which includes the insidious onset of the disease, overlapping symptoms, lack of specificity for diagnosis, lack of expedited referral pathway, and barriers to obtaining LN tissue samples (Antel and Verburgh, 2019).

6. Sensitivity and Specificity

Gold standard investigations or diagnostic procedures are commonly used procedures based on their ability to accurately diagnose people with the disease and people without the disease (Aschengrau and Seage, 2020). However, these tests are often expensive and invasive (Aschengrau and Seage, 2020), for instance in the case

of SEB which has been recommended as the gold standard procedure for the diagnosis of lymphoma. Sensitivity and specificity are measures of screening tests that determine the presence or absence of the disease in the preclinical disease (Aschengrau and Seage, 2020). Sensitivity refers to the proportion of correctly showing that a person has the disease in the preclinical phase. Specificity, expresses as a percentage, those correctly classified as not having the disease in the preclinical phase (Aschengrau and Seage, 2020).

7. Novel and Standard Investigative Pathway

The literature review provides various options to diagnosing LAP, however a significant gap exists in economic evaluation of costing the investigative pathways to diagnosis. Antel (2021) novel pathway provides a rapid novel pathway to investigating LAP in TB endemic settings and an economic evaluation on the pathway could assist policy makers in budgeting process.

8. The Value of Economic Evaluation and Costing

Economic evaluation plays an integral role in assisting in informing health care decisions (Drummond et al., 2015). The choice of one intervention over another has consequences and can impact the health of people, resources and have consequences outside the health sector (Drummond et al., 2015). Economic evaluation makes use of the best clinical evidence and considers the effects of alternatives on health, healthcare, and other valuable effective interventions for healthcare (Drummond et al., 2015). To maximise health, many researchers concentrate their attention on public health programmes and the evaluation of these programmes, which could sometimes lead to the non-health outcomes being ignored (Greco et al., 2016).

There are four types of economic evaluation frequently utilised to evaluated public health interventions: cost-effective analysis (CEA), cost-utility analysis (CUA), cost-

benefit analysis (CBA), and cost minimisation analysis (CMA) (Greco et al., 2016) with the key differences between them being linked to outcome measurements. CEA is one of the most common types of economic evaluation for both health technology assessment and evaluation of health programmes, often being used due to the need for evidence-based decision making (Greco et al., 2016). In a CEA incremental costs are compared to incremental outcomes in the form of an incremental cost-effective ratio (ICER) (Greco et al., 2016). CUA's are growing in popularity for evaluating public health programmes and use multidimensional outcome measures such as disability adjusted life years (DALYs) or quality-adjusted life years (QALYs) where utility and or quality weight is regarded as a measure of health-related quality of life (HRQoL) (Greco et al., 2016). CBA is not commonly utilized irrespective of analysing healthcare in high-income or low-middle-income countries, and this is mainly due to the difficultly in converting outcomes to a monetary metric (Greco et al., 2016). CMA is the simplest form of economic evaluation, where costs are compared when the outcomes are equal to determine the least costly outcome (Drummond et al., 2015). Whilst economic evaluation assists with decision-making, policymakers often face the challenge of equity and efficiency. Unlike equality, equity does not necessarily mean equal sharing of resources, rather it means allocation of more resources to disadvantaged groups or communities (Guinness and Wiseman, 2011). Horizontal (equal access with equal needs) and vertical equity (those with greater needs allocated provided with more access) are important concepts to be factored into decision making (Guinness and Wiseman, 2011).

In economic evaluation maximising the efficient use of resources factors in maximising the outcome for the given quantity of resources (Guinness and Wiseman, 2011). Allocative efficiency and technical efficiency are the two main types of efficiency, wherein the case of allocative efficiency resources are allocated to maximise health where the allocation of resources will result in Pareto efficiency and technical efficiency is also known as operational efficiency and ensures the maximum output for minimum input of resources (Guinness and Wiseman, 2011).

Discounting is an important component of economic evaluation and has an impact on ICERs for priority setting and can have an impact on ICERS for priority settings (Brouwer et al., 2005). Discounting refers to the future cost and allocation of resources to preventative health and depends on the weight given to future costs in economic evaluation which is often receives less weighting that present ones. (Brouwer et al., 2005). International guidelines propose the use of 3-5 % discounting rate and recommends using equal discounting rates for both cost and its effects (Brouwer et al., 2005).

In the recent few years, there have been many economic evaluation studies published with a focus on cost-effective treatments. In 2012, Soini et al. published a cost-effectiveness study on the sequential treatments of follicular NHL comparing first-line progression-free and progression-free second-line sequential treatment using Markov modelling (Soini et al., 2012).

Another economic evaluation was conducted in Colorado, United States of America in 2015/2016 to compare the use of axicabtagene with chemotherapy (Whittington et al., 2019). The results showed that treatment with axicabtagene resulted in 0.48 more life years and 0.34 more QALYs than chemotherapy which resulted in a cost-effectiveness estimate of $896 600 per QALY for public payers and $1615 000 per QALY gained for commercial payers (Whittington et al., 2019).

A retrospective study was conducted in Canada between 1997 and 2007 to evaluate the cost and cost-effectiveness of Rituximab when combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy and compared to CHOP chemotherapy alone in the treatment of diffuse large B cell lymphoma patients (Khor et al., 2014). The study found Rituximab when combined with CHOP was more likely to increase life expectancy by 3.2 months over five years at an additional cost of $16 298 which corresponded to a cost-effectiveness ratio of $61 984 per life-year gained and the probability of being cost-effective was 90% if the willingness to pay threshold was $100 000 per life-year gained.

In 2018, Bosch et al. published a research article on a retrospective study conducted on 1779 patients. Their sample included patients diagnosed with HL, large B cell, and peripheral T cell lymphomas (Bosch et al., 2018). The study compared the time

interval of outpatients to time of diagnosis to inpatients time to diagnosis of lymphoma and the associated cost (Bosch et al., 2018). They found the interval time to diagnosis was shorter with inpatients (12.3 days) when compared to outpatients (16.2 days, however, there was a higher mean cost associated with inpatients (Bosch et al., 2018). With the use of a micro-costing method, the mean cost was estimated at €4 040 (for the year 2016) for inpatients and € 1409 for outpatients which were statically significant (Bosch et al., 2018). Whilst this may benefit patients with lymphoma, the decision-makers would have to reflect on the significant cost implications given the resource limitations especially in LMIC.

Other economic evaluations included the cost of changes in life expectancy in patients with lymphoma (Wang et al., 2018), various cost-effective treatment options of lymphoma using Rituximab (Bonafede et al., 2018, Papaioannou et al., 2012), and the cost of first line treatment failure (Bonafede et al., 2018).

There is a gap in the economic evaluation and cost analysis of diagnostic tools or pathways used in clinical practice to diagnose lymphoma particularly in TB endemic regions.

9. Justification for Further Economic Research

In patients presenting with LAP, it is apparent that a cost-effective, fast and reliable diagnostic method is required for accurate diagnosis (Groneck et al., 2016). (Groneck et al., 2016, Thakkar et al., 2016). The choice of diagnostic method to evaluate LAP is based on several deliberations which include cost-effectiveness, reliability, accuracy, morbidity (Groneck et al., 2016), and based on this literature review the clinical assessment of the patients and risks associated with the patient. Based on the literature review and the WHO recommendation, the SEB approach is the gold standard method for the diagnosis of lymphoma, with CNB being reserved for deep-seated lesions and in patients where the risk of scarring, infection, and anaesthesia is a concern.

Based on Bosch et al. (2014), patients presenting with LAP often invoke concern for the patient and treating providers (Bosch et al., 2014). Whilst the standardised method recommended by WHO and many other institutions for investigating LAD is SEB (Seviar et al., 2021), over recent years there has been increasing use of USCNB to

investigate LAD as it has shown to have a higher diagnostic yield than FNA yet slightly lower than SEB (with SEB diagnostic yield being 97.5%). (Seviar et al., 2021). Despite the slightly lower diagnostic yield USCNB (with a diagnostic yield of 91.7%) requires fewer resources and is accurate for sub-classification of lymphomas (Seviar et al., 2021). The reliability of FNA has been questioned in the diagnosis of lymphoma as difficulties are often encountered with the assessment of the LN architecture (Gaddey and Riegel, 2016) hence its diagnostic abilities for lymphoma in particular are limited. With the use of USCNB, Groneck et al. (2016) suggested that the gauge of the needle and size did impact the results significantly, however, multiple cores from different areas of the LN without shearing and fragmentation produced more adequate samples than the size of the needles (Groneck et al., 2016). They further recommended CNB as a diagnostic method of choice for lymphomas, however, in the cases of small LN, alternate methods should be considered (Groneck et al., 2016).

In TB endemic areas, like SSA, FNA is often used as the diagnostic tool of choice, leading to delayed diagnosis of lymphoma (Antel et al., 2019). Antel et al. (2019) found that the longest delay in diagnosis was due to the health practitioner's high index of TB suspicion delaying LN biopsy (Antel et al., 2019).

This delay has led to patients presenting late with advanced stages of lymphoma which is associated with high mortality (Antel et al., 2019). In a randomised clinical trial published in 2017, 376 patients were randomised into two arms, one arm consisting of USCNB and the other SEB. USCNB was found to be €171 (year of conversion was not included) per biopsy in Italy, compared to SEB which cost €10 393 for major surgery and €3 056 for minor surgery based on LN location. According to Groneck et al (2016), SEB costs four times the amount of USCNB and requires interdisciplinary team coordination for the procedure when compared to USCNB which requires a single person and minimal resources as mentioned above (Groneck et al., 2016). SEB was also associated with more complications and longer waiting times (Pugliese et al., 2017). In patients presenting with cervical LAP, USCNB is a less costly, safe, and accurate method with follow-up in about 30% of cases requiring

follow-up SEB based on the study conducted by Headari et al. (2021) (Heidari et al., 2021).

Whilst there is significant literature on various options of diagnostic methods for LAD, diagnosis of lymphoma, and economic evaluations on treatment options (Bonafede et al., 2018, Papaioannou et al., 2012), a significant gap exists in the cost comparison between diagnostic pathways to rapidly exclude TB in TB endemic areas and improve time to lymphoma diagnosis. Antel (2021) recently recommended an evolving clinically novel pathway for the rapid diagnosis of lymphomas in a TB endemic setting, however, the costing of the algorithm has not yet been conducted (Antel, 2021). The pathway looks at excluding TB adenitis and rapidly moving on to LN biopsy, thus expediting the exclusion diagnosis of TB and decreasing the days to lymphoma diagnosis (Antel, 2021) thus, preventing the late presentation of lymphoma and reducing mortality (Antel et al., 2019).

Before the delays seen due to the SARS-CoV-2 pandemic, general delays in the diagnosis of lymphoma were highlighted in many articles from high income countries. Now with the SARS-CoV-2 pandemic, this delay will likely be exacerbate with de-escalation of services and the use of virtual consultation (Antel et al., 2020) with underdiagnosis of haematological symptoms and further delays in haematological investigations (Molica et al., 2020). The delayed diagnosis of lymphoma has been associated with late presentation of disease and poor prognosis (Antel et al., 2020) and will require rapid access pathways for the diagnosis of lymphoma to prevent further delays in diagnosis.

This cost comparison study will be conducted to address the literature gap of costing diagnostic pathways to rapidly diagnosing lymphoma. Antel's (2021) recommended novel pathway will be divided into subsections based on clinical assessment of the LN. The cost will be estimated and compared to the standard pathway cost estimate. The pathways have been recommended in TB endemic areas and will be of value to many countries with similar contexts. The outcomes of this cost study could assist decision-makers with budget planning and policy decisions.

10. Discussion

In this simple cost analysis, it is important to consider the impact of the novel pathway and the standard pathway. If the novel pathway is less costly and patients are diagnosed earlier, this would benefit the health system and reduce morbidity and mortality. Whilst this comparative cost analysis will be conducted from the provider's perspective, one could consider further research from a societal perspective given the limited research available on the diagnostic pathways.

