Edge Health

Circulating Biomarker Network of Excellence

Health economic evaluation of liquid biopsy diagnostics in five high-impact cancer pathways

May 2025

Introduction

In recent years, the NHS has faced increasing pressure on its services, particularly in meeting targeted cancer waiting times for prompt diagnosis and treatment initiation. According to Cancer Research UK, only 67% of people in England were diagnosed and started their first treatment within 62 days of an urgent referral in February 2025, compared to the 85% national target. Furthermore, 91.8% of patients in England began their treatment within 31 days of deciding on a treatment plan, below the desired 96% target.

Against this backdrop, genomic testing for cancer patients is increasingly being used to inform cancer diagnosis, prognosis, and treatment. Certain genomic variants can indicate the most effective treatment options for a particular cancer. Currently, a key step in the diagnosis of tumours involves taking a tissue sample through biopsy. This sample is then used for both diagnostic purposes and genomic testing. However, obtaining genomic information through tissue biopsy poses numerous challenges, including procedural invasiveness, the risk of complications, difficulties with reproducibility, and occasional issues with sampling representativeness.

The emergence of circulating tumour DNA (ctDNA) testing has gained considerable momentum as an alternative method to obtaining genomic information. This less-invasive technology enables the detection of genetic variations, usually through a simple blood draw, and has been shown to overcome many of the challenges posed by tissue biopsies. Such a shift in the technology of testing can redefine the standard of care and utilistaion of health care resource in the NHS.

As part of the NHS's first genomics strategy, "Accelerating Genomic Medicine in the NHS", NHS England is funding eight networks to establish evidence and adoption models for advanced genomic technologies. Following Edge Health's previous commission by the NHS North Thames Genomic Medicine Service (NTGMSA) in June 2023 to assess the health economics of ctDNA testing for advanced lung cancer diagnosis, Edge Health was commissioned again in 2024 by one of these networks - the Genomic Network of Excellence (Circulating Tumour Biomarker Testing) as an evaluation partner.

The goal was to evaluate and consolidate evidence on the introduction of liquid biopsy testing across five high-impact cancer pathways in the UK, where its inclusion was expected to yield significant benefits. These pathways included:

1. **Cancer of unknown primary (CUP)**
2. **Hepato-pancreato-biliary (HPB) cancer**
3. **Germ cell tumour (GCT)**
4. **Advanced breast cancer**
5. **Paediatric cancer**

This report from Edge Health sets out the conclusion of this work, which is based on extensive engagement with the ctDNA Genomic Network of Excellence during it's first year of commission, subject matter experts, and literature review on the impact of ctDNA testing in each pathway. Evidence is still in its early stages and developing rapidly. Wherever possible, this review draws upon the available literature, supplemented by insights from discussions with clinicians involved in care delivery. While most benefits were quantified, certain areas required qualitative assessment due to a lack of evidence. Additionally, benefits related to future research and development advancements were also not included in this assessment. All the scenarios have been modelled using the UK population as a starting point.

For the paediatric cancer pathway, a mapping exercise was conducted however, quantitative assessment was not pursued as potential benefits were not clearly established following consultations with clinical experts. This pathway will be explored in more detail in the next year of the Genomic Network of Excellence.

The outputs of this work, including this report, are indicative.

Executive summary – health economics of ctDNA testing

This report evaluates the health economics of ctDNA testing across cancer of unknown primary (CUP), hepato-pancreato-biliary (HPB) cancer, germ cell tumour (GCT), advanced breast cancer, and paediatric cancer. The findings highlight how ctDNA testing can be implemented in different ways depending on the specific clinical and economic challenges within each pathway.

In the cases of CUP and HPB, the modelling showed that ctDNA testing could demonstrate traditional benefits by reducing the need for multiple tissue biopsies and the complications associated with them. It could also minimise the requirement for genomic testing on tissue samples for patients with positive results, shorten pathway timelines, and ease NHS resource pressures. However, challenges still remain. For HPB, while ctDNA testing showed promising sensitivity at 85%, pilot data revealed a considerably lower specificity of 58% which is critical for avoiding mistreatment. For CUP, the real value of testing was identified earlier in the pathway, where patients often move between specialties before referral to the CUP team. However, applying testing broadly at this stage involves an ill-defined population and highly variable pathways due to the heterogeneity of CUP presentations. Due to this, the scenario was not included in the modelling.

Meanwhile, the application of micro-RNA (miRNA) testing for germ cell tumours presented a novel use case where testing replaces costly imaging during long-term surveillance. The testing approach aims to address a challenge within the pathway by reducing costs associated with expensive 3D imaging, decreasing the need for MDT discussions, and minimising patient exposure to repeated CT and MRI scans. Importantly, while the performance analysis of the miR-371a-3p biomarker suggests a sensitivity and specificity of >90%, the extent of the economic benefit will ultimately depend on the clinical implementation of the test after further validation, and the unit cost when implemented at scale in the NHS.

For advanced breast cancer, ctDNA testing in the late stage unlocks access to targeted therapies for patients with actionable mutations like ESR1 and PIK3CA. At the time of the evaluation, it offered a potential solution to serve unmet needs and create a path to treatment that would otherwise be largely inaccessible due to the absence of a tissue-based pathway. With the recent approval of Elacestrant and addition of ESR1 testing on the test directory, an assessment of liquid biopsy ctDNA against the now-established tissue biopsy pathway is warranted to fully evaluate the relative costs and benefits.

Beyond the immediate benefits, including **ctDNA testing in CUP, HPB, and advanced breast cancer future proofs the pathways** for new therapeutics. The tests modelled already include relevant gene targets within existing panels, ensuring compatibility with both current and future treatment options.

The results of this assessment reveal a range of cost-benefit ratios, **from 0.8 in HPB cancer to 2.3 in GCT**. These differences highlight the importance of tailored implementation to realise the value of ctDNA testing across each pathway. While a cost-benefit ratio above 1 is generally desirable for implementation, the threshold may be higher where intangible benefits outweigh direct cost savings.

The report also underscores a key challenge, obtaining robust and high-quality evidence to accurately inform economic models. As the evidence base continues to develop, particularly through pilot studies and real-world data collection, there is a critical opportunity to refine and validate these findings and strengthen the evidence base further.

Executive summary – health economics of ctDNA testing

Indication	Benefits	Costs	Net Impact	BCR Ratio	Clinical/Economic Use Case
1. Cancer of unknown primary (CUP)	£8,744,147	£7,050,524	(+) £1,693,623	1.24	Added post-CUP MDT, ctDNA testing aims to streamline the pathway particularly when previous tissue samples are inadequate (~40%). It offers better success rates (80% vs 57% with tissue biopsy), aids tissue-of-origin diagnosis and enables more effective favorable treatments. However, with current test costs the ideal early inclusion scenarios is likely unviable.
3. Hepato-pancreato-biliary (HPB)	£19,267,446	£23,123,375	(-) £3,855,929	0.83	Added as a non-invasive adjunct to tissue biopsies, giving clinicians more confidence to proceed and reducing diagnostic loops where patients undergo repeated biopsies to due to lack of tissue. Testing achieved a sensitivity of 85% and a specificity of 58% when compared to gold-standard histology.
2a. Germ cell tumour (GCT) – CT scan scenario	£1,925,010	£1,420,979	(+) £504,031	1.35	Aims to provide a less invasive and cheaper potential alternative to routine imaging (CT/MRI) for surveillance post treatment, reducing radiation exposure and healthcare costs. Extent of full replacement in place of CT/MRIs may however require further clinical validation despite a sensitivity and specificity of >90%.
2b. Germ cell tumour (GCT) – MRI scan scenario	£2,527,335	£1,077,105	(+) £1,450,230	2.35	
4. Advanced breast cancer – large panel	--	--	--	--	Acts as a pathway to access novel therapies that improve progression-free survival (e.g., ESR1, PIK3CA targets) where existing tissue-based testing infrastructure was insufficient at the time of evaluation.
5. Advanced breast cancer – small panel	--	--	--	--	
6. Paediatric Cancer	--	--	--	--	

Quantified

Only QALY benefits quantified

Mapped but not quantified

Terminology note – use of "savings"

In this report *savings* is an umbrella term for positive economic impact of ctDNA testing—ranging from direct cash-releasing benefits to efficiency/capacity gains (e.g., fewer GP appointments, shorter pathways). Because the headline benefit-cost ratios aggregate these impacts they should be interpreted with care and readers should scrutinise, on a pathway-by-pathway basis, which benefits are genuinely budget-releasing versus those that improve service efficiency.

Contents

What is ctDNA testing, and what are the benefits and challenges in delivering it?

As precision medicine advances, genomic testing is increasingly used to guide cancer diagnosis, prognosis, and treatment. Traditional approaches rely on invasive tissue biopsies, which can be challenging when tumours are inaccessible or when repeat testing is required. Circulating tumour DNA (ctDNA) testing – a non-invasive liquid biopsy that detects tumour-derived genetic material in blood – offers a promising alternative. To realise the full benefits of ctDNA testing, it must replace, rather than supplement, tissue testing where appropriate, particularly to avoid duplication, reduce costs, and streamline diagnostic pathways.

Across the pathways evaluated in this report, ctDNA testing offers numerous benefits over standard diagnostic pathways, including:

- **Faster diagnosis and treatment decisions**, improving patient outcomes and quality of life by ensuring timely access to appropriate therapies.
- **Positive psychological effects** for patients due to faster diagnosis and treatment.
- **Streamlining diagnostic pathways**, resulting in shorter diagnostic timelines and reduced resource utilisation.
- **Reducing unnecessary costs and complications** by avoiding repeated biopsies and limiting molecular profiling when ctDNA results are sufficient.
- **Supporting access to targeted therapies**, particularly where tissue-based genomic testing is not routinely available or feasible.
- **Enhanced surveillance**, enabling ongoing disease monitoring through a less invasive approach.

However, potential challenges also include:

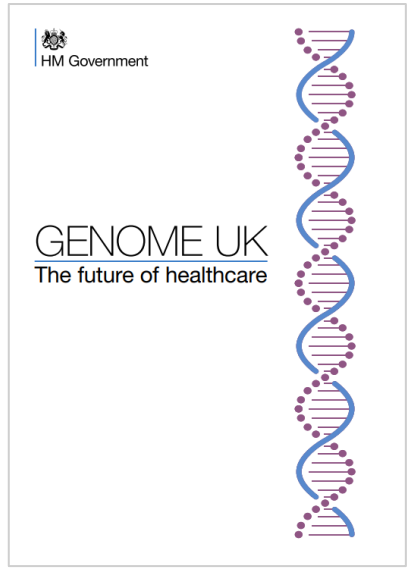
- **Logistical and financial costs** associated with implementing tests at scale.
- **Reorganising existing diagnostic pathways**, which may require additional resource investment and operational changes.
- **Promoting uptake in the clinical community,** particularly where established practices may be resistant to change.
- **Ensuring equitable access across NHS hospitals,** given variation in resources, infrastructure, and workforce capacity, which may create regional disparities in availability and benefit.

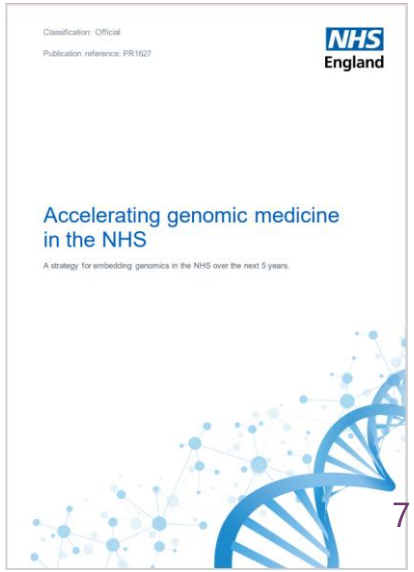
Genomic medicine in NHS England

The UK government's vision, outlined in the policy paper *"Genome UK: The Future of Healthcare"*, is **to create the most advanced genomic healthcare system in the world**, underpinned by the latest scientific advances, to deliver better health outcomes at a lower cost. For this to happen, it is important to incorporate the latest genomics advances into routine healthcare to improve the diagnosis, stratification and treatment of illness. No healthcare system in the world has yet introduced ctDNA testing at the national level, the UK has, hence, the opportunity to become a global leader in this field.

The Accelerating Genomic Medicine in the NHS Strategy sets out four priority areas, one of which focuses on **"Delivering equitable genomic testing for improved outcomes in cancer, rare, inherited and common diseases and in enabling precision medicine and reducing adverse drug reactions"**.

A key action within this domain involves *"Enabling the rapid evaluation and adoption of affordable, efficient, and innovative genomic technologies"*. This action aligns directly with the integration of ctDNA testing in diagnostic pathways and its potential to drive innovation and enhance treatment outcomes. Furthermore, NHSE has already implemented national treatment regulations that enable oncologists to administer anti-cancer medications based on ctDNA results. This groundwork has been laid, facilitating the swift integration of ctDNA findings into prescription practices.





1. *[Source: Office of Life Sciences policy paper, Genome UK: the future of healthcare; NHS England strategy publication, Accelerating genomic medicine in the NHS]*

Understanding ctDNA testing associated costs

Approximate Breakdown of ctDNA testing costs for CUP	
Component	Cost per patient
Cost of ctDNA testing	£1,700
Reagent costs	£272
Commercial kit	£646
Other consumables	£136
Staff costs	£204
Maintenance	£51
Overheads	£391
Cost of tubes	£21
Cost of transportation	£14
Cost of distribution	£6
Total per patient	£1,741

Source and use of cost estimates

Test cost estimates used in the CUP, HPB, and Advanced Breast analyses are based on delivery of 5,000 ctDNA tests annually across North Thames GMSA. GCT uses a different miRNA test and is costed separately.

Uncertainty and sensitivity analysis:

Test costs are indicative and not fixed. Sensitivity analyses have been conducted for each pathway to reflect potential changes in price as technology and delivery models evolve.

Treatment and sensitivity analysis:

Where relevant (e.g., CUP and Advanced Breast), we include scenarios with and without treatment costs to isolate the added value of ctDNA testing. Treatment costs are excluded in primary analyses to avoid skewing results, as these therapies can dominate total costs.

1

Cancer of Unknown Primary (CUP)

Structure of evaluation

The aim of this section of the report is to present a summary of the health economic results and accompanying materials that were developed during the evaluation of liquid biopsy ctDNA testing for cancer of unknown primary (CUP) patients. To do this, the following topics will be covered:

1) Background and summary of health economic results

2) Simplified diagnostic pathway, ctDNA inclusion scenario, and associated benefits

3) CUP population and tested population

4) Understanding and estimating the impact of the inclusion scenario

Background

1. Clinical Background & Diagnostic Challenge

Cancer of Unknown Primary (CUP) represents a diverse and challenging group of metastatic cancers characterised by an unidentified origin site. Although CUP is the 15th most common cancer in the UK, it ranks as the 6th leading cause of cancer-related deaths. The absence of a known primary site often results in patients undergoing prolonged and fragmented diagnostic journeys – frequently referred from one specialty to another – during which their condition may deteriorate. Each year, CUP accounts for 8,100 new cases in the UK[1].

Diagnostic delays and limited treatment options contribute to generally poor outcomes for CUP patients. By the time patients are correctly referred to a CUP secondary care team, only half are deemed suitable for treatment, while the remainder transition directly to palliative care. Even among those receiving treatment, around 80% undergo systemic chemotherapy – considered "unfavourable" treatment – because conventional diagnostics often fail to pinpoint the tumour's tissue of origin. Although genomic tests such as Whole Genome Sequencing (WGS) and Next Generation Sequencing (NGS) represent recommended standard of care, their use is limited in clinical practice by high costs and insufficient tissue samples. This gap highlights the need for more efficient and accessible diagnostic methods to improve patient care.

2. Evaluated Scenario: ctDNA at first CUP MDT

Liquid biopsies, particularly ctDNA, offer a promising solution. ctDNA can capture the molecular heterogeneity of CUP, facilitating stratification by genetic drivers and immune markers and potentially improving therapeutic decision-making and patient outcomes. This evaluation considers the introduction of ctDNA testing after the first CUP multidisciplinary team (MDT) meeting – once a clinical decision has been made to pursue treatment rather than palliative care. If implemented across the UK, approximately 4,050 patients annually could be tested using this approach. In this context, ctDNA testing could streamline diagnostics, reduce the need for invasive or inconclusive procedures, and help more patients access "favourable" treatments rather than defaulting to systemic chemotherapy.

Evidence supporting this approach includes the CUP-COMP study, led by the Christie NHS Foundation, which compared tissue and blood-based profiling in 117 patients[2]. The study found that blood-based profiling is a viable alternative when tissue samples are limited or if genomic information is urgently needed. Additionally, the CUPISCO international trial[3], which compares molecularly guided targeted therapy to chemotherapy, reported that 32% of patients initially considered with poor prognosis and "unfavourable" treatment had potentially actionable genomic alterations. This finding suggests that with genomic profiling, a significant proportion of CUP patients could be reclassified and offered more effective and "favourable" treatments.

Clinical input from the team at the Christie, along with key data from CUP-COMP, was used to inform assumptions in the economic modelling. The ctDNA test demonstrated an 80% success rate. It is assumed that all patients had at least one biopsy before referral to the CUP MDT however only 39% had sufficient tissue remaining for genomic analysis[4].

3. Forward View

CUP patients frequently express frustration with the diagnostic journey, often characterised by delays and referrals across multiple specialties before reaching the CUP team. Introducing ctDNA testing earlier in the pathway could help expedite diagnosis – either by identifying a tissue of origin sooner or by enabling quicker referral to CUP services. However, this inclusion is not modelled in the current evaluation as it would involve a more complex and undefined population (i.e. patients with malignancy of unknown origin across various tumour types), and operational questions remain about who should be tested, when, and where.

While precision oncology remains an important long-term goal, this evaluation focuses deliberately on the immediate diagnostic utility of ctDNA. Studies like CUPISCO provide evidence that molecularly guided treatment strategies may lead to better outcomes, but the immediate priority lies in improving diagnostic speed, accuracy, and access for patients currently navigating the CUP pathway.

1. *[Source: Cancer Research UK, 2017-2019]*
2. *[Source: Conway et al., 2024]*
3. *[Source: Krämer et al., 2024]*
4. *[Source: Huey et al., 2023]*

Summary of health economic results

Scenario: ctDNA testing after first CUP MDT

Treatment Costs Excluded (Core Scenario)

Total benefit: £8.7m
Total cost: £7.1m
→ **Net impact: +£1.7m**
Benefit Cost Ratio: 1.24

Treatment Costs Included

Total benefit: £14m
Total cost: £15.8m
→ **Net impact: -£1.8m**
Benefit Cost Ratio: 0.9

Healthcare system: Savings from tissue biopsies
- Avoided genomic testing on the tissue = **£5.2m**
- Avoided repeated tissue biopsy = **£1.3m**
- Avoided repeated tissue biopsy complications = **£172K**

Healthcare system: Savings from other avoided diagnostic procedures
- Avoided ultrasounds and IHC stains = **£374K**

Healthcare system: Savings from reduced pathway length of 2 weeks
- For patients who receive successful ctDNA testing (including avoided GP attendances, OP appointments, A&E and IP admissions) = **£1.6m**

Healthcare system: Savings from avoided mistreatment and consequences (*not included in BCR calculations without treatment)
- Unnecessary chemo-immunotherapy = **£4.8m**
- & associated toxicity = **£377K**

Summary of results:

This evaluation models the inclusion of ctDNA testing after the first CUP MDT for patients who will go on to treatment. **The core scenario generates an estimated net total benefit of £8.7 million against a total cost of £7.1 million, resulting in a net impact of +£1.7 million and a benefit-cost ratio of 1.24.**

The majority of savings are related to tissue biopsies. These accounted for an estimated £6.8 million. This includes £5.2 million from avoided genomic testing on tissue samples, £1.3 million from fewer repeated biopsies and £172,000 from reduced biopsy-related complications. Additional system-wide efficiencies totalling £1.6 million are realised through a shortened diagnostic pathway of two weeks, resulting in fewer GP attendances, outpatient appointments, emergency care visits, and inpatient admissions. Other savings from avoided diagnostic procedures, such as from ultrasounds used to guide tissue biopsies and IHC staining, total £374,000. Additionally, the model captures potential savings from avoided mistreatment and earlier alignment with targeted therapies, as it assumes that a portion of patients with "unfavourable" CUP will avoid systemic chemotherapy, which totals £4.8 million and its associated toxicity, which is £377,000.

Key assumptions:

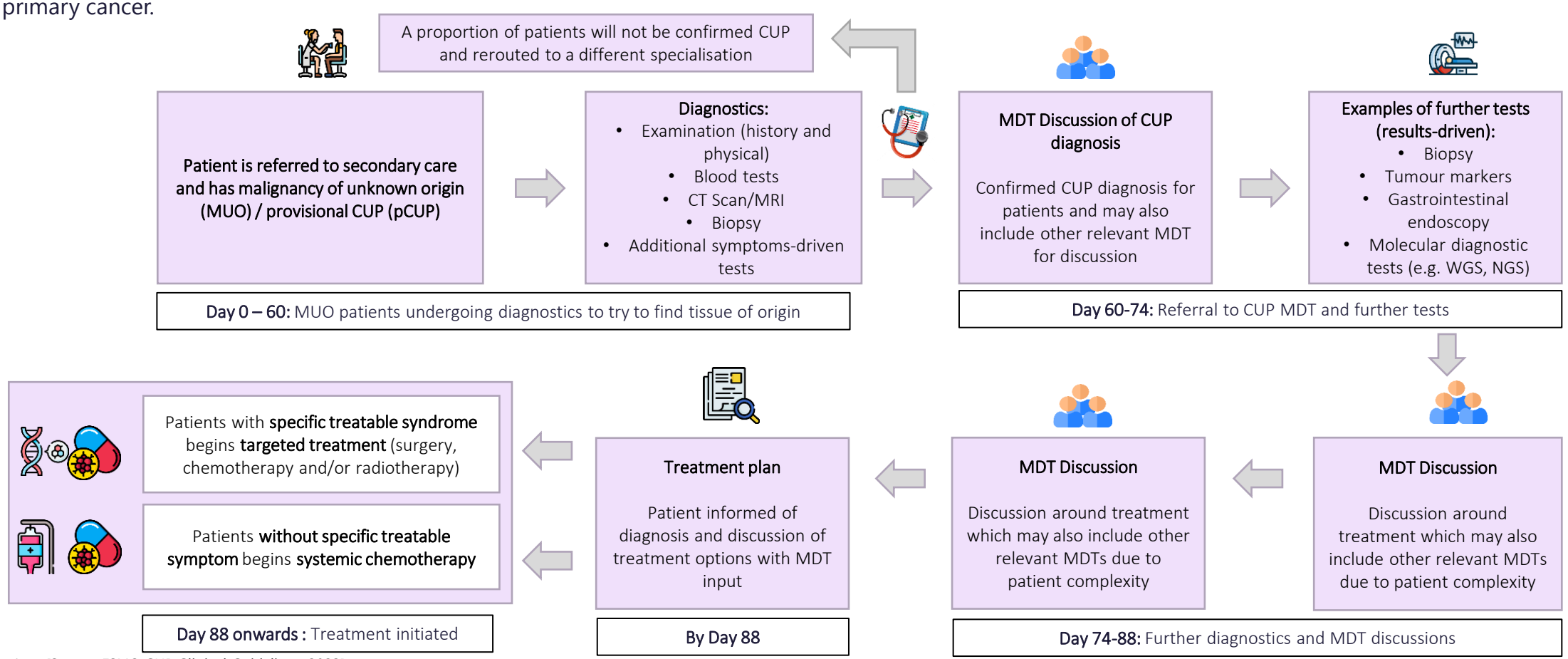
This evaluation puts forward two scenarios: one including treatment costs and one without. The core model excludes treatment costs as it reflects the most immediate application of ctDNA testing within current clinical practice. The scenario including treatment is more assumptions driven. Without supporting evidence from trials where ctDNA directly informs treatment decisions in clinical settings, it is more appropriate to focus on the diagnostic value of ctDNA as the primary outcome of this evaluation.

Moreover, the treatment cost scenario includes NICE-approved treatments, whose value has already been independently assessed. The key economic consideration is how ctDNA improves access to these treatments, so the focus should remain on its diagnostic value.

This evaluation also compares ctDNA testing to the recommended standard of care. Based on input from clinical experts, genomic testing is not routinely performed for most CUP patients, despite being available through the NHS Genomic Test Directory. Thus, the core scenario models an ideal scenario where 50% of patients would undergo WGS, which would be avoided if a ctDNA test yielded a conclusive result.

Simplified diagnostic pathway for CUP

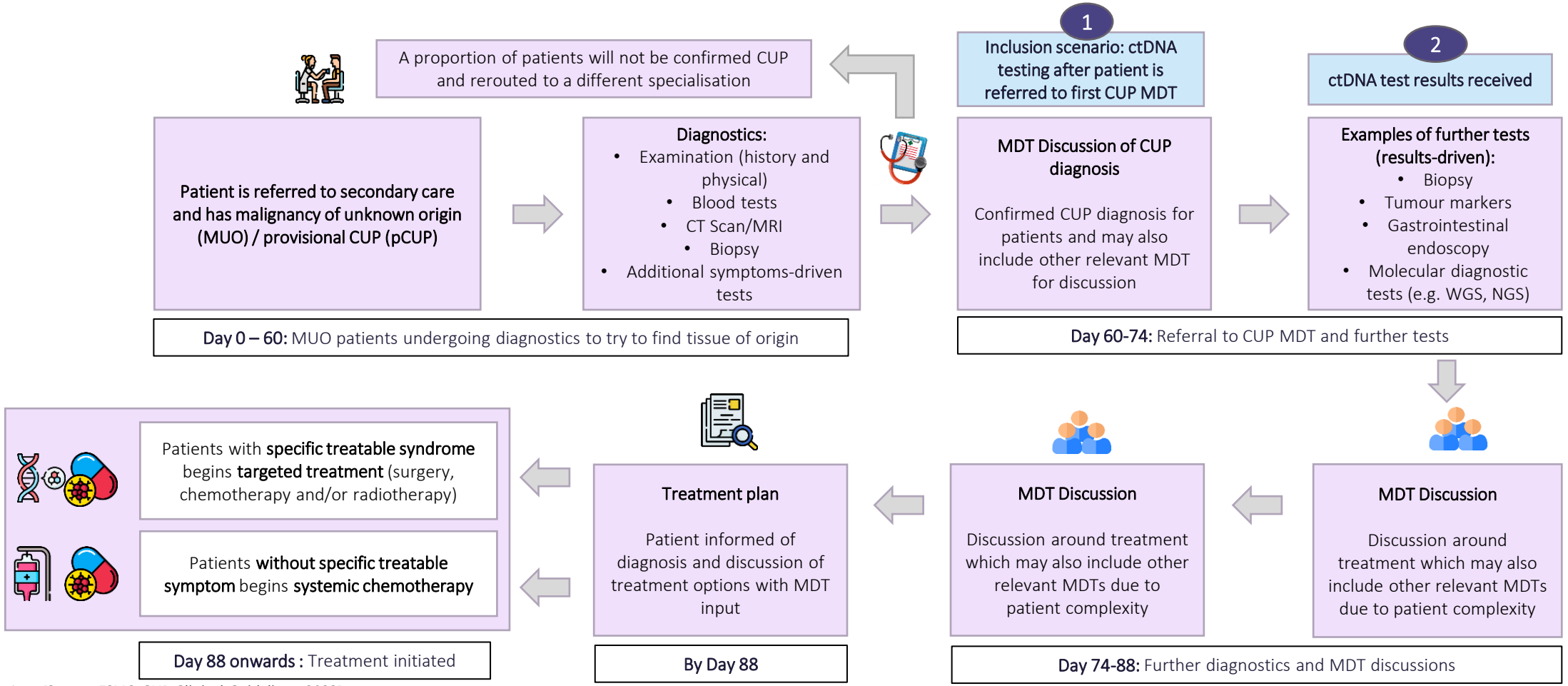
The diagram below sets out the current simplified standard diagnostic pathway for patients with CUP (based on ESMO, PCA guidelines and clinical input). Patients are initially referred to secondary care with a malignancy of unknown origin (MUO) and undergo various tests to identify the tumour's primary site. If the site remains unidentified, patients are referred to the CUP team. They may then carry out further symptom-guided testing before patients are classified for either "favourable" or "unfavourable" systemic chemotherapy. Based on current evidence, "favourable" treatment refers to patients being treated as if they had a known, site-specific primary cancer.