The opportunity cost of diagnosing lymphoma should be considered based on the current limited health care resources setting, and the opportunity cost will depend on what will be sacrificed and the value that will be placed on it to achieve maximum benefit for the resources (Drummond et al., 2015). Even in the best of times, the SA healthcare system is challenged by the quadruple burden of disease (TB and HIV, obesity and non-communicable disease, poor maternal and childhood mortality outcomes and injury and violence), and in early July 2020, the COVID-19 pandemic hit the SA health system further impacting the already strained health system (Standing Committee On Health, 2020). Given the current context in SA, with the current burden of the COVID-19 pandemic, the equitable and efficient use of resources is more critical than ever (Standing Committee On Health, 2020). The outcome of this cost comparison analysis will provide a series of scenarios for the DoH and the opportunity cost to implement the pathway will have to be considered by decision-makers in the context of the current health care system.

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PART C: MANUSCRIPT JOURNAL ARTICLE

A comparative cost analysis of two pathways to diagnosing lymphoma in a tertiary hospital, Western Cape, South Africa

A Comparative Cost Analysis of the Pathway to Diagnosing Lymphoma in a Tertiary Hospital, Western Cape, South Africa

Abstract

Background

In tuberculosis (TB) endemic areas, a fine needle aspirate (FNA) is frequently employed as the initial diagnostic tool when investigating lymphadenopathy (LAP), the sensitivity for lymphoma is low, and following a non-diagnostic result the next routine investigation is a lymph node excision biopsy. A significant gap exists in costing the diagnostic pathway to diagnosing lymphoma.

Objective

The study aimed to cost the diagnostic pathways: FNA as the initial diagnostic test, core-needle biopsy (CNB), and surgical excision biopsy (SEB) with the purpose to inform policy-making decisions and process guidelines.

Method:

Using secondary data at Groote Schuur Hospital (GSH), tertiary level hospital outpatient clinics, a cost analysis study was conducted using a combination of ingredients based costing and top-down costing from a provider's perspective. Data was collected between February- October 2018. Costs were annualized and inflated to 2021.

Results

More CNBs are currently being performed than SEBs at GSH, and when pathways were followed, CNB (US $567) initiated pathways were less costly compared to FNA (US$ 877) initiated pathways.

Conclusion

CNB provides an alternate option to SEB and based on the study conducted, CNB is pathways are less costly with expedited diagnosis, thus improving current pathway.

1. Introduction

1.1 Background:

Lymphadenopathy (LAP) often causes great emotional discomfort for both patients and doctors as it has a range of differential diagnoses and can lead to either the diagnosis being missed or delayed diagnosis of malignancy (Bosch et al. 2014). The term LAP is used to describe lymph nodes (LN) that have become abnormal due to size, consistency, and quantity. In TB-endemic areas like South Africa, extrapulmonary TB is the most common cause of LAP but there is a wide differential diagnosis including malignancy, infections, autoimmune, drugs, and miscellaneous (Thakkar, Ghaisas, and Singh 2016). Histopathology and/or microbiology test are required to exclude TB or to make an alternative diagnosis, the two most common and important being lymphoma or disseminated malignancy (Thakkar, Ghaisas, and Singh 2016), (Mohseni et al. 2014).

According to GLOBOCAN 2018, cancer was one of the leading causes of death before the age of 70 in 91 out of 172 countries with an increased incidence of cancer and mortality worldwide (Bray et al. 2018). Lymphoma is amongst the leading top 10 cancers in the world and one of the top 10 cancers that can be cured over time and the leading cause of cancer mortality in patients living with HIV is lymphoma (Achenbach et al. 2011; Bonnet et al. 2009; Yarchoan and Uldrick 2018). Broadly categorising lymphoma, there are three clinical groups of lymphoma: low grade or indolent lymphoma (e.g. chronic lymphocytic leukaemia (CLL), follicular and splenic lymphoma), high grade or aggressive lymphoma (e.g. diffuse large B cell lymphoma, Hodgkins lymphoma (HL) and peripheral T cell lymphoma) and the very high grade or aggressive lymphoma (e.g. acute lymphoblastic lymphoma, Burkitt's lymphoma, and plasmablastic lymphoma(Verburgh and Antel 2019; Swerdlow et al. 2016). Despite the use of antiretroviral therapy (ART), there appears to be a marked increased risk in people living with HIV/AIDS (PLWHA) with an incidence ratio of 11.5 for non-

Hodgkin's lymphoma (NHL) and an incidence ratio of 7.7 in HL (Antel et al. 2019; Yarchoan and Uldrick 2018).

Mycobacterium Tuberculosis (TB) is a common infectious disease affecting populations globally and one of the ten most common causes of death worldwide (Tahtabasi and Sahiner 2021). TB is an acid-fast bacillus and the probability of inhaling an infectious droplet and developing clinical TB over a lifetime is less than 10% (Meghji and Giddings 2015). In sub-Saharan Africa (SSA), despite the rapid molecular TB diagnostic techniques, diagnosing extra-pulmonary TB remains a challenge, and overlapping symptoms, with lymphoma in TB endemic areas leading to PLWHA being placed on empiric TB therapy, thus delaying the diagnosis of lymphoma (Antel et al. 2019).

LAP can be caused by malignancies, infections, autoimmune, iatrogenic, and miscellaneous (Gaddey and Riegel 2016). Malignancies include leukaemia's, lymphomas, Kaposi's sarcoma, metastases, and skin neoplasms and these patients often present with fever, night sweats, and weight loss (Gaddey and Riegel 2016).

Table Overlapping Symptoms, adapted from: Verburgh and Antel (2019) who describe five typical lymphomas 'presentation syndromes' with typical confounders.

1.2 Investigative Methods to diagnoses:

Fine Needle Aspiration (FNA) biopsy, surgical excisional biopsy (SEB), and core needle biopsy (CNB) are methods that can be used to obtain tissue sampling (Seviar et al. 2021) however, the World Health Organization (WHO) and many institutions and research groups recommend SEB followed by histopathological analysis (study of tissue or cells to aid diagnosis) as the diagnostic tool of choice for lymphoma and recognises ultrasound-guided core needle biopsy (USCNB) as an alternate diagnostic tool when the LN's are inaccessible or when the risk is high (Cuenca-Jimenez et al. 2021; Seviar et al. 2021; Johl et al. 2016)

Patients presenting with easily accessible and palpable LN's undergo FNA for cytology (FNAC), and if the diagnosis is nonconclusive, the patient is referred for SEB (Allin et

al. 2017). However, FNAC has poor sensitivity for the diagnosis of lymphoma, and only approximately 30% of cases of acid-fast bacilli are visualised (Antel et al. 2019). Furthermore, Antel et al. (2019) have argued that FNAC could show poorly developed granulomas which are broadly misinterpreted as TB specific and, patients with overlying symptoms and ineffective FNAC in TB endemic areas could have been incorrectly diagnosed and placed on empiric TB treatment leading to delays in the diagnosis of lymphoma (Antel et al. 2019). In the last few years, TB diagnostic tools have advanced and nucleic acid amplification which includes using WHO recommended Xpert MTB/RIF, which has now been superseded by Xpert MTB/RIF Ultra (Ultra) (Antel 2021). Ultra was recently recommended for use on FNA biopsies, thus excluding TB and expediting referral onto CNB (Antel et al. 2019).

A study conducted on 86 patients who presented with cervical LAD at a tertiary level referral centre between May 2016 and September 2018 was undertaken in India to evaluate the use of FNA and SEB (Pillai et al. 2021). Importantly all patients underwent SEB, and this tissue was examined as "histopathological results" are considered the gold standard in testing. (Pillai et al. 2021). FNA detected only 11 cases of lymphoma (58%) while after histopathology, 19 cases were confirmed in the cohort. Based on the results, 51% were diagnosed with a malignancy in the LN (Pillai et al. 2021). The authors recommend the use of FNA in low resource and TB endemic settings in younger patients as it is less costly and easier to administer at the primary level of care with fewer complications than CNB (Pillai et al. 2021; Oh et al. 2016).

Over the last few years, there has been some economic evidence published for the treatment and management of lymphoma (Soini et al. 2012). In 2018, Bosch et al. published a research article on a retrospective study conducted on 1779 patients and their sample included patients diagnosed with HL, large B cell, and peripheral T cell lymphomas (Bosch et al. 2018). The study compared the time interval of outpatients to inpatients and the associated cost (Bosch et al. 2018). They found the interval time to diagnosis was shorter with inpatients (12.3 days) when compared to outpatients (16.2 days), however, there was a higher mean cost associated with inpatients (Bosch et al. 2018). With the use of the micro-costing method, the mean cost was estimated at €4040 (for the year 2016) for inpatients and €1409 for outpatients. (Bosch et al.

2018). Whilst the shorter interval time may benefit patients with lymphoma as they could be placed on treatment earlier, the decision-makers would have to reflect on the significant cost implications given the resource limitations especially in LMIC. Other economic evaluations included the cost of life expectancy in patients with lymphoma (Wang et al. 2018), various cost-effective treatment options of lymphoma using Rituximab (Bonafede et al. 2018; Papaioannou et al. 2012), and the cost of frontline treatment failure (Bonafede et al. 2018).

Table 2: Comparison of the different investigative methods of LAD

Whilst there is significant literature on various options of diagnostic methods for LAD, diagnosis of lymphoma, and several economic evaluations on treatment options (Bonafede et al. 2018; Papaioannou et al. 2012), a significant gap exists in the cost comparison between diagnostic pathways to rapidly exclude TB in TB endemic areas and improve time to lymphoma diagnosis. Antel (2021) recently recommended an evolving clinically novel pathway for the rapid diagnosis of lymphoma in a TB endemic setting, however, the costing of the algorithm has not yet been conducted (Antel 2021). The pathway looks at excluding TB adenitis and rapidly moving on to LN biopsy, thus expediting the exclusion diagnosis of TB and decreasing the days to lymphoma diagnosis (Antel 2021) thus, preventing the late presentation of lymphoma and reducing mortality (Antel et al. 2019).

This cost comparison study was conducted to address the literature gap of costing diagnostic pathways to diagnosing lymphoma. Diagnostic pathways, such as Antel's (2021) recommended novel pathway which is divided into subsections based on clinical assessment of the LN, have been recommended in TB endemic areas and will be of value to many countries with similar contexts. The outcome of this cost study could assist decision-makers with budget planning and policy decisions in the resources constraints environment of tertiary settings.

2. Methods

2.1 Setting and Target population

We conducted a comparative cost analysis at Groote Schuur Hospital (GSH), a public sector tertiary hospital based in Cape Town, which serves the Western Cape population and receives referrals from the surrounding health care facilities which include primary health care and secondary level hospitals in both the private and public sector. The cross-sectional data utilised included information for 99 patients which were collected for a full 13-month period between November 2017 and October 2018 attending the REDCAP 'lumps and bumps' clinic at GSH (as part of a separate piece of research). Clinicians attending to these patients would complete the REDCAP patient information and the study coordinator extracted relevant data for patient information. Patient files were collected by the study coordinator to confirm or complete missing data. This data was collected by Associate Professor Verburgh and colleagues as part of a separate ongoing study which aims to establish the "Best Care" pathways for the investigation of LAP in a TB and HIV Endemic area and received Human Research Ethics Committee (HREC) approval from the University of Cape Town (HREC reference: 691/2021). Our partial economic evaluation focuses on a simple cost analysis of the standard and novel investigative pathways proposed by Antel (2021) and includes 83 outpatients (16 outpatients excluded) from the "Best Care" cross-sectional database (which was collected by Associate Professor Verburgh and colleagues). For the purpose of this cost analysis, inpatients (16) were excluded for the purpose of this study as they form a small proportion of the database and the focus of the cost analysis was on the outpatient clinic. Additional approval was obtained from GSH to conduct the partial economic evaluation at the hospital including institutional and ethical approval (approval date 12 January 2022; HREC reference 691/2021).