1. *[Source: ESMO CUP Clinical Guidelines, 2023]*
2. *[Source: Peninsula Cancer Alliance CUP Clinical Guidelines, 2022]*

Inclusion scenario for ctDNA in the pathway

Under the inclusion scenario, ctDNA testing is introduced after the first CUP MDT, once a clinical decision has been made to pursue treatment. For patients with a successful ctDNA result, clinicians can make treatment decisions earlier, reducing the need for additional symptom-guided testing or later-stage genomic testing on tissue. Due to its higher success rate, ctDNA may also enable more patients to access "favourable" treatments potentially leading to improved health outcomes.



1. *[Source: ESMO CUP Clinical Guidelines, 2023]*
2. *[Source: Peninsula Cancer Alliance CUP Clinical Guidelines, 2022]*

Cancer of Unknown Primary (CUP)

Benefits of inclusion scenario

Benefit but not quantified
Benefit and quantified

Including ctDNA testing in the pathway allows clinicians to access potentially faster and more accurate molecular results than tissue histopathology, enabling quicker treatment decisions and reducing the need for tissue-based genomic testing as clinicians can proceed with confidence. This helps avoid genomic testing on tissue, repeated tissue biopsies, limits complications, and reduces interim use of NHS resources while waiting for a treatment plan. Further, more patients will be able to access targeted "favourable" treatment, reducing the need for toxic chemotherapy and ultimately improving outcomes.

1. ctDNA testing is less invasive than tissue-biopsy – reduced repeated biopsies, biopsy complications

2. Results received faster than tissue-biopsy results — avoid cost of other genomic testing & can avoid hospital appointments in the meantime

6. More patients can access appropriate targeted therapy– leading to increased survival length and improved QoL

Patient is referred to secondary care and has malignancy of unknown origin (MUO) / provisional CUP (pCUP)

Diagnostics:
- Examination (history and physical)
- Blood tests
- CT Scan/MRI
- Biopsy
- Additional symptoms-driven tests

A proportion of patients will not be confirmed CUP and rerouted to a different specialisation

Day 0 – 60: MUO patients undergoing diagnostics to try to find tissue of origin

1

Inclusion scenario: ctDNA testing after patient is referred to first CUP MDT

MDT Discussion of CUP diagnosis

Confirmed CUP diagnosis for patients and may also include other relevant MDT for discussion

2

ctDNA test results received

Examples of further tests (results-driven):
- Biopsy
- Tumour markers
- Gastrointestinal endoscopy
- Molecular diagnostic tests (e.g. WGS, NGS)

Day 60-74: Referral to CUP MDT and further tests

3. Reduces the need for additional tests – patients don't have to go through unnecessary diagnostics for treatment plan

MDT Discussion

Discussion around treatment which may also include other relevant MDTs due to patient complexity

Day 74-88: Further diagnostics and MDT discussions

4. More patients can access appropriate targeted therapy– reduces need for expensive rounds of systemic chemotherapy

Treatment plan

Patient informed of diagnosis and discussion of treatment options with MDT input

By Day 88

5. Reduced toxicity – less patients will go on chemotherapy

Patients with **specific treatable syndrome** begins **targeted treatment** (surgery, chemotherapy and/or radiotherapy)

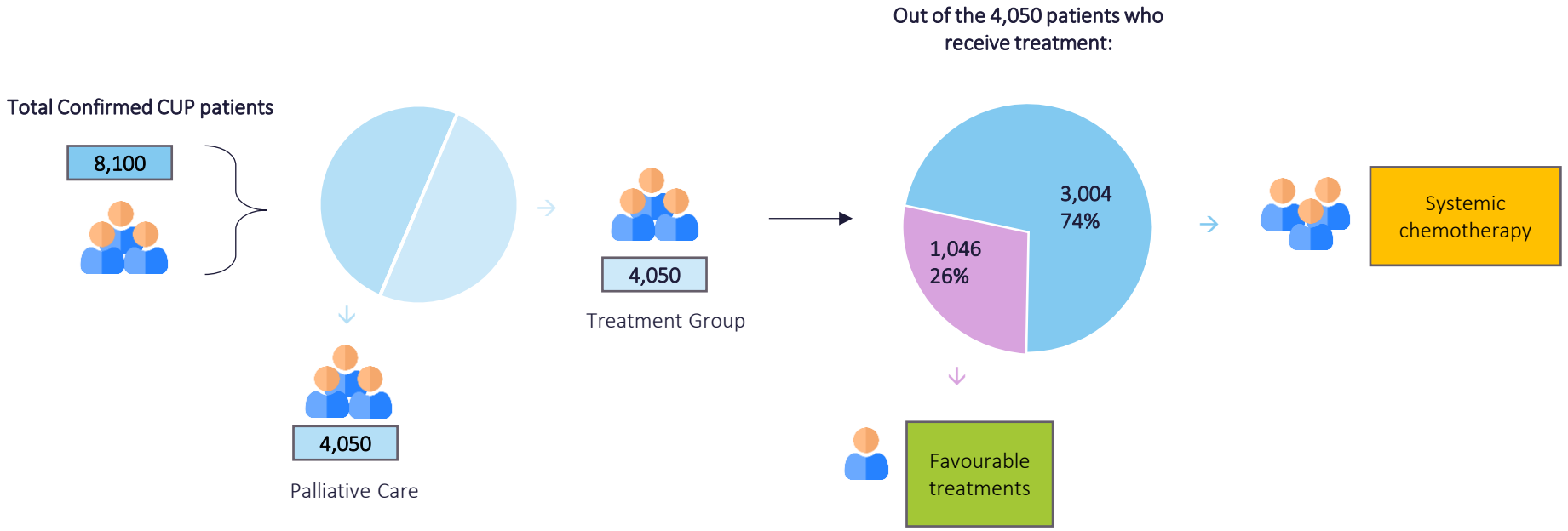
Patients **without specific treatable symptom** begins **systemic chemotherapy**

Day 88 onwards : Treatment initiated

1. *[Source: ESMO CUP Clinical Guidelines, 2023]*
2. *[Source: Peninsula Cancer Alliance CUP Clinical Guidelines, 2022]*

Understanding the CUP population

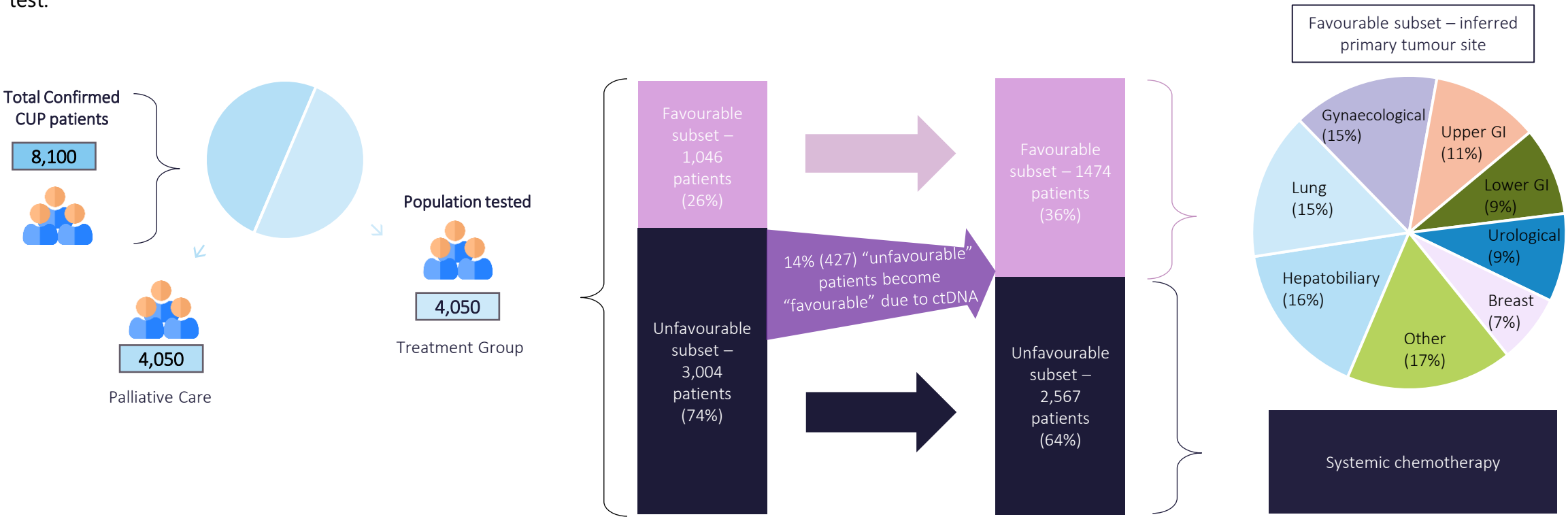
There are 8,100 confirmed CUP patients diagnosed in the UK each year. By the time they are seen by a CUP MDT, they are split into two groups: about half are too unwell for treatment and receive palliative care, while the other half undergo treatment. Of those treated, the majority (74%) receive systemic chemotherapy, an "unfavourable" treatment associated with poorer outcomes compared to those (26%) receiving "favourable" (more targeted) treatments.



1. *[Source: Cancer Research UK, 2017-2019]*
2. *[Source: ESMO CUP Clinical Practice Guidelines, 2023]*

ctDNA inclusion scenario population

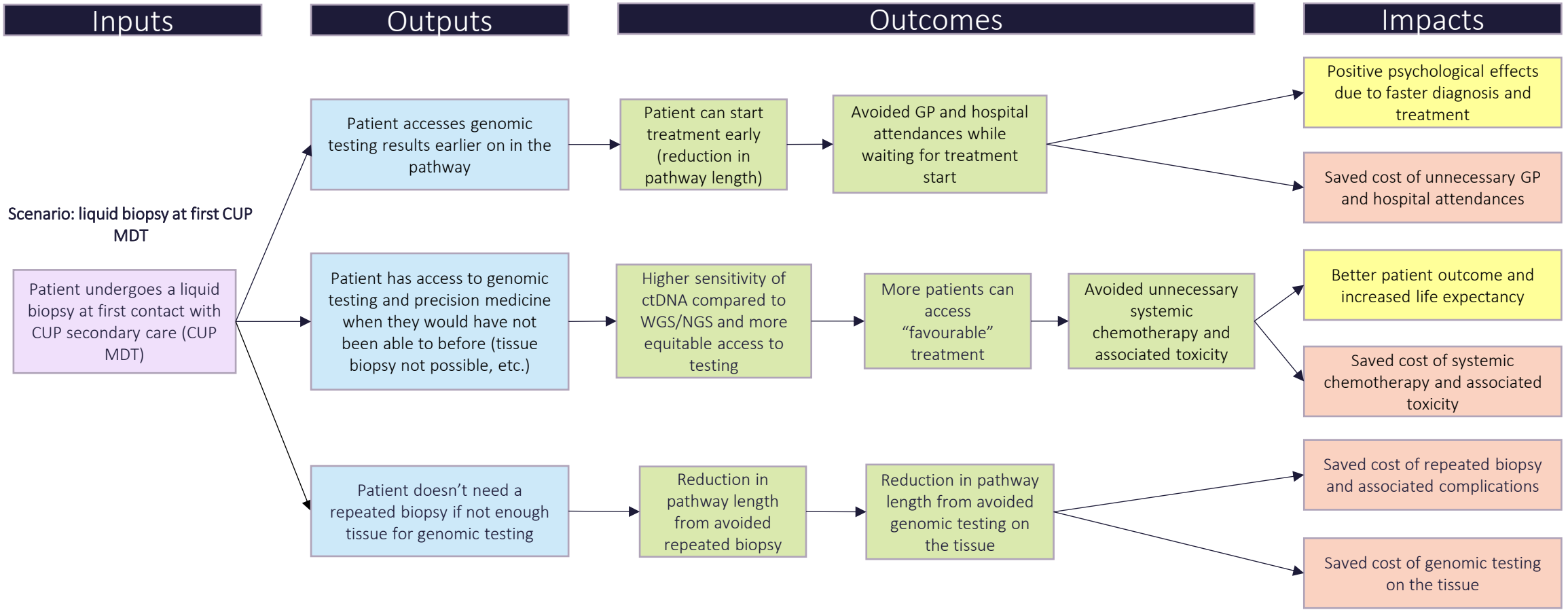
The population tested under the scenario shows that CUP patients in the treatment group receive ctDNA testing after a clinical decision is made at their first CUP MDT. An estimated 4,050 patients per year would be eligible for testing. Notably, ctDNA testing achieves a higher success rate for "blood-based profiling" (80%) compared to whole genome sequencing (57%). This increased likelihood of success enables more patients to detect potentially targetable genomic alterations, which can result in a change from "unfavourable" to "favourable" treatment pathways based on inferred primary tumour sites identified through the test.



1. *[Source: ESMO CUP Clinical Guidelines, 2023]*
2. *[Source: Cancer Research UK, 2017-2019]*
3. *[Source: Conway et al., 2024]*
4. *[Source: Krämer et al., 2024]*

Understanding impact of inclusion scenario

The logic model below will set out the impacts that ctDNA can have on the healthcare system and individual patients across the inclusion scenario.



Understanding the inclusion scenario: treatment costs

This evaluation puts forward two scenarios, one including treatment costs and without:

- **Without treatment costs**: this is the core model and reflects the most immediate and evidence-based application of ctDNA testing within current clinical practice.
- **With treatment costs:** this scenario is more speculative and explores the potential impact of ctDNA on treatment decisions. The additional aspects of this include:
  - **Benefits:** cost savings are driven by patients receiving "favourable" targetable therapies identified through ctDNA results, allowing them to avoid "unfavourable" systemic chemotherapy and its associated toxicity.
  - **Costs:** favourable treatments were estimated based on the most common first-line regimens for site-specific metastatic cancers (refer to slide 16). While these assumptions were clinically validated, they remain hypothetical until ctDNA-guided treatment becomes a standard part of care. Furthermore, the model assumes all patients with a targetable genomic alteration would be eligible for targeted treatments, which may overestimate real-world practice.

This evaluation uses the "without treatment costs" scenario as the core, given the limited trial evidence demonstrating that ctDNA directly informs and drives treatment decisions in clinical practice. Without robust data confirming its therapeutic impact, it is more appropriate to focus on the diagnostic value of ctDNA as the primary outcome of this evaluation.

Treatment costs breakdown	
Number of patients on "favourable" treatment because of ctDNA: 427	
Benefits	**Total Value**
Avoided systemic chemotherapy for patients converted to "favourable" treatment	£4,829,416
Avoided systemic chemotherapy toxicity for patients converted to "favourable" treatment	£376,517
Costs	**Total Value**
Cost of targeted "favourable" treatment for patients – calculated through each proportion of patients on site-specific cancers and multiplying by cost of most common first-line treatment and median progression-free-survival time on treatment	£8,737,661
Total Net Impact	**-£3,531,728**

Estimating benefits of ctDNA scenario (without treatment costs)

The estimated impacts of ctDNA testing on a population of around 4,050 patients every year are presented below. Overall, the benefits outweigh the costs with a benefit cost ratio of 1.24, producing a net impact of ~£1.7 million. However, the LB and UB ranges from 0.73 and 1.44, which is largely driven by the type of tissue-based genomic testing that CUP patients would receive in the comparator arm*. Further, this scenario does not consider treatment costs.

Inputs	Outputs	Benefits*	Value		
			Value	**Lower Bound**	**Upper Bound**
Patient does ctDNA after they are decided to undergo treatment	Patient will be able to avoid unnecessary diagnostic testing, undertake a precision medicine approach to their treatment, and due to reduced pathway length, they will be able to avoid additional healthcare utilisation	Cost of genomic testing on the tissue (+)	£5,225,035	£2,526,811*	£6,488,440*
		Cost of repeated tissue biopsies (+)	£1,345,802		
		Cost of tissue biopsy complications (+)	£171,627		
		Cost of unnecessary diagnostics (+)	£374,123	£260,561**	£487,685**
		Reduction in pathway length (+)	£1,627,560	£813,780***	£1,627,560***
		Total benefits	**£8,744,147**	**£5,118,581**	**£10,121,114**
		Cost of ctDNA tests (-)	£7,050,524		
		Total costs	**£7,050,524**		

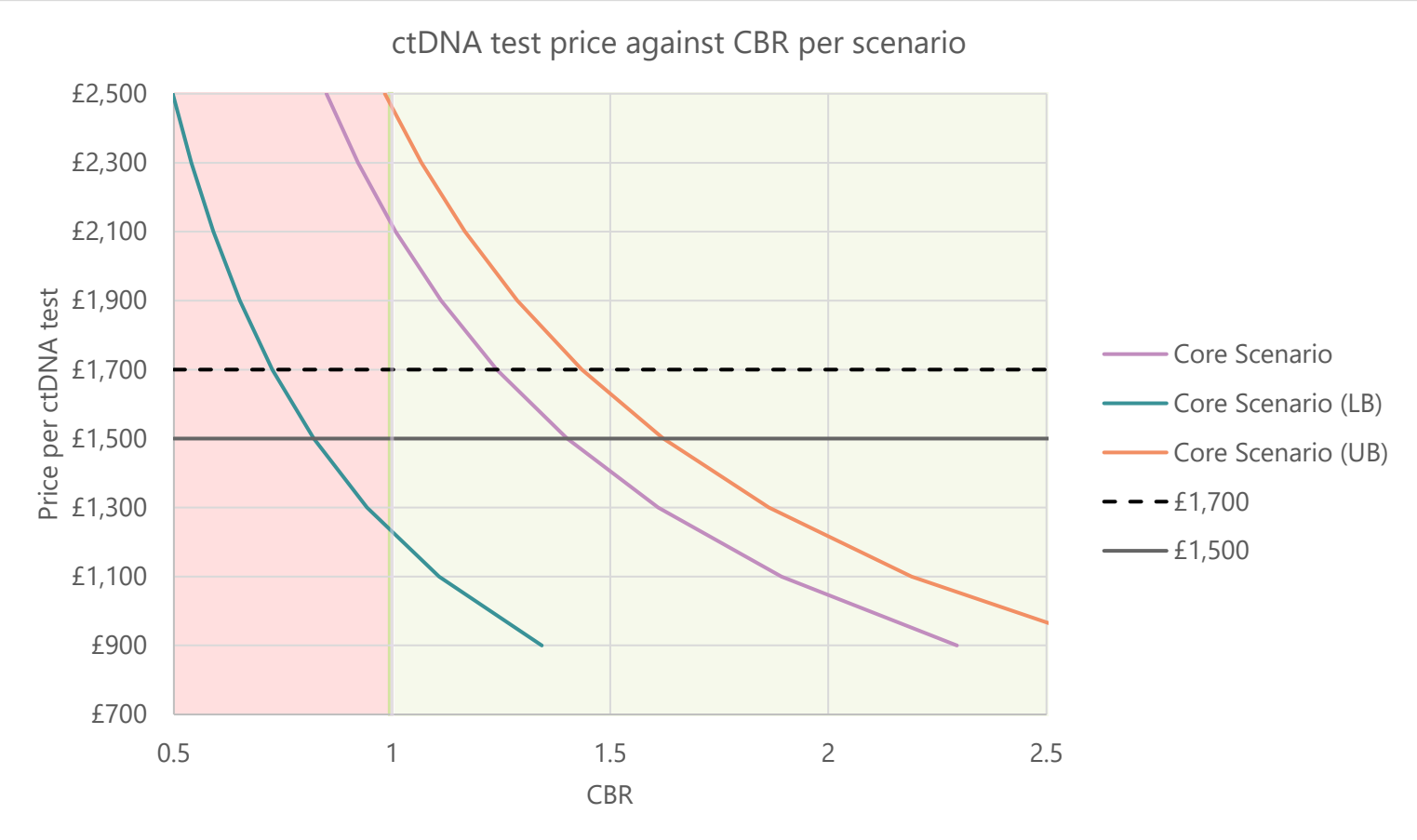
ctDNA inclusion scenario for CUP population undergoing treatment	**Value**	**LB**	**UB**
Tested population		**4,050**	
Benefit cost ratio	**1.24**	**0.73**	**1.44**
Net impact	**£1,693,623**	**-£1,931,943**	**£3,070,590**

* The range in value reflects the variability of the comparator arm for standard of care – the core scenario reflects 50% of patients receive WGS, the LB reflects 100% of patients receive NGS and the UB reflects 50% receive NGS and 50% receive WGS

** Cost saving from avoiding unnecessary diagnostics refer to avoided ultrasounds and IHC stains (assumed that ctDNA will eventually replace IHC stains) – the LB and UB reflects range of pricing for these diagnostics

*** Cost saving from reduced pathway length assumes that ctDNA reduces the pathway length by, on average, 2 weeks (clinically validated by NHSE lung pilot) for patients – the LB reflects a more conservative estimate of 1 week

Sensitivity testing cost-neutral price scenarios



The chart illustrates how ctDNA test cost affects the benefit-cost ratio in the core CUP scenario **without considering treatment costs.** The lower bound (conservative) and upper bound (optimistic) assumptions sensitivity tested.

Cost-neutrality is estimated to be achieved at approximately at **£2,120** but ranges from **£1,220** in the lower bound scenario and **£2,470** in the upper bound scenario. The drive in variability between the lower bound and upper bound is highly dependent on the tissue-based genomic testing that CUP patients would receive in the comparator arm.

Estimating benefits of ctDNA scenario (with treatment costs)

The estimated impacts of ctDNA testing on a population of around 4,050 patients every year are presented below. Overall, the costs marginally outweigh the benefits with a benefit cost ratio of 0.89. However, this scenario includes treatment costs, which is more speculative and requires further clinical research to validate such assumptions.

Inputs	Outputs	Benefits*	Value		
			Value	**Lower Bound**	**Upper Bound**
Patient does ctDNA after they are decided to undergo treatment	Patient will be able to avoid unnecessary diagnostic testing, undertake a precision medicine approach to their treatment, and due to reduced pathway length, they will be able to avoid additional healthcare utilisation	Cost of genomic testing on the tissue (+)	£5,225,035	£2,526,811*	£6,488,440*
		Cost of repeated tissue biopsies (+)	£1,345,802		
		Cost of tissue biopsy complications (+)	£171,627		
		Cost of unnecessary diagnostics (+)	£374,123	£260,561**	£487,685**
		Reduction in pathway length (+)	£1,627,560	£813,780***	£1,627,560***
		Cost of systemic chemotherapy and associated toxicity (+)	£5,205,933		
		Total benefits	**£13,950,080**	**£10,324,514**	**£15,327,047**
		Cost of ctDNA tests (-)	£7,050,524		
		Cost of targeted treatments (-)	£8,737,661		
		Total costs	**£15,788,185**		

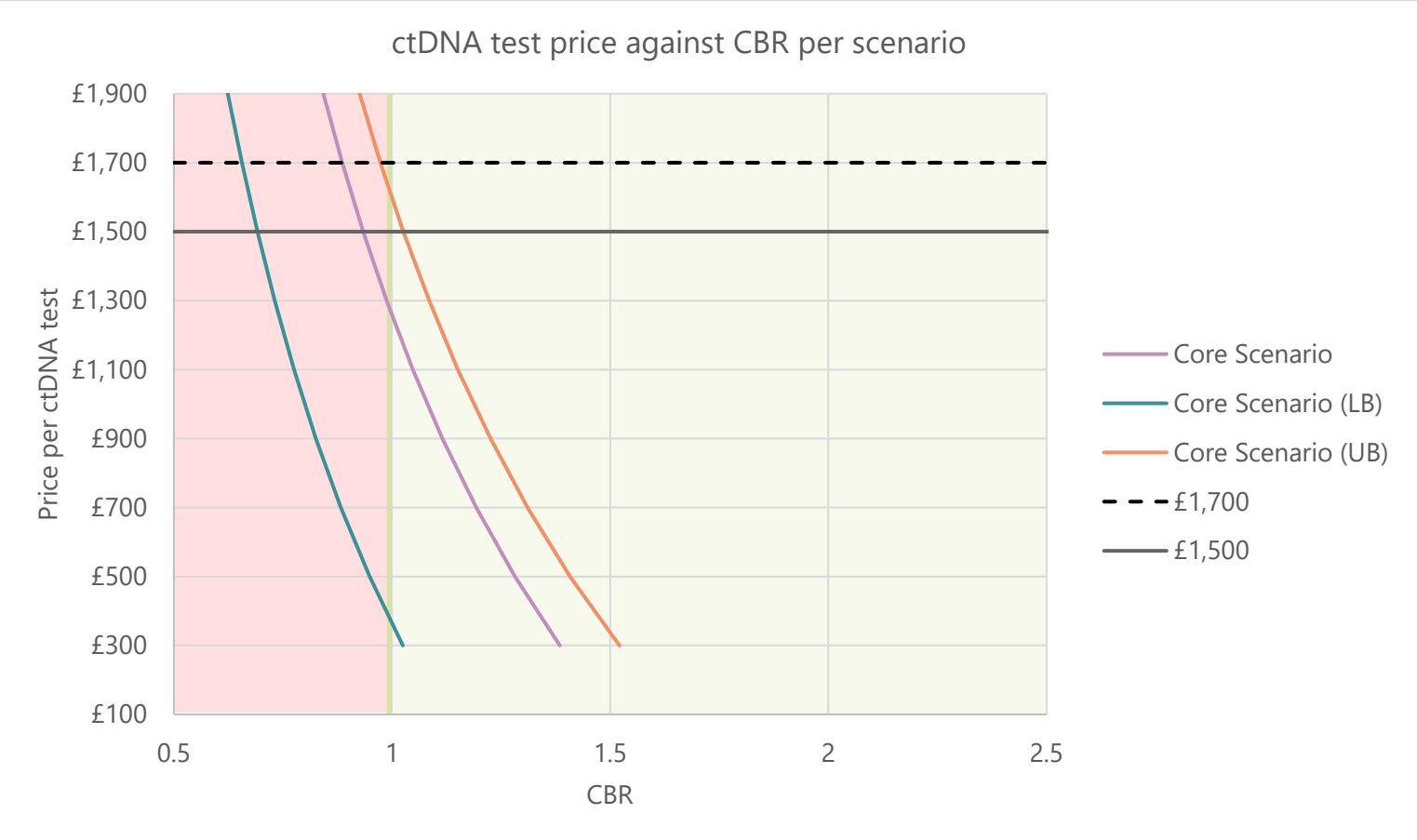
ctDNA inclusion scenario for CUP population undergoing treatment	**Value**	**LB**	**UB**
Tested population		**4,050**	
Benefit cost ratio	**0.88**	**0.65**	**0.97**
Net impact	**-£1,838,105**	**-£5,463,671**	**-£461,138**

* The range in value reflects the variability of the comparator arm for standard of care – the core scenario reflects 50% of patients receive WGS, the LB reflects 100% of patients receive NGS and the UB reflects 50% receive NGS and 50% receive WGS

** Cost saving from avoiding unnecessary diagnostics refer to avoided ultrasounds and IHC stains (assumed that ctDNA will eventually replace IHC stains) – the LB and UB reflects range of pricing for these diagnostics

*** Cost saving from reduced pathway length assumes that ctDNA reduces the pathway length by, on average, 2 weeks (clinically validated by NHSE lung pilot) for patients – the LB reflects a more conservative estimate of 1 week

Sensitivity testing cost-neutral price scenarios



The chart illustrates how ctDNA test cost affects the benefit-cost ratio in the core CUP scenario **considering treatment costs.** The lower bound (conservative) and upper bound (optimistic) assumptions sensitivity tested.