The unstructured interviews and information gathering were conducted at the surgical 'lumps and bumps' clinic, acute care surgical clinic, and the REDCAP 'lumps and bumps' clinic. The clinic is operated five days a week for various haematological diseases, however, once a week on a Tuesday the clinic is dedicated 2 hours to lumps and bumps for FNAs and CNBs. The SEBs are undertaken at the acute care clinic

(operates weekly on Thursday for 4 hours) or surgical 'lumps and bumps 'clinic (operates weekly for 4 hours). The SEB diagnosis if benign is either communicated telephonically by the specialist surgeon or referred to the referring clinic if further interventions are required. Based on the unstructured interviews with medical staff, ~288 outpatients attend the three clinics annually for procedures: 12 FNAs and 132 CNBs were administered at the REDCAP 'lumps and bumps' clinic; 144 SEBs were performed at the acute care clinic and surgical 'lumps and bumps' clinic.

Figure 1: Novel investigative pathway used to diagnose Lymphoma, adapted from Antel (2021)

2.2 Costing method

The cost analysis was conducted using a combination of ingredient-based costing (bottom-up) and top-down costing from a health care provider perspective. Costing data were collected retrospectively and included data from 2012-2021. Annual and unit costs were estimated in South African Rands (ZAR) using 2021 as the base year. All costs were then converted to United States Dollars (USD) (US$ 1 = R 15,54 average estimated between January 2021 to November 2021) (SARS 2021)The average consumer price index (CPI) for the year of the data collected and the average CPI for 2021 were applied to inflate the cost when required (SA 2021). The data were collected from three clinics performing procedures for LAP investigation through unstructured interviews with medical and support staff both on-site and online.

2.3 Ingredient costing

Capital costs (building space, furniture, and equipment) and the recurrent cost of consumables, laboratory, and radiology tests were costed utilizing the ingredient-based costing approach. The quantities for the ingredient-based costing were obtained through unstructured interviews.

The building space utilised was estimated by manually measuring the area used for the procedures and apportioned to the procedures based on time utilised per clinic.

The cost of the building replacement value per square meter (R33 544,20/ US$ 2 158) was evaluated using the Order of Magnitude Estimator for new hospitals used by the Department of Health Infrastructure Unit tool to estimate budgets and assist with planning of new infrastructure. The value per square meter was estimated and multiplied by the area used per square meter (CSIR; Department of Health Infrastructure Unit 2012). The estimated building and furniture cost was apportioned to procedures based on time utilised by the clinic and multiplied by the number of patients attending the clinics per month and year where procedures were conducted.

The prices were estimated by averaging the costs from quotations received from pharmaceutical companies, direct expenditure from GSH (Malherbe 2021; Seaton 2021), and market value costing (average of three costing where possible) from online sources for 2021.

The capital costs represent an upfront expenditure that depreciates over a period of time and does not always appear on the annual reports (Drummond et al. 2015). Capital items were amortized to adjust for the opportunity and depreciation cost, and a 3% discounted rate was applied to allow for international comparison as recommended by the WHO (Hellebo et al. 2021; Anna Vassall 2017). The estimated lifetime of 30 years was utilized for the building, 10 years for furniture, and 5 years for smaller pieces of equipment (Hellebo et al. 2021; Cunnama et al. 2016).

To calculate the total cost of the consumables per procedure, we obtained the utilisation rate of the consumables per procedure through the unstructured interviews and multiplied the average cost per unit price. The annual cost was determined by multiplying the total cost of consumables utilised per procedure by the number of patients attending the clinic (single visit) per year for 2021.

The list of investigations (laboratory and radiology testing) was obtained from the unstructured interviews and 99 patient “Best Care” database. The 2021 price list for all laboratory investigations was obtained from National Health Laboratory Services (NHLS) (Westhuizen 2021) except urine Lipoarabinomannan assay (urine-LAM) which was obtained from a national private laboratory as the price was not available from NHLS at the time of the study. The price of a chest x-ray was obtained telephonically from the two private sector radiologists where patients pay either a fee for service

rate or insured rate. The average cost of a single view x-ray was used as part of the series of baseline tests to exclude TB.

2.4 Costing of Personnel

Information and specifics on time spent in consultation and on procedures, as well as additional information on personnel (medical, support, and administrative staff) such as cadre of staff were obtained through online unstructured interviews initially due to COVID-19 restrictions and on-site once permission to regain access to GSH was granted. The annual salaries and grading for 2018 were obtained from the online published document by the Department of Public Service and Administration for medical personnel. The annual salaries and grading for support and administrative staff were obtained for 2015 and inflated to 2021 (Health 2015). The annual salaries were divided by the number of workdays in 2021 and then further in the number of working hours. These average personnel costs per hour were then multiplied by the number of hours spent per patient consult, follow-up, and procedure to obtain the total personnel cost per patient per procedure.

2.5 Step-down costing

A step-down costing method is a systematic approach to calculating indirect cost (cost not directly associated with the procedure or services) and apportioning the total cost to the department or clinic (Drummond et al. 2015). The overhead costs for the study included utility costs (electricity, water, sewage, and waste removal), administrative costs (telephone, internet, stationery, and printer consumables), and cleaning and security costs (cleaning materials, cleaning, security contracts, and laundry). Maintenance was also included in this overhead cost. The overhead cost was based on the total overhead expenditure with the assumption that all patients utilised the resources equally and overhead expenditure was divided by the number of patients attending GSH for the year 2017 and estimated using the patient day equivalent (PDE) method of weighing outpatient visits at a third of the resource use of inpatients (Hellebo et al. 2021; Anna Vassall 2017)

PDE outpatient = annual inpatient days X 0,33+ annual outpatient visit

The overhead cost obtained for 2017 was placed into relevant categories for the procedures and summed. The PDE formula was applied, and the total overhead cost was divided by the PDE to obtain the overhead cost per patient which was then inflated to 2021 using CPI. The annual overhead cost for 2021 was determined by multiplying the overhead cost by the number of patients attending the clinics annually and with a single follow-up visit per patient. Training costs were excluded from the expenditure list and were not included in the overhead cost or bottom-up costing. Future costing of in-house training conducted by senior registrars and consultants would be beneficial.

2.6 Sensitivity analysis

The cost of a CNB varies based on the use of the Magnum BARD® gun and ultrasound. To assess the impact on the cost of CNB, a simple two-way sensitivity analysis was conducted. The cost of CNB with and without using ultrasound and the use of a disposable gun compared to the use of a reusable Magnum BARD® gun. The cost of the procedures varies based on the cadre of staff performing the procedure, this was illustrated further using a simple 2-way sensitivity analysis.

3. Data Analysis

The data was collated and analysed using Microsoft Excel for Microsoft 265 Version 2112. The costing was tabulated for the purpose of comparison and pie charts were used to visually analyses the proportion of expenditure per procedure. The REDCAP 'lumps and bumps' clinic operational hours are currently eight hours per month and the other two clinics (acute care surgical clinic and 'lumps and bumps' clinic) operate every week, accounting for 32 hours per months (4 hours per clinic per week). The operational time of the clinics was used and apportioned to the time utilised per procedure to estimate the different costs.

A decision tree was developed to follow the pathways of the outpatients from the "Best Care" database and estimate the cost to diagnostic pathways. The proportions for each branch were inputted from the "Best Care" database and the empirical costing of the procedures (FNA, CNB, SEB) and investigations (baseline, additional testing) was added.

The number of procedures to diagnosis was estimated per disease and tabulated with costing. The disease prevalence in the sample population was computed over the period of data collection to provide the cost of the diagnosis per disease.

4. Results

4.1 Baseline characteristics of the study population

Table 3 presents the baseline demographical characteristics of the study sample from the "Best Care" database(Antel, Louw, et al. 2020; Antel, Oosthuizen, et al. 2020). 54% of the sample was made up of females, with the average age was estimated at 45,08 years, with most of the patients belonging to the South African (SA) mixed ethnic group and closely followed by the SA Black ethnic group. 19,28 % of females were diagnosed with "other" conditions, whilst majority of males (14,46%) were diagnosed as lymphoma. 33,73 % (majority) of the sample population presented with LAP between the ages of thirty and thirty-nine. The prevalence of disease was estimated for the sample population between November 2017 and October 2018.

Table 3: Demographics and Disease Prevalence in sample population (n=83)

4.2 Estimated summary of the Procedure cost

The annual cost per outpatient procedure is summarised in Table 4, Table 5, and Table 6 for FNA, CNB, and SEB, respectively. For the FNA and CNB procedure, 93% of the cost is attributed to the recurrent cost. Procedural tests (tissue samples obtained at the time of procedure sent to the laboratory for testing) and personnel contributed 43% and 38% respectively of the total FNA procedure cost. While the personnel cost (36%) for CNB was a higher contributor to the total cost than the procedural cost (28%). However, for CNB the capital equipment and consumable cost varied based on the use of ultrasound and type of biopsy gun utilized (either disposable or

reusable). Recurrent cost contributed 82% of the total SEB procedural cost overall, of which personnel contributed 30% and SEB consumables contributed 23%, overhead, and maintenance 8%, and the SEB procedural test contributed 21%. The personnel cost was driven by the medical and surgical registrar salaries for all three procedures. Baseline blood and radiology testing is a significant cost driver; with chest x-ray contributed 39% of the total cost of $95, followed by Gene Xpert (14,7%) and CD4 count (13,68%). Baseline tests are mainly conducted as part of the initial consultation whether that be FNA or CNB (or SEB). The laboratory cost was estimated to be higher for the FNA ($98) than the CNB ($67) and SEB ($67). The estimated time per procedure was approximately 2,01 hours including follow-up consultations, however, for SEB the follow-up consultation was done by the referral clinic or telephonically, and hence we used the same estimate as that for FNA and CNB.

Table 4: Summary of FNA procedural cost estimate
Table 5: Summary of CNB procedural cost estimate
Table 6: Summary of SEB procedural cost estimate
Table 7: Baseline test with the cost for Initial work-up and additional test
Table 8: The procedure laboratory cost

4.3 Sensitivity analysis

Table 9 represents the varying cost within the CNB procedure when a CNB is undertaken with the use of an ultrasound machine as opposed to without. A minimal change to the price (US$ 1) was noted. The cost of the CNB procedure is also sensitive to the type of biopsy gun utilised, with single-use biopsy guns estimated to be less than 8% less costly than reusable or multi-use biopsy gun (Magnum BARD® gun). Table 10 represents the cost of the procedure most sensitive to the cadre of staff performing the procedure. When procedure is task shifted to an Intern medical doctor, the cost of all the procedures decreased significantly.

Table 9 and 10: CNB sensitivity analysis and Task Shifting Analysis

4.4 Decision tree

A decision tree was employed using Treeplan software to follow the pathway of patients to being diagnosed after presenting with LAP. The initial decision followed 2 pathways, FNA and CNB as per the decision made by the clinician. The route is divided into 5 or fewer branches depending on the investigative procedure diagnosis (TB, lymphoma, malignancy, other and non-diagnostic). The pathway continued for the cases that required a confirmatory procedure. 92% of the 83 outpatients received an FNA, and 23% had a confirmed diagnosis through FNA (with baseline blood and radiology testing). The cost of the TB diagnosis was US$ 323 (cost of FNA with baseline blood and radiology testing). Of the 76 patients who underwent FNA, 77% of the outpatients required additional procedures to confirm the diagnosis, with 65,8% of the 76 outpatients having FNA plus CNB estimated was at US$ 564 (cost of FNA, baseline blood, and CNB) and 1,3% of the 76 outpatients required FNA, SEB, CNB estimated at $878.

The 8,4% (7 outpatients) of the 83 patients underwent CNB with baseline tests and 71% of the 7 patients had their diagnosis confirmed at an estimated cost of $336. The 29% of patients who underwent CNB required an additional CNB, and the diagnosis cost was estimated at $577. The prevalence of TB was the highest in the sample population with the highest odds ratio (OR) as depicted in Table 11.

Table 11: Prevalence of disease between November 2017 and October 2018 in the sample population

The total cost to diagnose the sample population was $ 43 427 (see Table 12), with FNA plus CNB making up 65% of the total cost to confirm diagnosis as they contributed to the highest number of procedures.

Table 12: Cost of the pathway based on the procedures (n=83)

5. Discussion

The cost analysis was conducted to estimate the cost and compare the estimated cost of the novel and standard pathway to diagnosing lymphoma at a tertiary hospital in the Western Cape, South Africa. The sample population of outpatients (n=83) between November 2017 and October 2018 had a higher proportion of mixed ethnicity (41%) and black ethnicity (40%) groups presenting for investigations. The analysis revealed a higher prevalence of lymphoma in males (15%) when compared to females (8%), similar to the study conducted at Chris Hani Baragwanath hospital (Reddy, Venter, and Pather 2015).

The cost estimated for each procedure showed FNA (US$ 228) as the least costly procedure followed by CNB (US$ 241) and SEB (US$ 314) respectively. However, FNA can be considered a precursor test, which gives an initial indication of the direct cost of the diagnosis and is important for ruling out specific diagnoses but is seldom conclusive for lymphoma. Both CNB and SEB provide more tissue from the LAP which in turn allows for multiple histological tests to be undertaken which are crucial in the diagnosis of lymphoma, malignancies, and other diseases. This means that a vast range of diagnoses is possible using one of the two procedures (CNB or SEB). Given that the specialised needs for CNB are fewer, there is the potential to decrease the time to diagnosis for patients as well as reduce the pressure on theatres and specialised staff performing SEBs at a tertiary hospital such as GSH.

Personnel and procedural tests drove the cost across all three investigative procedures, with personnel contributing the highest proportion (35% on average for all three procedures). The personnel cost was driven up by the need to have a medical registrar or surgical registrar and could be reduced through task shifting and training of medical personnel. The sensitivity analysis confirmed if medical interns were trained to conduct the procedures, the cost would be significantly reduced for all three procedures. (Table 10). For the CNB, which requires less specialised skill by shifting the staff performing the procedures to general practitioners, medical officers, and/or medical doctor interns. Baseline tests are part of the initial investigations to exclude TB, which is important as South Africa is a TB endemic area (Puvaneswaran and Shoba 2012). The cost of baseline tests is a significant cost driver to the total cost

of the procedure and may be lower for countries that have lower rates of TB infection. The SEB capital building cost is higher than the building cost for FNA and CNB as a larger area is utilised for the procedure. In this work we utilised the same cost per meter squared for the three procedures, however, this is a limitation as SEB is conducted in an operating theatre. As no sedation and local anesthetic are used for FNA, CNB, and SEB, these procedures are suitable for a non-theatre setting with a lower cadre of staff. This is particularly the case for CNB guided by a handheld ultrasound with a doppler which aids an insertion avoiding vessels.

Based on the sensitivity analysis, with all other costs held constant, the cost of CNB varied with the use of ultrasound and the selected choice of a biopsy gun. The reusable Magnum BARD® was the preferred biopsy gun that was used in practice; however, the choice of biopsy gun was dependent on the availability of consumables and the single-use biopsy gun. The number of patients attending the clinics and procedures conducted (utilisation) was used to estimate the cost of the procedure. This is a limitation, as the database is small and the number of patients attending outpatient clinics for LAP had significantly decreased due to the COVID-19 pandemic in keeping with the global pattern of delayed access health care services due to COVID-19 restrictions, fear, and contracting COVID-19 and de-escalation of services (Molica et al. 2020).

Based on the database, a higher number of FNA plus CNBs (60% of the total) were conducted over the study period when compared to the other combination of procedures. Whilst the WHO recommends SEB as the gold standard investigation of LAP especially when there is a suspicion of lymphoma or malignancy, the trend has changed in recent years as more clinicians are increasingly performing FNA and CNBs as the initial diagnostic workup (Frederiksen et al. 2015). This is in keeping with our findings at GSH hospital based on the current practice and the database analysis.

The pathways in the decision tree which are represented by the costs in Table 11 illustrate the impact of TB diagnostic costs in TB endemic areas, with the highest prevalence of TB (prevalence 36% and OR 57) and the highest cost per disease diagnosis (US$ 14 597) of the four categories (‘TB’, ‘Lymphoma’, ‘Malignancy’ and ‘Other’) within our sample population. The two pathways which resulted in the shortest path to diagnosing TB was FNA, and FNA followed by CNB, hence making

these two pathways the least costly path to diagnosing TB. We noted a high prevalence of lymphoma in the sample. Due to the utilisation of Ultra, the TB pathway was truncated by being diagnosed with simple laboratory tests. 25 of the patients with lymphoma diagnosis (30% of the total outpatient cohort) were initially investigated using FNA (with the additional tests) as 'Other' or part of the 'non-conclusive' group, in 58 patients the FNA failed to make a diagnosis and the patient moved down the decision tree. The 'Other' part of the cohort (20 patients) either underwent a CNB or SEB procedure and 8 patients were diagnosed with lymphoma after a CNB procedure, thus a small number requiring repeat biopsy. Three outpatients were diagnosed as 'non-conclusive' and required an additional CNB which led to one out the three being diagnosed with lymphoma. Whilst one of the outpatients who received a SEB procedure, (which had a non-conclusive result), required a CNB to diagnose lymphoma. These patients would have remained undiagnosed or may have had a delayed diagnosis had the 76 outpatients not received access to the additional investigations of CNB or SEB to confirm their diagnosis.

Furthermore only 18 (22%) of the 83 outpatients received a confirmatory diagnosis from the initial baseline blood test and FNA procedure requiring no additional procedures. The other 78% of outpatients required an additional test and hence the cost increased with the maximum cost for diagnosis being US$ 877.

The seven patients who underwent CNB as their initial workup with baseline laboratory and radiology are estimated to have incurred a maximum of US$ 576 to confirm a diagnosis, thus two out the seven patients required an additional investigative test to confirm the diagnosis. From this we concluded that CNB was a less costly option to diagnose lymphoma, however the assumption is based on a small database (83 outpatients) and the proportion undergoing CNB was very small, which may not provide a fair comparison.

Literature review was limited from developing countries, in particular the Africa region, hence majority of the literature review was based on economic evaluation. Another limitation of this work is that we were unable to obtain prices from GSH for some of the equipment, consumables, laboratory and radiology testing, and so utilised market values. However, three quotes were obtained, and average prices

were utilized. The number of patients attending the outpatients was lower during the current global COVID-19 pandemic and this could alter the top-down calculations, thus possibly increasing the overhead cost significantly. We are aware that the public sector receives discounts on some items, however for some of the items we have used market values. As a general limitation, costing is context specific and so caution should be taken when generalizing this work to other settings.

6. Conclusion and Policy Recommendations

To our knowledge, this study has provided the first estimates of FNA, CNB, SEB procedures at a tertiary facility in South Africa, which has positive budgetary implications in tertiary hospitals in TB endemic areas. The study has provided a thorough analysis of the cost of the pathways taken to diagnose lymphoma and other diseases and can be incorporated into a future economic evaluation on investigating pathways to diagnosing lymphoma. Transparency was gained through ingredient-based and top-down costing approaches. Despite WHO recommended guidelines and management of LAP, the trend of SEB being considered as an initial investigative work-up has changed (Frederiksen et al. 2015) and the outpatients at GSH mainly follow the FNA plus CNB pathway. In TB endemic areas like SA, investigations to exclude TB is important and has an impact on the cost to manage LAP. When the outpatients followed the pathway of CNB as the initial investigative workup, the pathway to the confirmatory diagnosis was less costly. Given the resource-constrained environment in the South African health care system which is burdened by both the quadruple burden of disease and the COVID-19 pandemic (Standing Committee On Health 2020) and based on the outcome of the study, we recommend tertiary hospital decision-makers to considers the training and task shifting of CNB to other less costly medically trained personnel within the scope of practice as HPCSA sets out in its guidelines especially in the primary health care facilities, which could both reduce the personnel cost and improve the time to diagnosis for outpatients, which could have a positive impact for the effect of treatment and patient prognosis. GSH could consider CNB as the initial workup of the LAP due to the lower cost to the diagnosis of lymphoma and other diseases as a guideline to manage LAP. Training of

personnel at secondary-level hospital and primary-care clinics to conduct CNBs would reduce referrals and cost, with expediting the time to diagnosis. There will be value in additional research on a larger sample population with an estimation of the cost-effectiveness of CNB in comparison to SEB should be undertaken, as well as an expanded cost analysis from the patient's perspective

The use of single-use biopsy gun could be used more frequently as they result in a less costly procedure when compared to the re-usable Magnum Bard gun.

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8. Tables and Figures

Table 1: Overlapping symptoms, adapted from (Verburgh and Antel 2019)

Signs and Symptoms	Presentation	Confounders/ Differential Diagnosis
1. B -symptoms (triad described in presentation) (Verburgh and Antel 2019)	Inexplicable temperature >38°C, drenching night sweats, and >10% weight loss for the last six months.	Constitutional symptoms are confounded by other diseases like those that present with similar symptoms. These include HIV, TB, connective tissue disease, solid organ cancers, and endocrine conditions.
2. Significant LN	Non-painful LNs that are frequently equal in size and rubber hard texture. Whilst LN present typically for >3 weeks and are > 1,5 cm in size in lymphoma, the LN can present as a smaller LN in lymphoma	Other conditions that present with peripheral LN that can confound the diagnosis of lymphoma include viral conditions like HIV, herpes; bacterial infections like Staphylococcus aureus, TB; malignancy, and connective tissue disease. (Mohseni et al. 2014).
3. Cytopenia	Lymphomas invade the bone marrow suppress normal cell production and commonly result in anaemias.	Other haematological confounders include acute myeloid leukaemia's (AML) or myelodysplastic syndrome (MDS). The differential diagnosis for cytopenia is wide and traverses across many systematic and immunological conditions.
4. Lymphocytosis	Due to the spill of tumour cells into the bloodstream, typically after bone marrow invasion. These blood-	A differential blood count is often not requested and is one of the pitfalls of diagnosing lymphoma. It is recommended that a white cell count (WCC) be included in a differential count and abnormal

	borne cells are easily diagnosed as cancer cells.	haemoglobins done in hospital wards should be followed by full blood counts (FBC), differential counts, and blood film.
5. Tumour masses	The masses grow indolently in body cavities and later cause dysfunction of the organs resulting in symptoms like mediastinal masses, pleural effusions, or in the case of B cell lymphoma can cause gastrointestinal obstruction.	Histological diagnosis is the key to establishing the cause of the tumour mass and is supported by imaging. In young patients, lymphoma is the primary cause of mediastinal masses and is an important differential diagnosis of lung cancer in all ages. In TB endemic areas, patients presenting with pleural effusions are commonly commenced on empiric TB treatment, which is acceptable, however, it is recommended that they are followed up two weeks later with lymphoma being considered as the differential diagnosis.