Cost-neutrality is estimated to be achieved at approximately at **£1,250** but ranges from **£350** in the lower bound scenario and **£1,600** in the upper bound scenario. The drive in variability between the lower bound and upper bound is highly dependent on the tissue-based genomic testing that CUP patients would receive in the comparator arm.

2

Hepato-pancreato-biliary (HPB) cancer

Structure of evaluation

The aim of this section of the report is to present a summary of the health economic results and accompanying materials that were developed during the evaluation of liquid biopsy ctDNA testing for late stage hepato-pancreato-biliary (HPB) cancer patients. To do this, the following topics will be covered:

1) Background and summary of health economic results

2) Simplified diagnostic pathway, ctDNA inclusion scenario, and associated benefits

3) HPB population, sub-types, and tested population

4) Understanding, estimating, and sensitivity testing the impact of the inclusion scenario

Background

1. Clinical Background & Diagnostic Challenge

Pancreatic (PC) and biliary tract cancers (BTC) are aggressive malignancies within the broader hepato-pancreato-biliary (HPB) cancer spectrum that have the worst prognosis of any solid cancer,[1] with an estimated 17,800[2] new cases annually in England in 2022. Most patients present with advanced-stage disease (Stage III or IV), when timely diagnosis is critical. However, current diagnostic pathways depend on invasive procedures such as endoscopic ultrasound (EUS) and image-guided biopsies. These are technically challenging, prone to complications, and often inconclusive, resulting in diagnostic delays and repeat procedures. One in four patients experience a "diagnostic loop" in which they return for another tissue biopsy, before a confirmed diagnosis is reached[3].

2. Evaluated Scenario: ctDNA in parallel with tissue biopsy

This evaluation builds on the ACCESS service project led by The Royal Marsden, which trialled the use of ctDNA liquid biopsies in an augmented diagnostic pathway for 212 patients with suspected stage 3/4 PC and BTC. An inclusion scenario is replicated in the model with liquid biopsy ctDNA testing alongside the first tissue biopsy when imaging suggests advanced disease. In this instance, the ctDNA acts as a non-invasive adjunct, supporting earlier decision-making, reducing repeated biopsies, and reducing the need for tissue-based molecular profiling. Applied across England, an estimated 13,286 patients per year would be tested, including a small proportion later found not to have cancer or with an alternative diagnosis.

Key data from the ACCESS project supported by clinical input from The Royal Marsden team were used to inform model assumptions. The ctDNA test demonstrated a sensitivity of 85% and a specificity of 58%[3]. Compared to a historical cohort, patients in the liquid biopsy pathway experienced a 20% absolute reduction in the need for multiple invasive procedures[3] (17% vs. 37%, N=140) and a 7-day faster turnaround time[3] (median 10 vs. 17 days). Tissue-based molecular profiling was also reduced by 35%. Importantly, 62% of the ACCESS patients reached the NHS target of 28 days to diagnosis with a median of 23 days as well as 55% of patients also reaching the NHS target of 62 days to treatment.

3. Forward View

While precision oncology remains an important long-term consideration, this evaluation is focused on the immediate diagnostic value of ctDNA integration. In pancreatic cancer, most patients still do not have access to first-line targeted therapies, limiting the current relevance of treatment selection in economic modelling. The most common driver mutation, oncogenic KRAS, is found in over 90%[4] of cases but remains untargeted in routine practice. Although multiple efforts to develop KRAS-directed therapies are ongoing, their clinical application is still emerging.

Against this backdrop, the case for ctDNA inclusion is centred on its ability to address diagnostic challenges: reducing reliance on invasive procedures, decreasing time to diagnosis, and enabling more efficient use of NHS resources.

1. *[Source: NIH Cancer Stat Facts, 2022]*
2. *[Source: Cancer Registration Statistics, 2022]*
3. *[Source: NIHR SBRI liquid biopsy HE report, 2024]*
4. *[Source: Lee & Pant, 2023]*

Summary of health economic results

Scenario: parallel ctDNA testing with first tissue biopsy

Total benefit: £19.3m
Total cost: £23.1m

→

Net impact: -£3.9m
Benefit Cost Ratio: 0.83

Healthcare system: Savings from invasive procedures (IPs)
- Avoided genomic testing on the tissue = **£7.5m**
- Avoided repeated tissue biopsies and other IPs = **£8.8m**
- Avoided repeated tissue biopsy complications = **£781K**

Healthcare system: Savings from reduced pathway length of 1 week
- For patients who receive successful ctDNA testing (including avoided GP attendances, OP appointments, A&E and IP admissions) = **£2.2m**

Healthcare system: Savings from avoided mistreatment and consequences
- Due to the limited availability of molecularly guided treatments for pancreatic (PC) and biliary tract cancer (BTC) patients in the first-line setting, and insufficient evidence to support robust assumptions, these potential benefits were not quantified in the current model.

Summary of results:

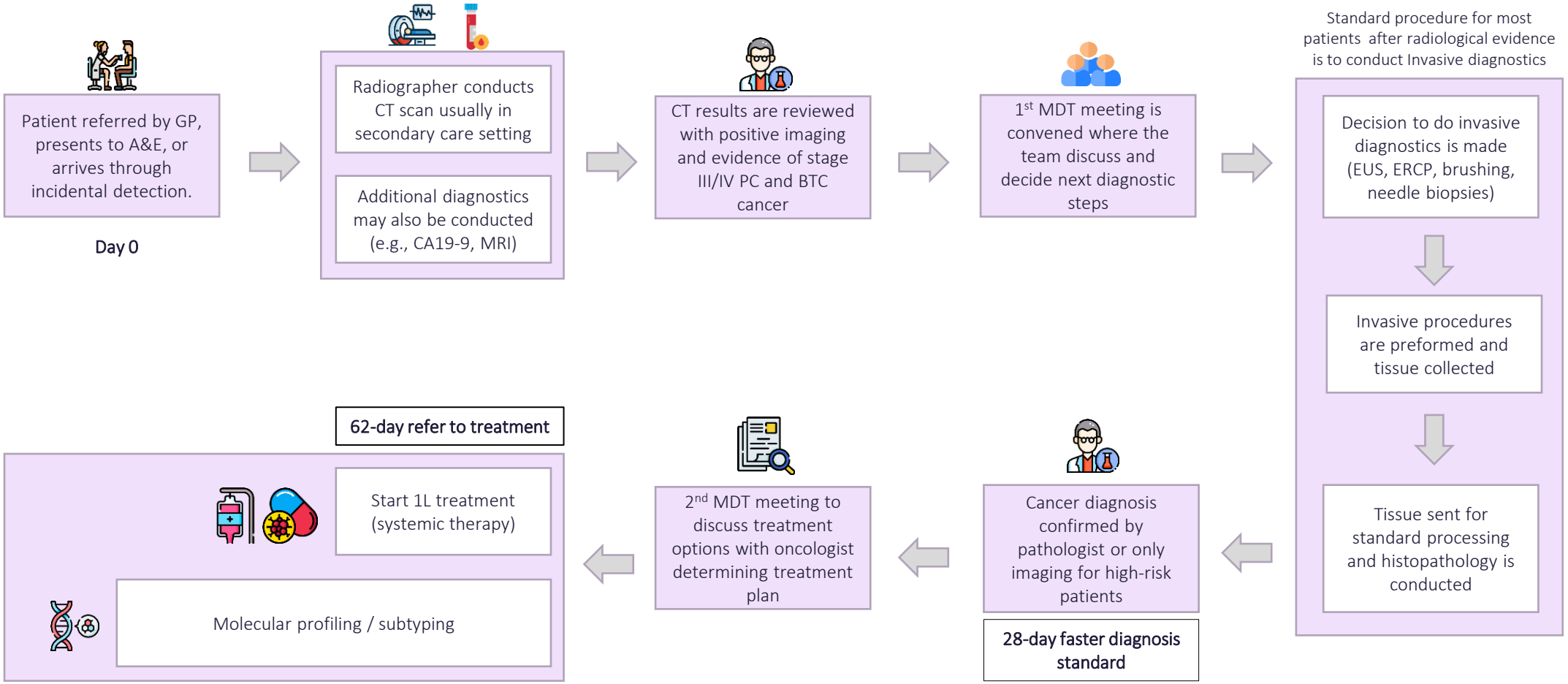
This evaluation models the inclusion of ctDNA testing alongside the first tissue biopsy for patients with pancreatic and biliary tract cancers. **The core scenario generates an estimated net total benefit of £19.3 million against a total cost of £23.1 million, resulting in a net impact of –£3.9 million and a benefit-cost ratio of 0.83.**

The majority of savings arise from reductions in invasive procedures as patients avoid diagnostic loops. These accounted for an estimated £17.1 million. This includes £7.5 million from avoided genomic testing on tissue samples, £8.8 million from fewer repeated biopsies and other invasive interventions, and £781,000 from reduced biopsy-related complications. Additional system-wide efficiencies totalling £2.2 million are realised through a shortened diagnostic pathway of one week, resulting in fewer GP attendances, outpatient appointments, emergency care visits, and inpatient admissions.

Although the model captures only the diagnostic efficiencies of ctDNA testing, further potential savings from avoided mistreatment and earlier alignment with targeted therapies were not quantified. This reflects the current limited availability of molecularly guided treatments in the first-line setting for these cancers, as well as the need for further evidence to support robust assumptions in the benefit calculation.

Simplified diagnostic pathway for PC and BTC

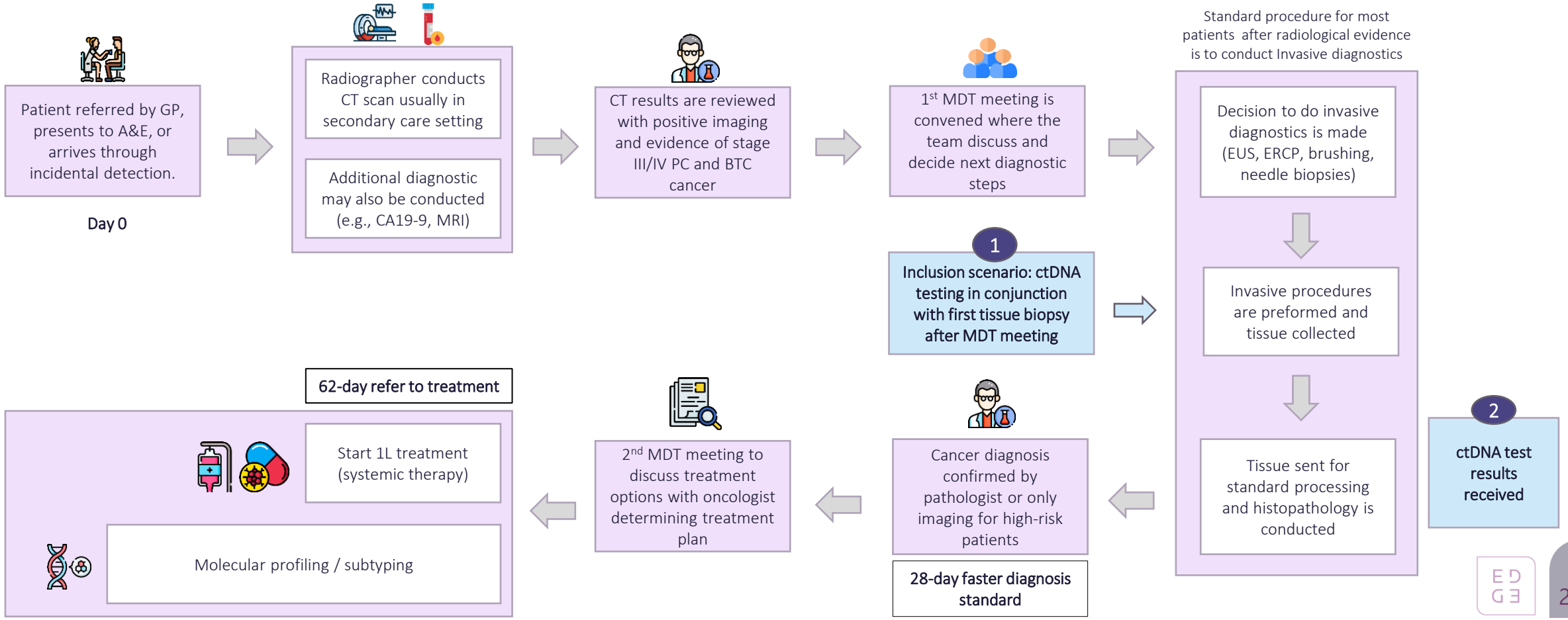
The diagram below shows a simplified diagnostic pathway (based on a NIHR Health Research Centre report and discussions with clinicians) for patients with suspected advanced pancreatic or biliary tract cancer. Patients are referred after imaging shows suspicious findings, and diagnosis relies on invasive procedures where tissue samples are taken.