Table 2. Comparison of the different investigative methods of LAD

FNA	CNB/USCNB	SEB
1. Safe and simple technique	1. Safe and simple technique	1. Gold standard for the diagnosis of lymphoma
2. Quickly and easily performed as an inpatient or outpatient investigation	2. Quickly and easily performed as an inpatient or outpatient investigation	2. Requires planning of theatre time and multi-disciplinary team-lead to delays
3. Minimally invasive	3. Less invasive than SEB	3. Invasive, mostly done as an inpatient
4. Assist with evaluation of unexplained LAP	4. Alternative investigation for LAP in high-risk patients for theatre and deep-seated LNs	4. Technique recommended for the investigation of LAP, used for small LAP
5. Inexpensive technique, few resources required	5. More resources required, but less than a SEB	5. More resources required than FNA and CNB
6. Distorts sampling tissue architecture	6. Retains tissue sample architecture, larger gauge needle used	6. Retains the tissue architecture and the whole lymph node is removed
7. Limited diagnostic yield when compared to CNB and SEB	7. Better diagnostic yield than FNA	7. Better diagnostic yield than FNA and CNB
8. Low risk of complications	8. Low risk of complications	8. Higher risk of complications than CNB and FNA

9. Can be performed lower cadre of staff	9. Required trained operators and can be performed by a lower cadre of staff	9. Required trained operators and can be performed by a lower cadre of staff
10. Minimal complications	10. Complications: haemorrhage, nerve injury, pneumothorax, tumour seeding.	10. Complications: wound infection, scarring, anaesthetic
11. Recommended as the first-line investigation in TB endemic areas	11. Utilises a Magnum BARD® gun, or single-use biopsy gun	11. Removal of the entire lymph node through
12. Performed with or without an ultrasound	12. Performed with or without an ultrasound	12. Performed with or without an ultrasound
13. Local anaesthetic	13. Local anaesthetic	13. Local anaesthetic

Figure 1: Novel investigative pathway used to diagnose Lymphoma, adapted from Antel (2021)

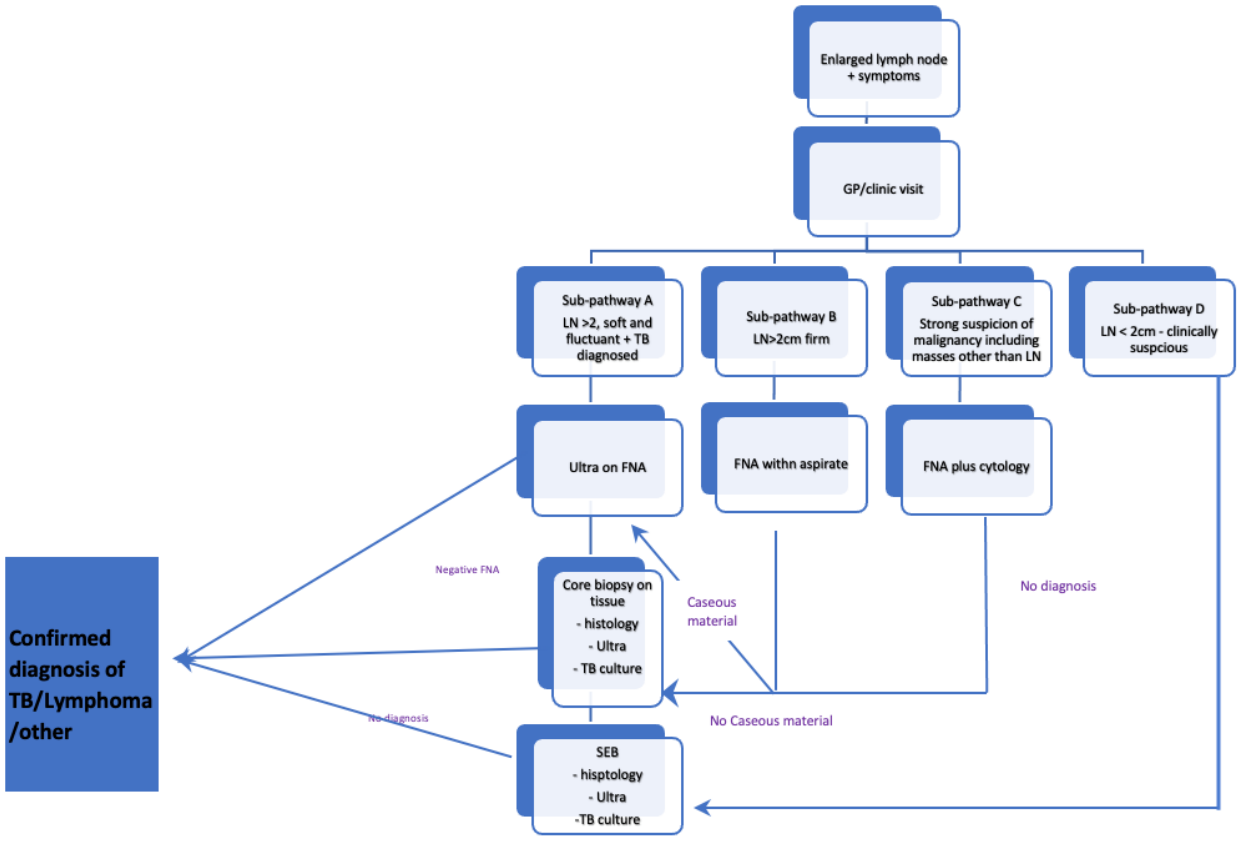


Table 3: Demographics and Disease Prevalence in sample population (n=83)

	Females	%Prevalence	Males	%Prevalence	Totals	%Prevalence
Totals	n	%	n	%		%
TB	12	14,46%	10	12,05%	22	26,51%
Lymphoma	7	8,43%	12	14,46%	19	22,89%
Malignancy	10	12,05%	6	7,23%	16	19,28%
Other	16	19,28%	10	12,05%	26	31,33%
					Totals	
White	5	6,02%	1	1,20%	6	7,23%
Black	17	20,48%	16	19,28%	33	39,76%
Mixed	21	25,30%	13	15,66%	34	40,96%
unknown	0	0,00%	3	3,61%	3	3,61%
other	2	2,41%	5	6,02%	7	8,43%
						0,00%
					Totals	
20-29	6	7,23%	3	3,61%	9	10,84%
30-39	13	15,66%	15	18,07%	28	33,73%
40-50	11	13,25%	8	9,64%	19	22,89%
>50	15	18,07%	12	14,46%	27	32,53%
Mean Age					45,08	

Table 4: Summary of FNA procedural cost estimate

FNA	Annual cost for outpatients in ZAR 2021	Annual cost for outpatients in US$ 2021	Cost per outpatient in ZAR 2021	Cost per outpatient in US$ 2021
Capital				
Building	R 1 133,48	$ 73	R 94,46	$ 6
Furniture	R 200,97	$ 13	R 16,75	$ 1
Equipment	R 80,86	$ 5	R 6,74	$ 0
Total capital	R 1 415,31	$ 91	R 117,94	$ 8
Recurrent				
Personnel	R 16 341,08	$ 1 051	R 1 361,76	$ 88
Consumables medication	R 620,56	$ 40	R 51,71	$ 3
Overheads and maintenance	R 4 453,44	$ 287	R 371,12	$ 24
FNA procedure test	R 148,96	$ 1 179	R 1 526,31	$ 98
Total recurrent cost	R 21 564,05	$ 2 557	R 3 310,90	$ 213
Total procedure cost	R 24 394,67	$ 2 739	R 3 546,79	$ 228
Other investigations				
Urine LAM test	R 3 264,00	$ 210	R 272,00	$ 18
Base line lab test and radiology	R 17 687,40	$ 1 138	R 1 473,95	$ 95
Total cost	R 45 346,07	$ 4 087	R 5 292,74	$ 341

**Medication refers to the local anesthetic utilised in this procedure*

Table 5: Summary of CNB procedural cost estimate

CNB	Annual cost for outpatients in ZAR 2021	Annual cost for outpatients in US$ 2021	Cost per outpatient in ZAR 2021	Cost per outpatient in US$ 2021
Capital				
Building	R 12 400,65	$ 798	R 93,94	$ 6
Furniture	R 2 198,65	$ 141	R 16,66	$ 1
Equipment	R 1 660,42	$ 107	R 12,58	$ 1
Total capital	R 16 259,72	$ 1 046	R 123,18	$ 8
Recurrent				
Personnel	R 180 247,62	$ 11 598	R 1 365,51	$ 88
Consumables medication	R 94 528,34	$ 6 083	R 716,12	$ 46
Overheads and maintenance	R 48 987,81	$ 3 152	R 371,12	$ 24
CNB procedure test	R 138 091,80	$ 8 886	R 1 046,15	$ 67
Total recurrent cost	R 461 855,56	$ 29 719	R 3 498,91	$ 225
Total procedure cost	R 494 375,01	$ 31 811	R 3 745,27	$ 241
Other investigations				
Urine LAM test	R 35 904,00	$ 2 310	R 272,00	$ 18
Base line lab test and radiology	R 194 561,40	$ 12 519	R 1 473,95	$ 95
Total cost	R 724 840,41	$ 46 641	R 5 491,22	$ 353

Table 6: Summary of SEB procedural cost estimate

SEB	Annual cost for outpatients in ZAR 2021	Annual cost for outpatients in US$ 2021	Cost per outpatient in ZAR 2021	Cost per outpatient in US$ 2021
Capital				
Building	R 55 962,09	$ 3 601	R 388,63	$ 25
Furniture	R 7 150,29	$ 460	R 49,65	$ 3
Equipment	R 558,52	$ 36	R 3,88	$ 0
total capital	R 63 670,89	$ 4 097	R 442,16	$ 28
Recurrent				
Personnel	R 209 773,63	$ 13 498	R 1 456,76	$ 94
Consumables medication	R 161 000,84	$ 10 360	R 1 118,06	$ 72
Overheads and maintenance	R 53 441,24	$ 3 439	R 371,12	$ 24
SEB procedure test	R 150 645,60	$ 9 694	R 1 046,15	$ 67
Total recurrent cost	R 574 861,32	$ 36 990	R 3 992,09	$ 257
Total procedure cost	R 702 203,10	$ 45 184	R 4 876,41	$ 314
Other investigations				
Urine LAM test	R 39 168,00	$ 2 520	R 272,00	$ 18
Base line lab test and radiology	R 212 248,80	$ 13 657	R 1 473,95	$ 95
Total cost	R 953 619,90	$ 61 362	R 6 622,36	$ 426

Table 7: Baseline test with the cost for Initial work-up and additional test

Baseline investigations				
Laboratory and radiology	Cost in ZAR		Cost in US$	
FBC	R	65,19	$	4
DIFF	R	35,74	$	2
LDH	R	102,57	$	7
U and E	R	95,81	$	6
HIV Elisa	R	62,01	$	4
CD4 Count	R	204,08	$	13
Gene Xpert	R	215,70	$	14
Sputum AFB	R	27,74	$	2
Sputum TB culture	R	84,78	$	5
Chest x-ray single view	R	580,33	$	37
	R	1 473,95	$	95
Additional test				
Urine LAM	R	272,00	$	18

Table 8: The procedure laboratory cost

Laboratory test conducted on tissue samples				
FNA procedure tests				
Gene Xpert	R	215,70	$	14
TB auramine	R	30,36	$	2
TB ZN	R	19,50	$	1
TB culture	R	84,78	$	5
FNA cytology	R	1 175,97	$	76
Total	R	1 526,31	$	98
CNB procedure tests				
Gene Xpert	R	215,70	$	14
TB auramine	R	30,36	$	2
TB ZN	R	19,50	$	1
TB culture	R	84,78	$	5
Histology-PCR	R	695,81	$	45
Total	R	1 046,15	$	67
SEB procedure tests				
Gene Xpert	R	215,70	$	14
TB auramine	R	30,36	$	2
TB ZN	R	19,50	$	1
TB culture	R	84,78	$	5
Histology-PCR	R	695,81	$	45
Total	R	1 046,15	$	67

Table 9: CNB sensitivity analysis

Sensitivity analysis								
Total CNB cost	Equipment cost per patient		Consumables and medication		Cost per patient		Cost per CNB USD$	
CNB with US and Magnum BARD gun	R	138,37	R	716,12	R	3 747,87	$	241
CNB with US and single use gun	R	81,76	R	483,00	R	3 458,14	$	223
CNB without US and Magnum BARD gun	R	121,11	R	716,12	R	3 730,62	$	240
CNB without US and single use gun	R	64,51	R	483,00	R	3 440,89	$	221

Table 10:

Sensitivity analysis when task shifting								
Procedure type	**Intern procedure**	**Intern consult**	**Number of Outpatients**	**Total for Procedure per annum with consult**	**Total for procedure per annum with Consult ($)**	**Total for procedure per annum without consult**	**Total for procedure per annum without consult ($)**	
FNA	R 287,03	R 280,29	12	R 6 807,85	$ 438,06	R 3 444,34	$ 221,63	
CNB	R 274,06	R 280,29	132	R 73 174,32	$ 4 708,52	R 36 175,70	$ 2 327,78	
SEB	R 288,33	R 415,80	144	R 101 395,79	$ 6 524,47	R 41 520,12	$ 2 671,68	
Procedure type	**Community Service MO procedure**	**Community Service MO consult**	**Number of Outpatients**	**Total for procedure per annum with consult**	**Tota for procedure l per annum with Consult ($)**	**Total for procedure per annum without consult**	**Total for procedure per annum without consult ($)**	
FNA	R 335,76	R 363,84	12	R 8 395,18	$ 540,20	R 4 029,14	$ 259,26	
CNB	R 325,58	R 363,84	132	R 91 002,54	$ 5 855,70	R 42 976,15	$ 2 765,37	
SEB	R 330,11	R 499,35	144	R 119 441,22	$ 7 685,63	R 47 535,26	$ 3 058,73	
Procedure type	**Medical officer procedure**	**Medical officer consult**	**Number of Outpatients**	**Total for procedure per annum with consult**	**Total for procedure per annum with Consult ($)**	**Total for procedure per annum without consult**	**Total for procedure per annum without consult ($)**	
FNA	R 462,16	R 580,52	12	R 12 512,13	$ 805,11	R 5 545,91	$ 356,86	
CNB	R 459,20	R 580,52	132	R 137 242,39	$ 8 831,08	R 60 614,04	$ 3 900,30	
SEB	R 438,45	R 716,03	144	R 166 244,45	$ 10 697,26	R 63 136,34	$ 4 062,61	

Table 11: Prevalence of disease between November 2017 and October 2018 in the sample population

Procedures to Confirmed diagnosis	Prevalence	Odds Ratio (OR)	Cost per disease
TB	36,14%	56,60%	$ 14 597
Lymphoma	25,30%	33,87%	$ 12 270
Malignancy	18,07%	22,06%	$ 8 800
Other	20,48%	25,76%	$ 7 759

Table 12: Cost of the pathway based on the procedures (n=83)

	TB	Lymphoma	Malignancy	other	Cost for diagnosis	Total number of procedures conducted for diagnosis	Total cost of procedures
FNA	11	0	0	7	$ 323,07	18	$ 5 815
CNB		2	1	2	$ 335,84	5	$ 1 679
FNA+CNB	17	15	11	7	$ 564,06	50	$ 28 203
FNA+ SEB+CNB	0	1	0	0	$ 877,84	1	$ 878
FNA+CNB+CNB	0	1	1	0	$ 805,06	2	$ 1 610
FNA+CNB+SEB	1	1	1	1	$ 877,84	4	$ 3 511
CNB+CNB	1	1	1	0	$ 576,83	3	$ 1 731
	30	21	15	17		83	$ 43 427

PART D: APPENDICES

A comparative cost analysis of two pathways to diagnosing lymphoma in a tertiary hospital, Western Cape, South Africa

Appendices

Appendix 1

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45-E52- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

28 October 2021

HREC REF: 691/2021

Dr L Cunnama
Health Economics Unit
Falmouth Building -FHS
Email: Lucy.cunnama@uct.ac.za
Student: frdwaa001@myuct.ac.za

Dear Dr Cunnama

PROJECT TITLE: A COMPARATIVE COST ANALYSIS OF TWO PATHWAYS TO DIAGNOSING LYMPHOMIA IN A TERTIARY HOSPITAL, WESTERN CAPE, SOUTH AFRICA-MASTERS CANDIDATE- DR WAARISA FAREED-BREY-SUB-STUDY LINKED TO 829/2020

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020; 06 July 2020 & 01 July 2021.

Approval is granted for one year until the 30 October 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

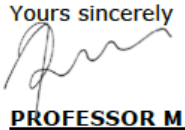
The HREC acknowledge that the student: Dr Waarisa Fareed-Brey will also be involved in this study.

Please quote the HREC REF 691/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely



PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 2

Western Cape Government

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: GSHReserach.Request@westerncape.gov.za

DR LUCY CUNNAMA
HEALTH ECONOMICS UNIT

E-mail: lucy.cunnama@uct.ac.za

Dear Dr Cunnama

RESEARCH PROJECT: A Comparative Cost Analysis of Two Pathways to Diagnosing Lymphoma in a Tertiary Hospital, Western Cape, South Africa. Masters Candidate: Dr Waarisa Fareed-Brey

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 October 2022.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) Kindly submit a copy of the publication or report to this office on completion of the research.
n) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.
o) Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 12 January 2022

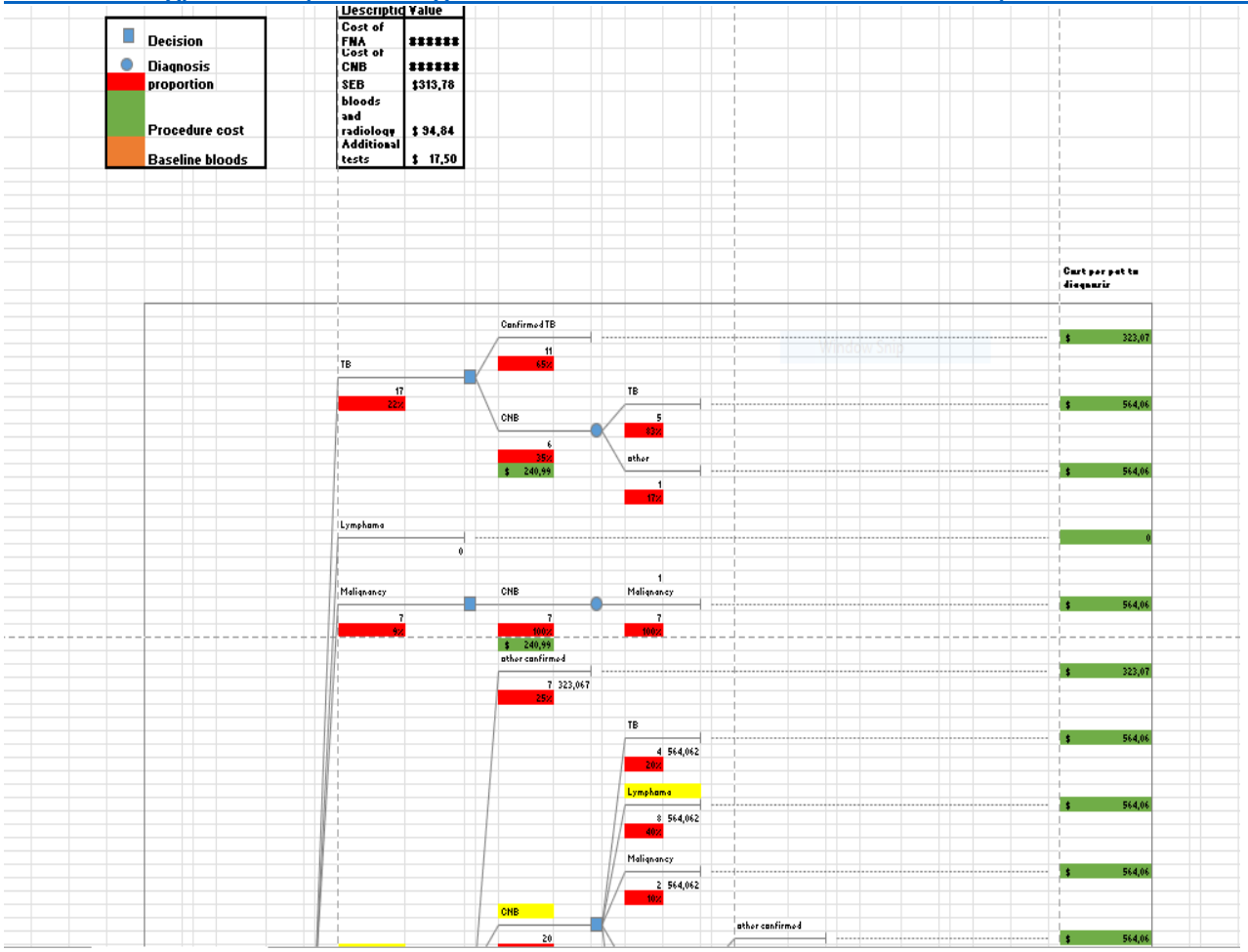
C.C. Mr. L. Naidoo, Dr. B. Jacobs, Mr. A. Mohamed

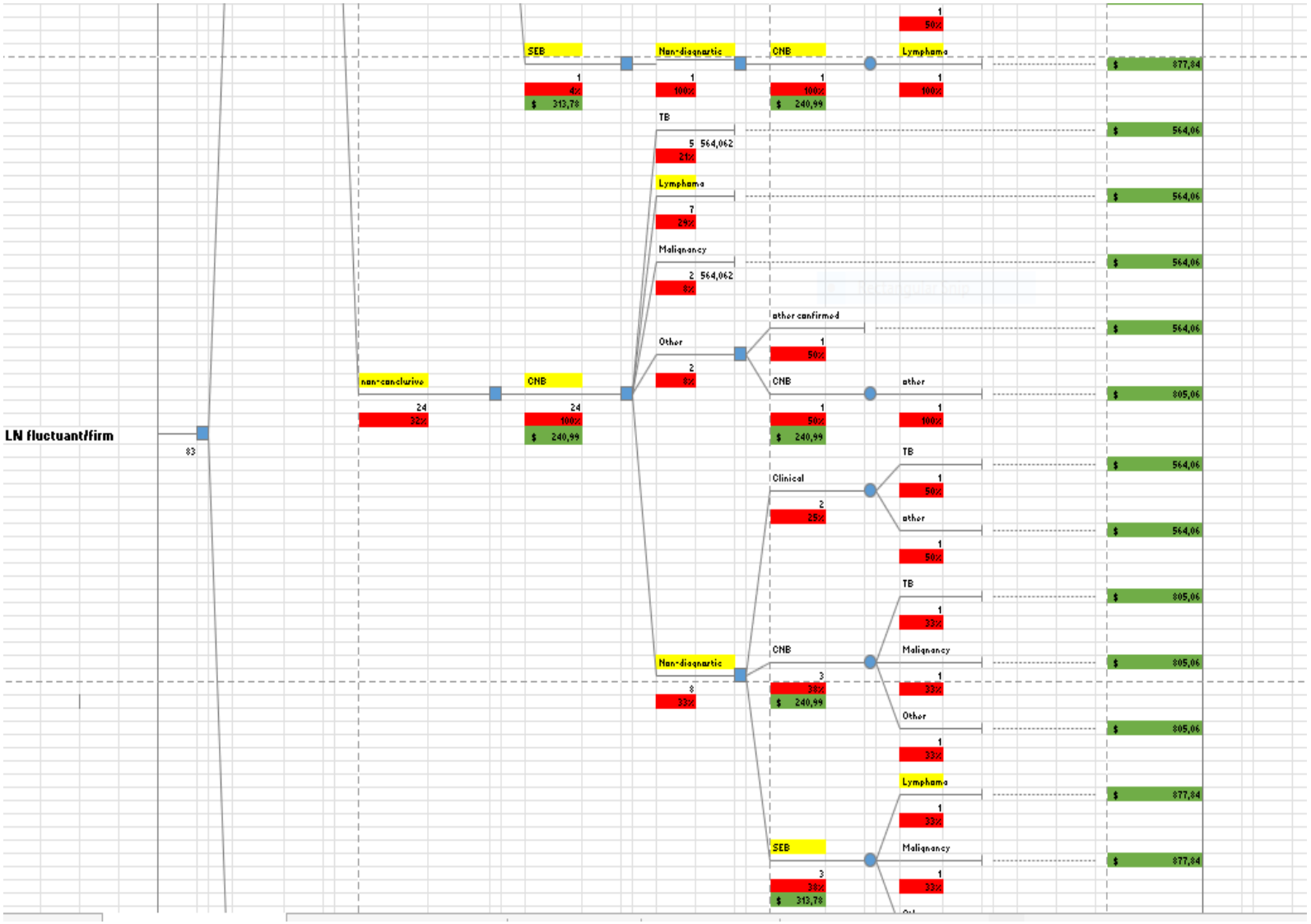
G46 Management Suite, Old Main Building,
Observatory 7925
Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935
www.westerncape.gov.za/health

Appendix 3

Link to the Decision Tree: https://docs.google.com/spreadsheets/d/1k1MLdxXQ1vRmxVtEo62DpC-55Xa_mABg/edit?usp=sharing&ouid=102719875255819137954&rtpof=true&sd=true