1. *[Source: NIHR SBRI liquid biopsy HF and SLR report]*

Inclusion scenario for ctDNA in the pathway

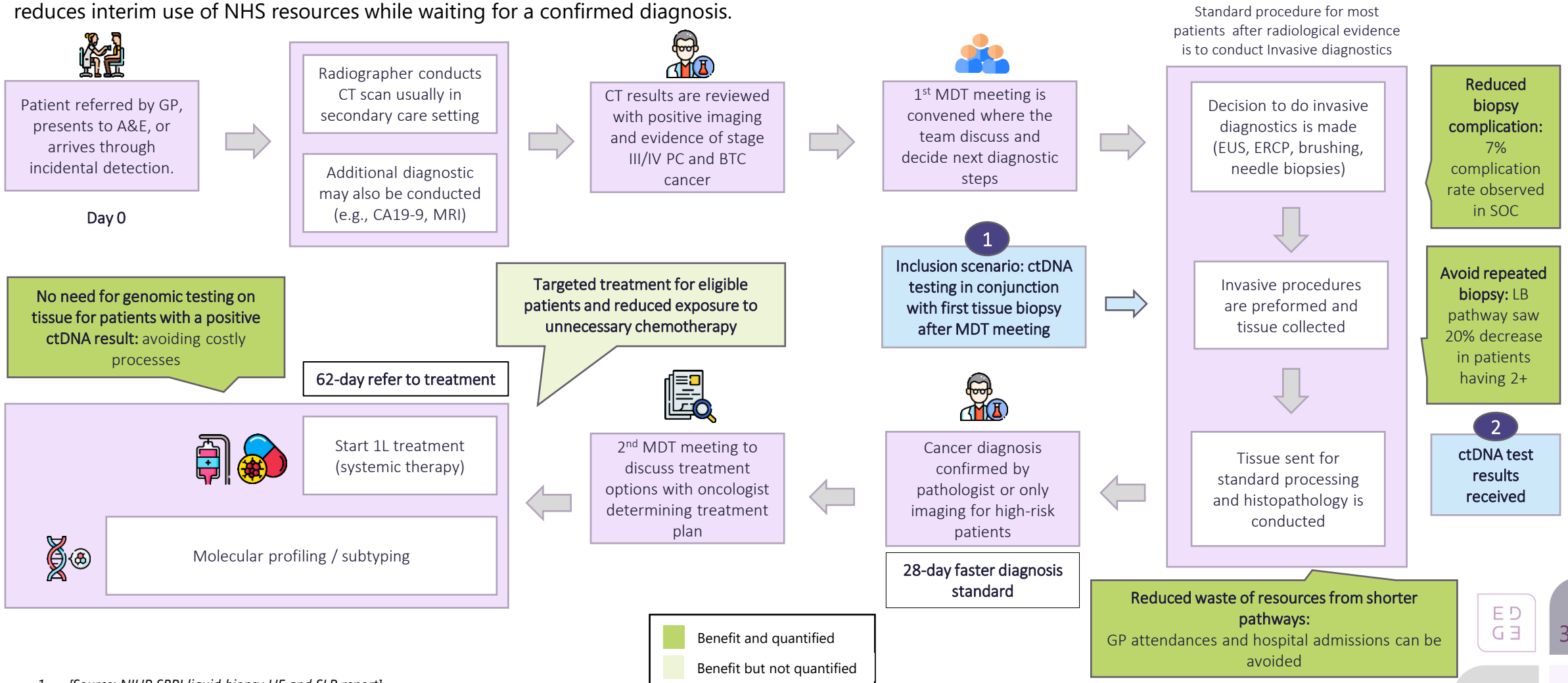
Under the inclusion scenario, ctDNA testing is introduced in parallel with the first tissue biopsy, with results typically available before standard histopathology is completed. For patients with a positive ctDNA result, clinicians can make treatment decisions earlier, either relying on the ctDNA result alone or using it alongside tissue findings when needed. If ctDNA provides molecular information upfront, later-stage genomic testing on tissue can often be avoided altogether.



1. *[Source: NIHR SBRI liquid biopsy HF and SLR report]*

Inclusion scenario for ctDNA in the pathway

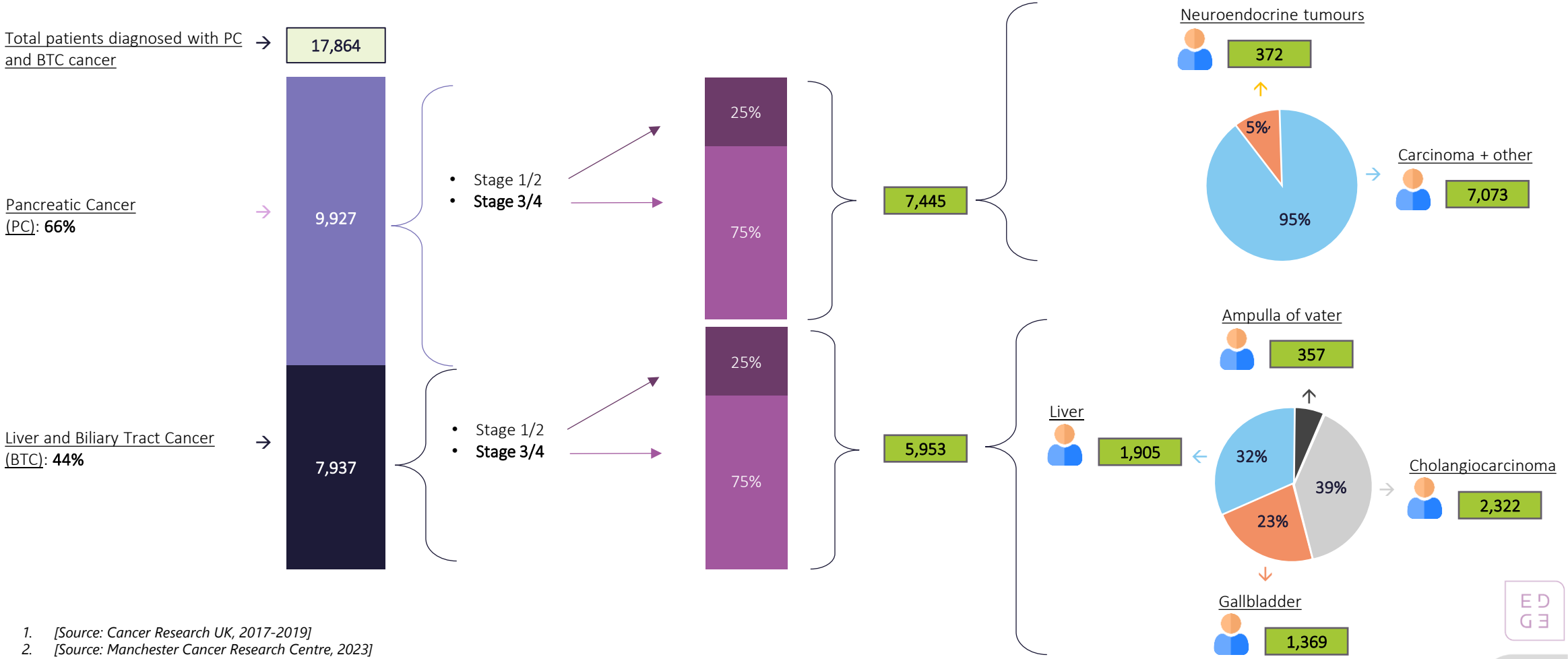
Including ctDNA testing in the pathway allows clinicians to access molecular results faster than tissue histopathology, enabling quicker treatment decisions and reducing the need for tissue-based genomic testing as clinicians can proceed with confidence. This helps avoid repeat biopsies, limits complications, and reduces interim use of NHS resources while waiting for a confirmed diagnosis.



1. *[Source: NIHR SBRI liquid biopsy HF and SLR report]*

HPB population and sub-types

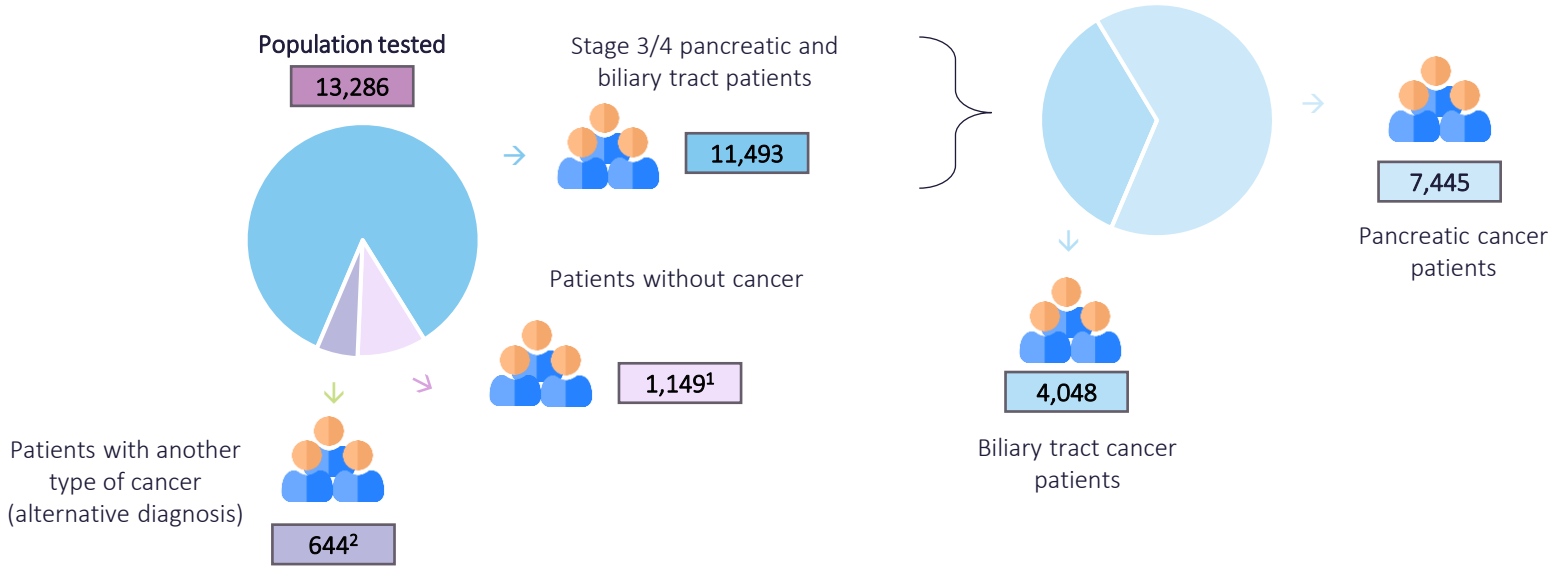
In 2022, 17,864 patients were diagnosed with HPB cancer, including 9,927 with pancreatic cancer and 7,937 with liver and biliary tract cancer. Approximately 75% of cases were diagnosed at stage 3/4. The main subtypes of pancreatic cancer are pancreatic carcinomas and neuroendocrine tumours, while biliary tract cancer primarily includes cholangiocarcinoma and gallbladder cancer.



1. *[Source: Cancer Research UK, 2017-2019]*
2. *[Source: Manchester Cancer Research Centre, 2023]*
3. *[Source: Cancer Registration Statistics, 2022]*

Tested population for ctDNA inclusion scenario

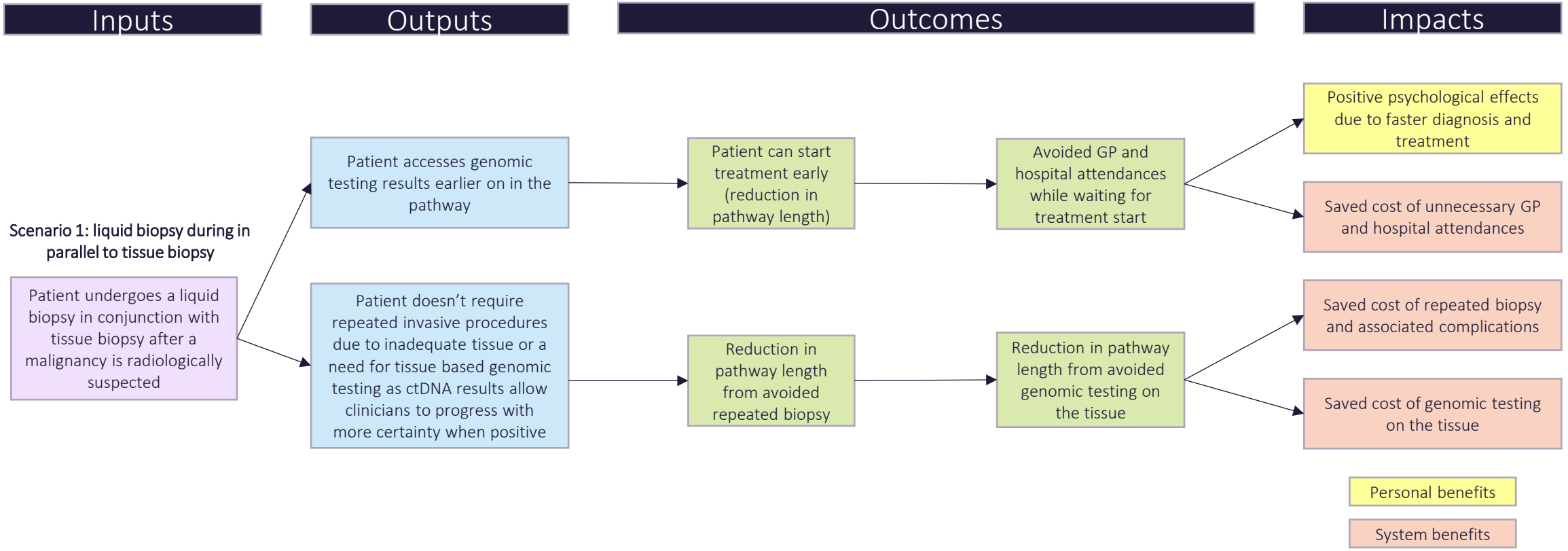
The population tested in the inclusion scenario consists of patients with suspected late-stage pancreatic or biliary tract cancer. Although liver cancer is part of the broader hepato-pancreato-biliary (HPB) spectrum, it follows a distinct diagnostic pathway and is therefore excluded from this analysis. The estimated 13,286 patients eligible for testing fall into three groups: (1) those with confirmed Stage III/IV pancreatic or biliary tract cancer including subtypes such as neuroendocrine tumours, pancreatic carcinomas, cholangiocarcinoma, gallbladder cancer, and ampullary cancer; (2) patients who are later found not to have cancer; and (3) patients who receive an alternative cancer diagnosis.



1. *10% of patients end up not having pancreatic cancer after diagnostics [Source: Manzia et al., 2010]*
2. *ACCESS project stated that 12/212 (6%) of patients had an alternative diagnosis [Source: NIHR SBRI liquid biopsy HE report]*

Understanding impact of inclusion scenario

The logic model below sets out how the impacts that ctDNA testing in the HPB pathway can have on the healthcare system and individual patients.



Estimating benefits of ctDNA scenario

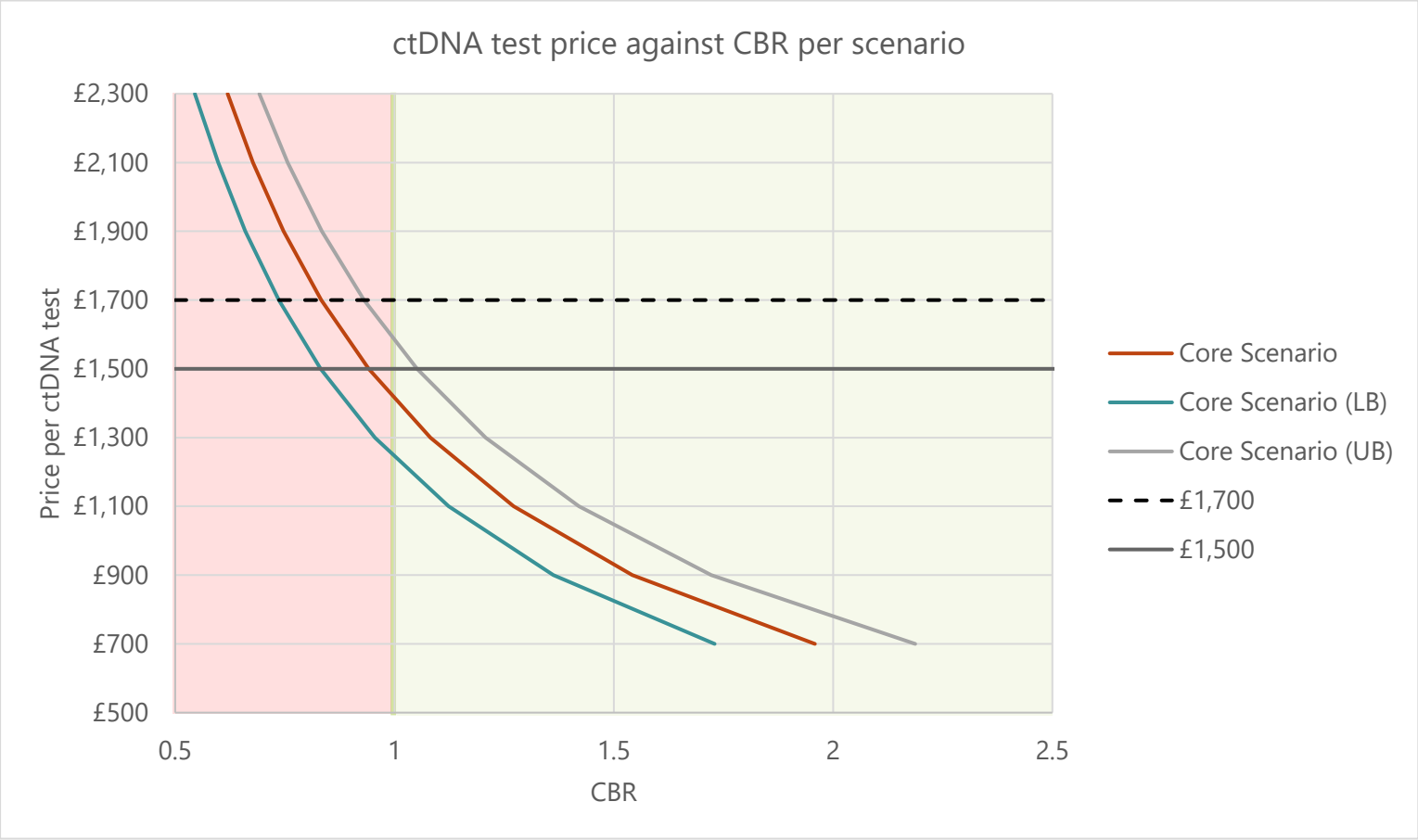
The estimated impacts of ctDNA testing on a population of around 13,286 patients every year are presented below. Overall, the costs marginally outweigh the benefits with a benefit cost ratio of 0.83. The potential benefit of improving targeted treatment was not quantified here.

Inputs	Outputs
Patient undergoes ctDNA in parallel to tissue biopsy	Patient will be able to avoid unnecessary diagnostic testing, and due to reduced pathway length, they will be able to avoid additional healthcare utilization

Benefits	Value	Lower Bound	Upper Bound
Cost of genomic testing on the tissue (+)	£7,499,261	£5,249,483	£9,749,039
Cost of repeated invasive procedures (+)	£8,772,637	£8,772,637	£8,772,637
Cost of tissue biopsy complications (+)	£781.223	£781.223	£781.223
Reduction in pathway length (+)	£2,214,325	£2,214,325	£2,214,325
Total benefits	**£19,267,446**	**£17,017,668**	**£21,517,224**
Cost of ctDNA tests (-)	£23,123,375		
Total costs	**£23,123,375**		

ctDNA inclusion scenario for HPB population undergoing treatment	Value	LB	UB
Tested population		**13,286**	
Benefit cost ratio	**0.83**	**0.74**	**0.93**
Net impact	**-£3,855,929**	**-£6,105,708**	**-£1,606,151**

Sensitivity testing cost-neutral price scenarios



Given the HPB scenario was relatively sensitive to overall testing costs, additional sensitivity analysis was conducted to understand the impact of lowering overall costs on the results of the modelling.

The chart illustrates how ctDNA test cost affects the benefit-cost ratio in the core HPB inclusion scenario, with both lower bound (conservative) and upper bound (optimistic) assumptions sensitivity tested.

Cost-neutrality is estimated to be achieved at approximately **£1,405** in the core scenario. Ranging from **£1,235** in the lower bound to **£1,575** for the upper bound.

3

Germ Cell Tumour

Structure of evaluation

The aim of this section of the report is to present a summary of the health economic results and accompanying materials that were developed during the evaluation of liquid biopsy miRNA testing for germ cell tumour (GCT) patients. To do this, the following topics will be covered:

1) Background and summary of health economic results

2) Simplified diagnostic pathway, miRNA inclusion scenario, and associated benefits

3) GCT population and tested population

4) Understanding and estimating the impact of the inclusion scenario

Background

1. Clinical Background & Diagnostic Challenge

Malignant germ cell tumours (GCTs) represent a rare but clinically significant group of cancers affecting both paediatric and adult populations. The vast majority arise in the testes, with smaller proportions occurring in the ovaries and extragonadal sites. Testicular cancer, the most common malignancy in young adult males, accounts for over 2,300 cases annually in the UK[1].

While conventional serum tumour markers (STMs) such as alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH) are used in diagnosis and monitoring, their sensitivity remains limited, detecting disease in only ~50% of patients[2]. This gap underscores the need for a more accurate and universal biomarker for malignant GCTs. A promising solution is the use of a circulating microRNA (miRNA) biomarker, miR-371a-3p, detected via a qRT-PCR assay. Studies have demonstrated that miR-371a-3p achieves 94% specificity and 90% sensitivity[2].

2. Evaluated Scenario: miRNA during surveillance period

This evaluation models the inclusion of circulating miRNA testing in the GCT pathway specifically for surveillance rather than initial diagnosis, making it a unique use case among the indications assessed in this report. Applied across the UK, an estimated 2,375 patients per year would be tested and following this cohort, over the 5-year surveillance period, an estimated total of ~11,000 to ~15,000 miRNA tests will be required. GCT patients have long and varied follow-up schedules due to high progression-free survival rates, with standard surveillance protocols typically requiring 4–6 CT or MRI scans[3]. These imaging modalities contribute to healthcare costs and expose patients to cumulative radiation risks.

The model assesses a scenario in which the miRNA assay replaces routine CT/MRI imaging in follow-up, providing a less invasive alternative for disease monitoring. Additionally, the impact of miRNA testing on reducing the need for multidisciplinary team (MDT) discussions is evaluated. This analysis builds on existing health economic evidence, including a US-based study that estimated potential annual savings of up to $69 million through reduced imaging and improved surveillance strategies[4]. By extending this assessment to the NHS setting, the evaluation quantifies the potential cost savings achievable through miRNA-based surveillance in GCT management.

3. Forward View

Testicular cancer is the most common cancer in men aged 20-35, and outcomes are highly favourable – with over 95% of patients cured[1]. As a result, the focus is increasingly shifting toward minimising the long-term side effects of surveillance, especially given the young age of most patients and their high likelihood of survival. Reducing the physical and psychological burden of repeated imaging is therefore an important priority.

Beyond testicular cancer, there may also be value in exploring the use of circulating miRNA testing in other types of GCT, such as central nervous system (CNS) GCTs. These are extremely rare and diagnostically challenging as most are AFP/HCG marker-negative and located in surgically inaccessible regions of the brain. Research suggests that elevated miRNA levels may precede histological confirmation by up to two years[5], highlighting the potential role of miRNA testing in reducing diagnostic delays in these cases.

1. *[Source: Cancer Research UK, 2017-2019]*
2. *[Source: Dieckmann et al., 2017]*
3. *[Source: Guidelines for the Management of Testicular Cancer (West Midlands Expert Advisory Group), 2016]*
4. *[Source: Charytonowicz et al., 2019]*
5. *[Source: Murray et al., 2020]*

Summary of health economic results

Scenario: miRNA testing at diagnostic clinic and throughout the surveillance period (replace CT/replace MRI)

CT Scan Scenario:
Total impact: £1.9m
Total cost: £1.4m
→ **Net impact: +£500K**
Benefit Cost Ratio: 1.35

MRI Scan Scenario:
Total impact: £2.5m
Total cost: £1.1m
→ **Net impact: +£1.5m**
Benefit Cost Ratio: 2.35

Healthcare system: Avoided 3D imaging (modelled as either CT or MRI scans)
- Avoided cost of CT scans (~5.3 scans) = **£1.7m**

OR
- Avoided cost of MRI scans (~ 3.5 scans) = **£2.4m**

Healthcare system: Savings from reducing unnecessary clinical time such as MDT meetings (modelled as either CT or MRI scans)
- Reduced MDT meeting costs = **£208K**

OR
- Reduced MDT meeting costs = **£147K**

Summary of results:

This evaluation models the inclusion of ctDNA testing alongside the diagnostic clinic and throughout the surveillance period for patients.

- **CT scan scenario generates an estimated net total benefit of £1.9 million against a total cost of £1.4 million, resulting in a net impact of +£500K and a benefit-cost ratio of 1.35.**
- **MRI scan scenario generates an estimated total benefit of £2.5 million against a total cost of £1.1 million, resulting in a net impact of +£1.4 million and a benefit cost ratio of 2.35.**

Most of the cost savings in this model come from reducing unnecessary scans – estimated at £1.7 million for CT scans or £2.4 million for MRI scans, depending on which follow up schedule and scan modality is assumed. These figures reflect scan use over a 5-year surveillance period for one cohort of patients, though they are likely conservative, as surveillance can extend up to 10 years in some cases. Scan frequency varies by tumour type (seminoma vs non-seminoma) and disease stage. In addition to imaging costs, reducing the number of scans also lessens the clinical time required for scan review, such as during MDT meetings, leading to estimated savings of approximately £208,000 (CT pathway) or £147,000 (MRI pathway).

While the model captures key savings and efficiencies linked to miRNA testing, it does not quantify potential benefits from shortened pathway times, such as reduced waiting time for scan results. These improvements are often linked to reduce anxiety around scans and better psychological support for patients. However, as these benefits are typically non-cash releasing, they were not included in the economic model.

Surveillance period (CT scan vs MRI scan):

Surveillance protocols for testicular cancer relapse vary across the UK, with differences in the use of CT or MRI based on local resources and capacity. To reflect this variation, two scenarios were modelled: one using CT scans – typically lower cost per scan but with a higher frequency (on average – total of 5.3 scans) – and another using MRI scans, which are more expensive but used less frequently (on average – total of 3.5 scans).