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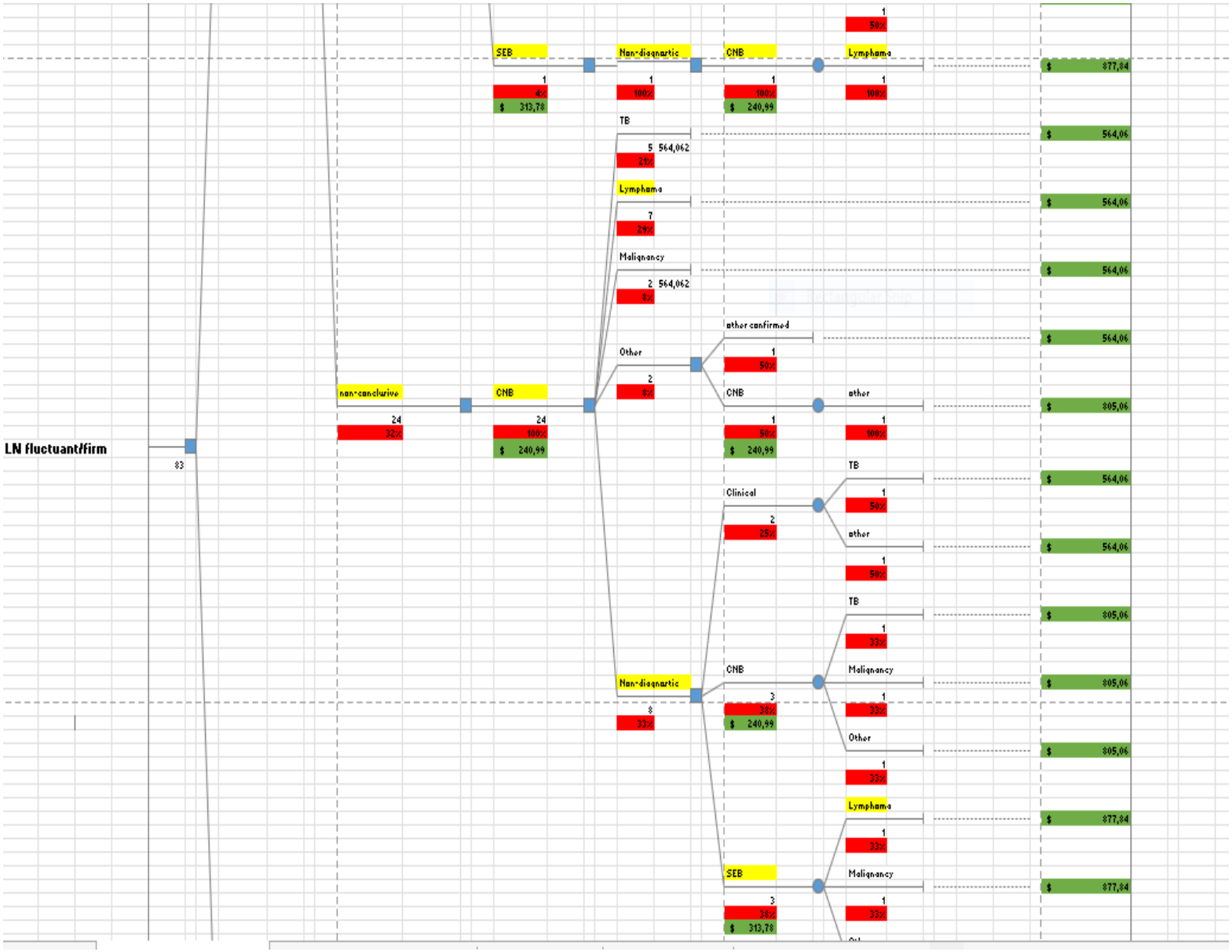
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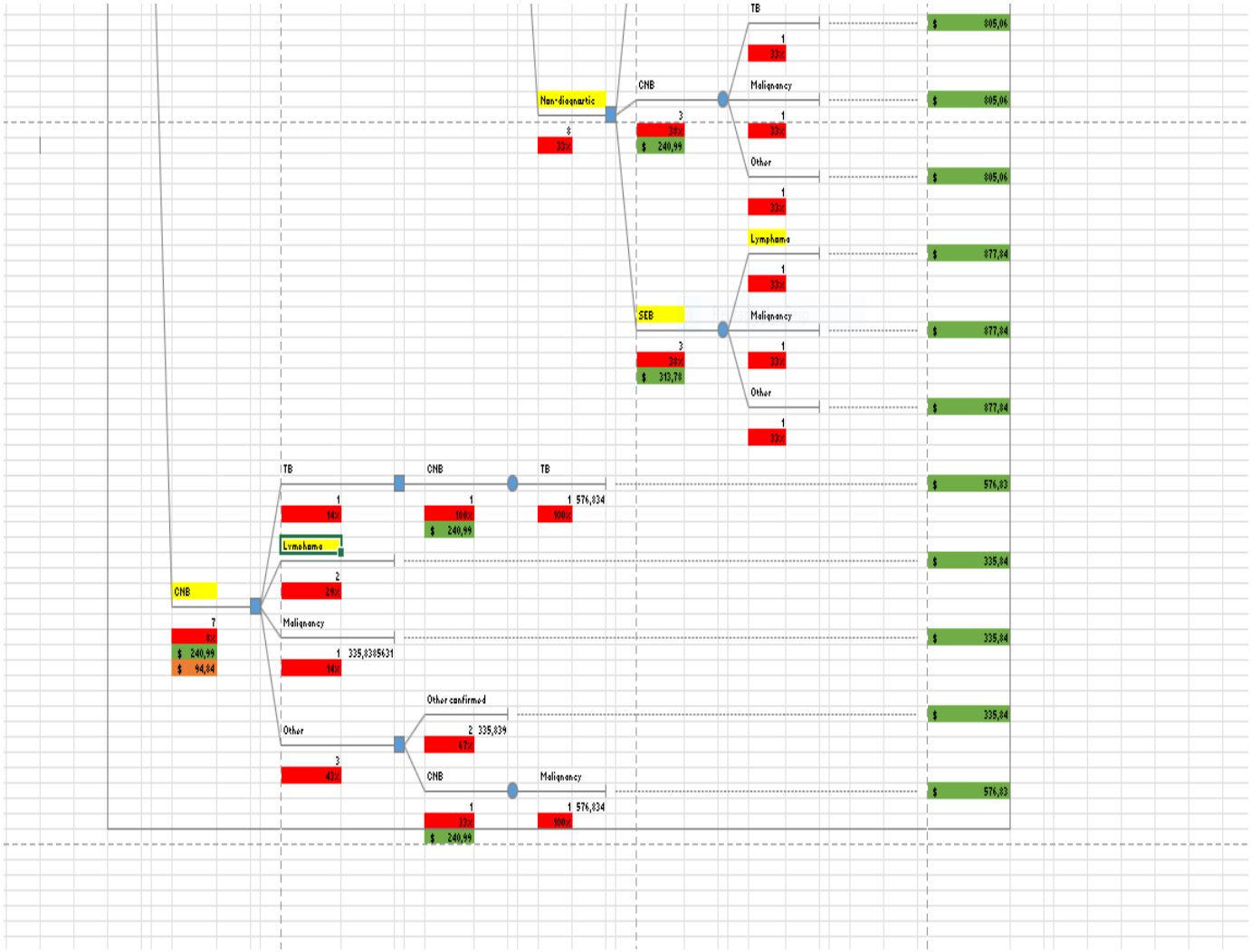
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Appendix 4: Authors instruction

Instructions for authors

Health Economics, Policy, and Law

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Guest editorials will be invited pieces in which authors will provide a short, analytical commentary on a topical issue. The recommended length for guest editorials is 2,000 words. Some issues of the journal may also contain review articles (5,000 words) and debate essays (3,000 words). Review articles will feature a discussion of two or three books on a related theme while debate articles will assess an area within the scholarly disciplines or policies pertinent to health. For specific comments on the appropriateness of an idea for a review article, debate essay or a research article generally, please contact Adam Oliver at a.j.oliver@lse.ac.uk.

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1. Manuscripts should be clearly typed in double spacing and should have a left-hand margin of at least 25 mm/1 inch and a right-hand margin of at least 40mm/1.5 inches. Type size should be no smaller than 12 points. Contributors are asked to retain an exact replica themselves for use in answering copy-editor's enquiries and correcting proofs.
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Le Grand, J. (2003), *Motivation, agency, and public policy: of knights & knaves, pawns & queens*. Oxford: Oxford University Press.
Harsanyi, J.C. (1982), 'Morality and the theory of rational behaviour', in A. Sen and B. Williams (Eds), *Utilitarianism and beyond*. Cambridge: Cambridge University Press.

Arrow, K.J. (1963), 'Uncertainty and the welfare economics of medical care', *American Economic Review*, 53(5): 941-73.

4. Tables and Figures. Each table and figure should be on a separate sheet, numbered and collected together at the end of the article, after the References. Their place in the text should be indicated by a space and the words 'Table X (Figure X) about here'. Tables should be clearly laid out and designed to fit into a space 190 x 120mm. Vertical lines between columns should be omitted, and horizontal lines limited to the top and bottom of the table, with an additional line below the column headings. Totals and percentages should be labelled, and units identified. Figures should not contain more detail than can be clearly shown in a space 190 x 120mm.

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Last updated 5th May 2020

Appendix 6: HREC amendment request and approval

School of Public Health and Family Medicine
Isikolo Sempilo Yoluntu kunye Namayeza Osapho
Departement Openbare Gesondheid en Huisartskunde

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25th January 2022

Professor Blockman
Faculty of Health Sciences
Human Research Ethics Committee

Dear Professor Blockman,

Re: A comparative cost analysis of two pathways to diagnosing lymphoma in a tertiary hospital, Western Cape, South Africa – Request for minor change to approval

HREC approval reference: 691/2021

The following documents are attached:

1. Current HREC approval
2. Secondary database approval (and annual progress report/ renewal)

I would like to reference our previous ethics approval dated 28 October 2021. The study aims to provide the costs of the two pathways to diagnose lymphoma, namely the novel and standard pathway options, based on the algorithm proposed by Antel (2021). The initial proposed study protocol anticipated we would utilise data collected in 2016 to diagnose lymphoma at Groote Schuur Hospital (GSH), however after deliberation our preference is to utilise data collected at the lymph node clinic at GSH (with previous approval reference HREC (674/2017)) with the purpose to inform policy-making decisions and process guidelines through provision of cost and cost-effectiveness data.

The main study was conducted in 2017 and updated progress was approved until the 30 November 2022 (HREC approval (674/2017)). The proposed study is being conducted as part of Dr. Waarisa Fareed-Brey's Master's in Public Health (MPH) dissertation specialising in Health Economics.

Please contact me for any further information that may be required.

Sincerely,

Dr. Lucy Cunnama

Senior Lecturer
Health Economics Unit and Health Economics Division
School of Public Health and Family Medicine
Faculty of Health Sciences, University of Cape Town

School of Public Health and Family Medicine
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Health Economics Unit and Health Economics Division
School of Public Health and Family Medicine
Faculty of Health Sciences, University of Cape Town

PART E: Policy Brief

A comparative cost analysis of two pathways to diagnosing lymphoma in a tertiary hospital, Western Cape, South Africa

HIGHLIGHTS

SEB is the technique of choice for the investigation of investigation of enlarged lymph nodes as recommended by the World Health Organisation and many other research groups

The trend is changing, and more clinicians are using CNB in South Africa

In the study conducted at GSH, FNA was shown to be the least costly procedure, but additional tests were required to confirm the diagnosis

The pathway to diagnosis lymphoma diagnosis lymphoma was costed and when CNB was used it costed US$ 576 compared to FNA which costed up to US$ 877 to make a diagnosis

The main cost driver was the staff time required to perform the procedures

The CNB procedure costed less when a single use biopsy gun was used compared to the Magnum BARD® multi-use gun

Title: What is the least costly pathway to diagnose Lymphoma (cancer) in South Africa?

Executive Summary

Large lymph nodes are a concern for patients and doctors and the need to diagnose the cause accurately is vital. In developing countries like South Africa with high numbers of people living with tuberculosis, the diagnosis is often missed or delayed due to overlapping symptoms. A pathway was proposed by a study conducted at Groote Schuur Hospital (GSH) to improve the time to diagnose and make diagnosing the cause of enlarged lymph nodes accurate (Antel et al., 2019); however, without the cost of the pathway to diagnosis, it makes it difficult for decision-makers to assess the budgetary implications. A costing study was done at GSH to evaluate the cost of each pathway, which showed that when a core needle biopsy was performed first, the cost of making a diagnosis was cheaper than starting with other procedures.

What is lymphoma?

Lymphoma is a cancer of the lymph nodes. Lymph nodes are little bumps you feel when your body is fighting an infection, these bumps help to fight the infection and increase in size when doing so. When you have cancer of these bumps, they also increase in size

Introduction

In countries like South Africa where we live with tuberculosis (TB), people are often diagnosed with TB when they have enlarged lymph nodes due to overlapping symptoms like a cough, fever (higher than 38°C), weight loss for six months, and profuse sweating at night (Verburgh and Antel, 2019, Antel and Verburgh, 2019). Despite us having the best tests to exclude TB, these overlapping symptoms of lymphoma, cancer, and other disease are often not diagnosed correctly or there is a delay in diagnosing them which leads to patients coming for help when they are very ill (Bosch et al., 2014).

Another challenge we face in South Africa is that patients living with HIV (human immunodeficiency virus) have an increased risk of developing lymphoma even when on treatment (antiretrovirals). During the COVID-19 pandemic, we faced additional challenges as a country, with certain health services being made unavailable, lockdown, and people living in fear of getting COVID-19 who did not go to hospitals. The overlapping symptoms of the diseases, higher risk in patients living with HIV, and the need to diagnose correctly led to a study being conducted by at Groote Schuur Hospital (GSH) which suggested a pathway to diagnosing the cause of enlarged lymph nodes, in particular lymphoma (Antel, 2021). The pathway (Figure 1) follows a different route which includes three different procedures to make the correct diagnosis. The three procedures include:

Fine needle aspirate (FNA): in this technique, a small sample is taken from the lymph node by inserting a fine needle into the lump. The tissue is placed on a slide and sent to the laboratory for tests to make a diagnosis. This is done in the doctor's rooms and at the time of consulting the doctor.

Core needle biopsy (CNB): this technique is done using a biopsy gun (which helps to hold the needle steady) to obtain a small sample using a needle which is slightly larger than the tissue obtained from the FNA and is sent to the laboratory for testing to help make a diagnosis. The procedure is done in the doctors rooms and sometimes the doctor uses an ultrasound machine.

Surgical excision biopsy (SEB): this is a technique done in theatre to remove the lymph node which is then sent to the laboratory for testing. SEB is the technique of choice recommended by the World Health Organisation and many other research groups. (Seviar et al., 2021, Cuenca-Jimenez et al., 2021, Johl et al., 2016)

A study was then conducted in 2021/2022 by the University of Cape Town, Health Economics Unit to cost the pathways from the health providers' view and to determine which was the least costly pathway to diagnose enlarged lymph nodes in particular lymphoma

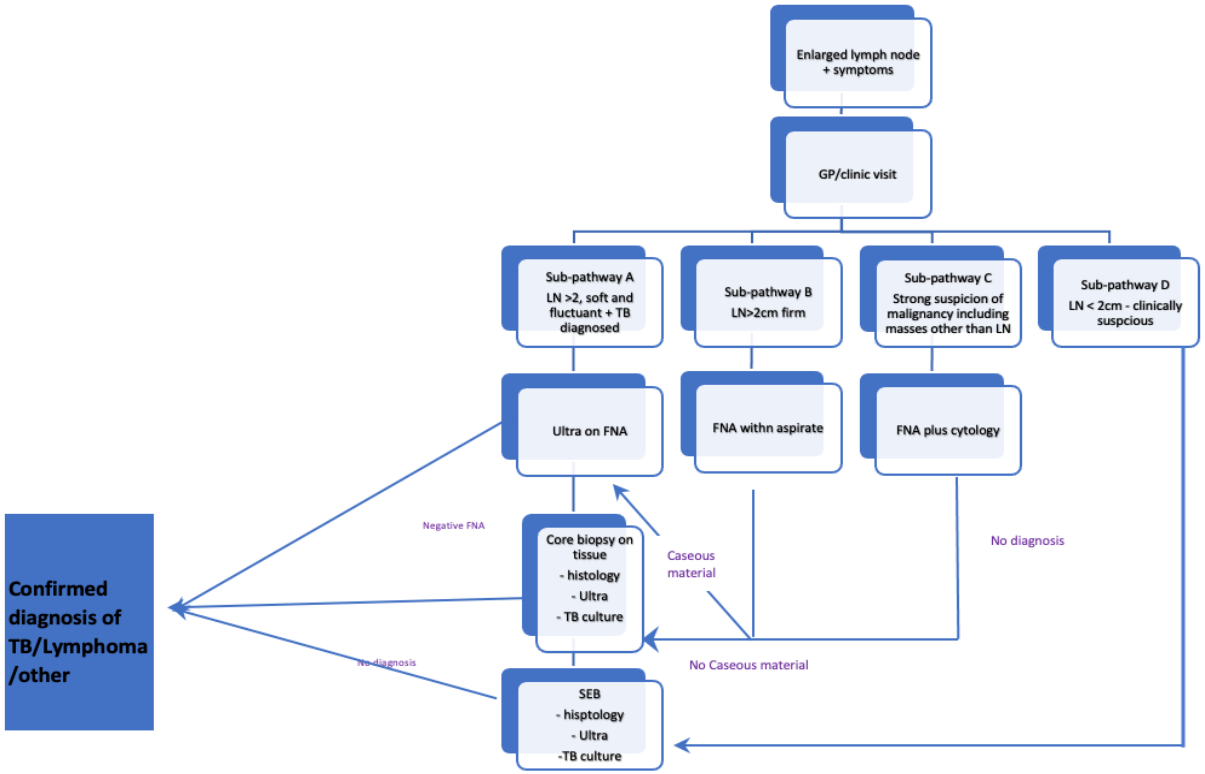

Figure 1: Novel investigative pathway used to diagnose Lymphoma, adapted from Antel (2021)

Approach

The study was conducted at GSH in the Western Cape. This is a tertiary hospital, so patients can only access the hospital services by being referred by primary and secondary clinics or hospitals. Information on 99 patients was obtained from another study conducted between November 2017 and October 2018 (13 months) after receiving approval from the Human Research Ethics Committee and GSH. A simple cost analysis was completed on 83 outpatients (patients not sleeping over at the hospital) and inpatients were excluded. The costing was completed using the information obtained from the three different clinics (REDCAP 'lumps and bumps', Acute

Care clinic, and ‘lumps and bumps’ clinic) where the procedures are currently being performed. FNA and CNB are performed at the REDCAP ‘lumps and bumps’ clinic, whilst SEB is performed at the Acute care and ‘lumps and bumps’ clinic in theatre. The list of items used, persons required for each procedure, and measuring the spaces used for the procedures was obtained through online and site interviews and site visits to the clinics.

Once the information was gathered, prices were obtained from pharmaceutical companies, online shopping websites, and GSH. The actual value per square metre was calculated by using a tool that is usually used by the department of infrastructure to calculate the building cost (CSIR; Department of Health Infrastructure Unit, 2012). The cost of each procedure, initial test work-up tests, and additional tests were calculated. Some of the costs were estimated on allocated time to procedure and the number of patients attending the clinic. The cost was plotted onto a pathway that the 83 outpatients followed. This enabled the researcher to estimate the cost of a diagnosis for the different routes followed and calculate the number of people who currently have a particular disease.

Procedure type	Cost
FNA	$ 228
CNB	$ 241
SEB	$ 257
Initial tests	$ 95
Additional tests	$ 18

Table 1: Unit cost per procedure

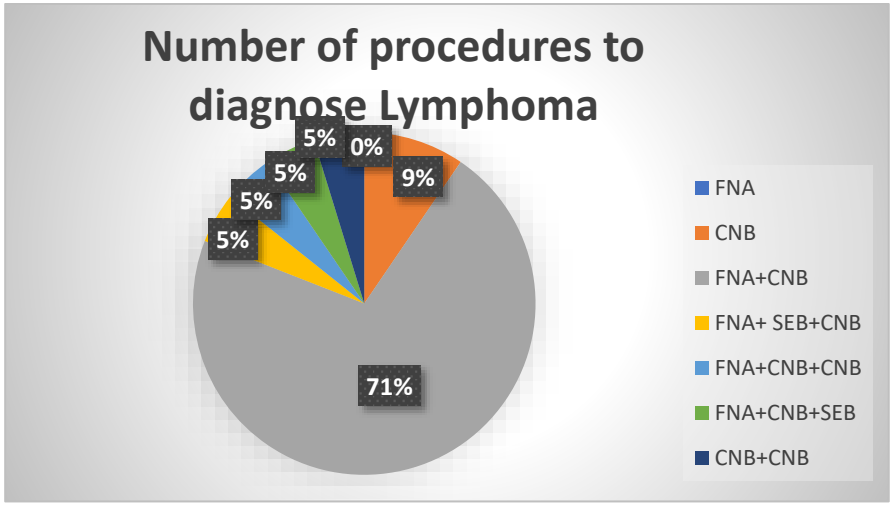

Figure 2: Proportion of procedures in the pathway

Key Findings:

The clinics were attended by more males (46%) than females (54%). However, more females (15%) were diagnosed with TB than males (12%) and more males (15%) were diagnosed with lymphoma compared to females (8%) (see Figure 3)

- The cost of each procedure is indicated in Table 1 with FNA as a standalone test being the least costly.
- For all the procedures the main cost driver was people required for the procedure followed by the tests sent to the laboratory for diagnosis in FNA and CNB and for SEB the second highest cost driver was the cost of the products required for the procedure.
- The cost of CNB increased by $1 when an ultrasound machine was used and by 8 % when the Magnum BARD multi-use gun was used compared to the single-use gun which was less cost costly.
- When FNA was used at the initial procedure, additional tests were required to confirm the diagnosis which increased the cost. The pathway was followed for FNA and CNB as the initial test used to investigate the patient. The route that followed CNB was to diagnose lymphoma was estimated at US$ 576 and the path that followed FNA as the initial test to diagnose lymphoma was between US$ 564 and US$ 877 and 71% required FNA and CNB for a diagnosis.
- Based on the setting and in keeping with other research in SA (Antel et al., 2019) the diagnosis that contributed to the highest cost was TB followed by lymphoma.

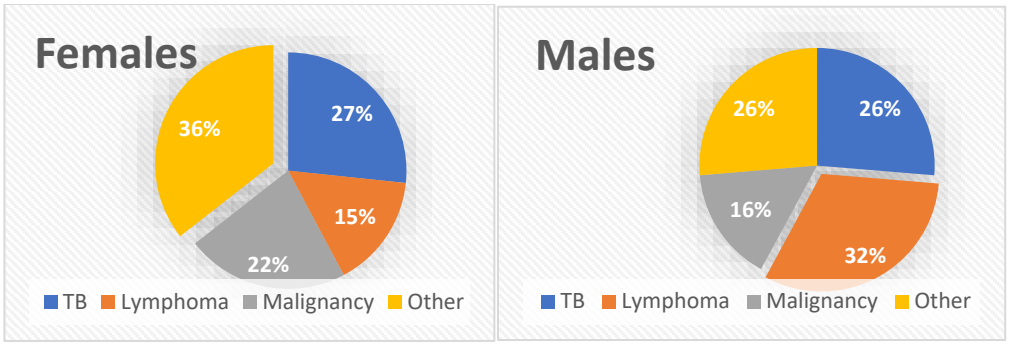

Figure 3: Disease conditions male versus female

Conclusion

- The WHO recommends SEB as the test of choice to diagnose the cause of enlarged lymph nodes, however, over time more clinicians have started using CNB.
- The cost analysis of the pathway has shown that even though the FNA procedure cost the least from all 3 procedures additional procedures were required to make a diagnosis, which meant it would cost more to make a diagnosis when FNA was used as the initial test.
- The least costly route to diagnosing lymphoma and other diseases is to use CNB as the initial test to investigate enlarged lymph nodes.

Policy Recommendations

- To decrease the cost at tertiary hospitals decision-makers should consider the training of medical officers and interns to perform CNB in primary and secondary health care facilities
- To perform additional research studies on the cost and cost-effectiveness of CNB and SEB and the cost impact from a patient perspective
- Tertiary hospitals to consider using CNB as the initial work-up for patients with enlarged lymph nodes
- To consider the use of single-use biopsy guns which are less costly rather than the re-usable Magnum

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