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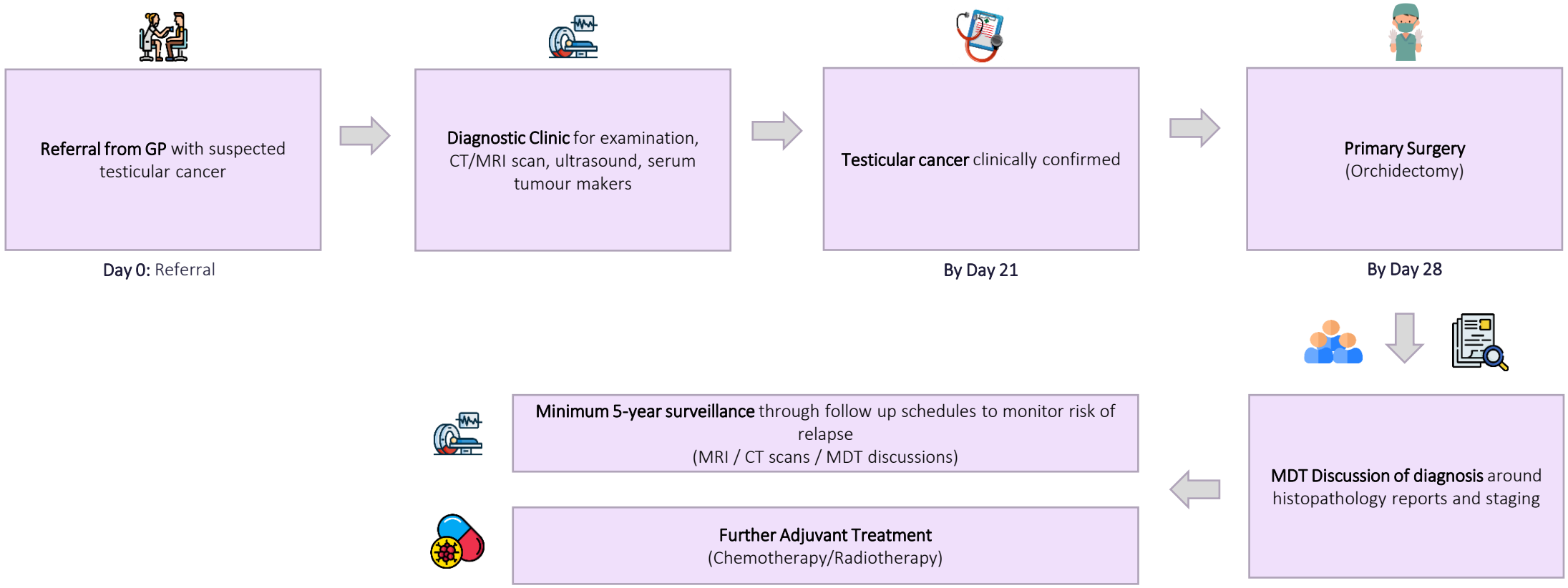
1. *CT Scan surveillance schedule [Source: Guidelines for the Management of Testicular Cancer (West Midlands Expert Advisory Group), 2016]*
2. *MRI Scan surveillance schedule [Source: Anglian follow up schedule – clinical input]*

Simplified diagnostic pathway for GCT testicular cancer

The diagram below shows a simplified diagnostic pathway (based on a NHSE Guidelines for the Management of Testicular Cancer and discussions with clinicians) for patients with suspected testicular cancer. Patients undergo various diagnostics, which include imaging and serum tumour markers, before testicular cancer is clinically confirmed. The primary treatment for testicular cancer is primary surgery, then patients who are cured will then be put on a minimum 5-year surveillance period to monitor risk of relapse.



1. *[Source: Guidelines for the Management of Testicular Cancer (West Midlands Expert Advisory Group), 2016]*

Simplified diagnostic pathway for GCT testicular cancer – surveillance period

The table below outlines the minimum number of scans required over a five-year surveillance period, with variability based on imaging modality (CT vs MRI), tumour type, and disease stage. CT-based schedules involve more frequent imaging, averaging approximately 5.3 scans, while MRI-based schedules require around 3.5 scans over the same period.

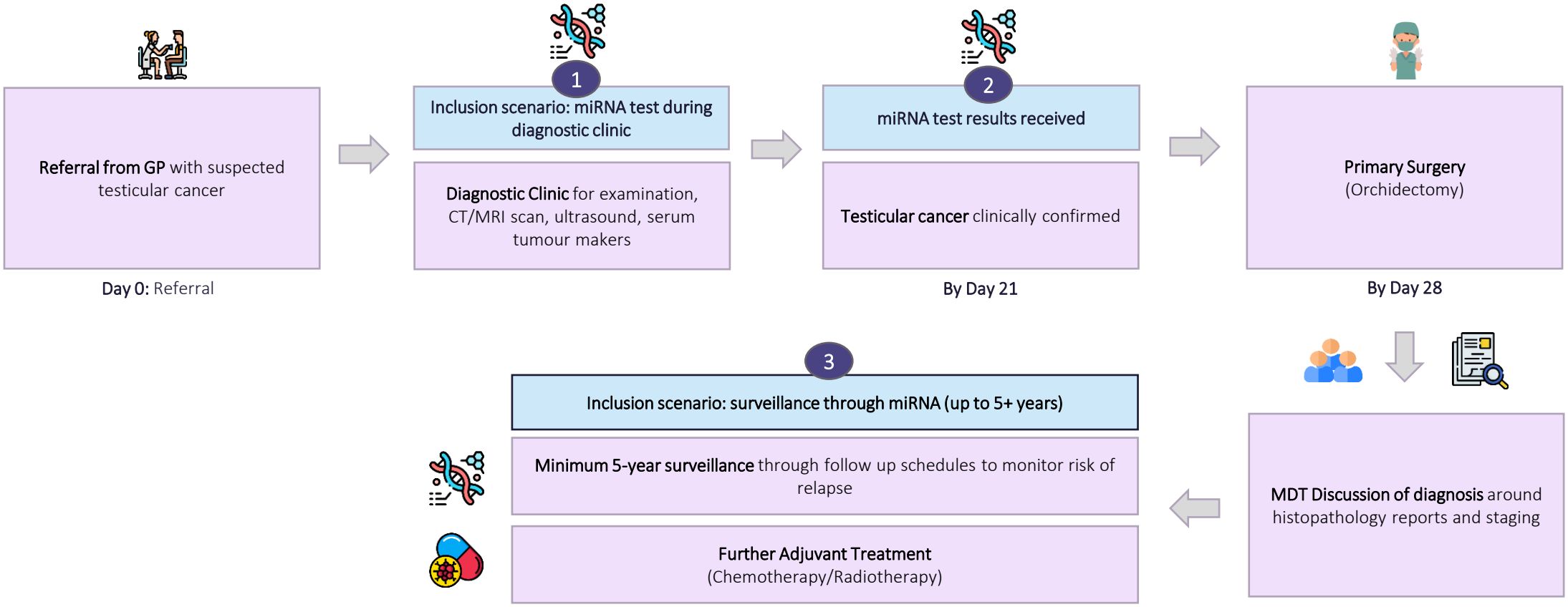
Please note: these figures reflect routine surveillance only – additional scans may be required if clinical concerns arise during follow up

	Number of CT Scans				Number of MRI Scans			
Post-treatment year	Stage 1 Seminoma	Stage 1+ Seminoma	Stage 1 Non-Seminoma	Stage 1+ Non-Seminoma	Stage 1 Seminoma	Stage 1+ Seminoma	Stage 1 Non-Seminoma	Stage 1+ Non-Seminoma
Year 1	2	2	2	2	1	1	2	2
Year 2	1	2	1	2	1	1	1	1
Year 3	1	1	1	1	1	1	0	0
Year 4	1	1	0	1	0	0	0	0
Year 5	0	0	0	0	1	1	0	0
Total	5	6	4	6	4	4	3	3

1. *CT Scan surveillance schedule [Source: Guidelines for the Management of Testicular Cancer (West Midlands Expert Advisory Group), 2016]*
2. *MRI Scan surveillance schedule [Source: Follow up schedule from clinical input]]*

Inclusion scenario for miRNA testing and benefits

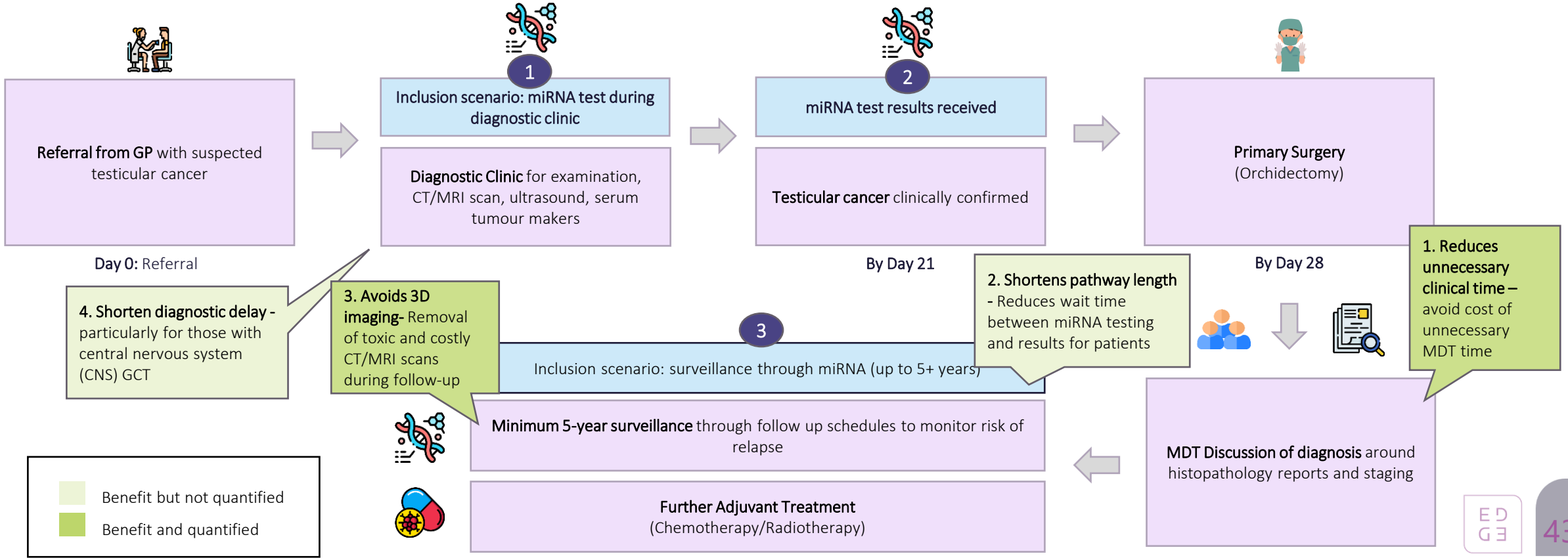
Under the inclusion scenario, miRNA testing is introduced at the diagnostic clinic and used throughout the surveillance period as a more effective tool for monitoring relapse risk. The initial test, taken at diagnosis, serves as a baseline reference for ongoing surveillance, effectively replacing routine imaging within the follow-up schedule.



1. *[Source: Guidelines for the Management of Testicular Cancer (West Midlands Expert Advisory Group), 2016]*

Inclusion scenario for miRNA testing and benefits

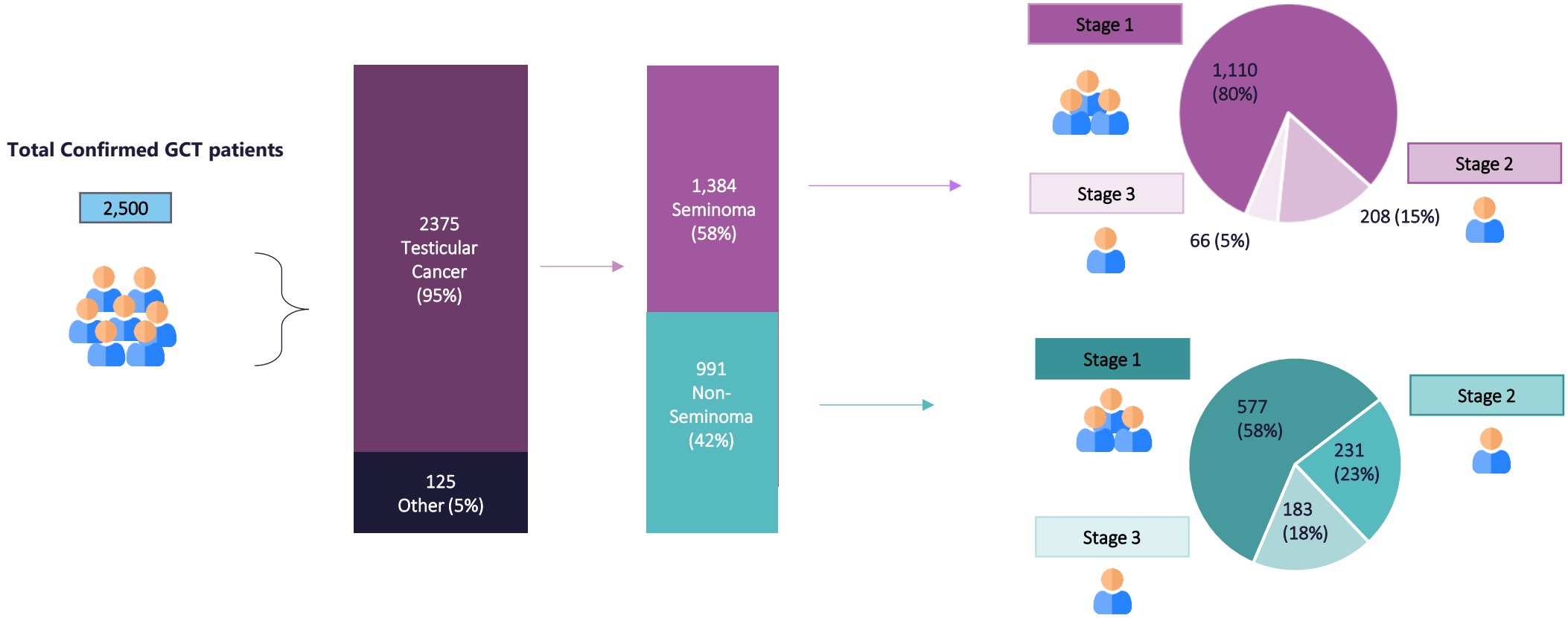
Including miRNA testing in the surveillance period was modelled to replace imaging and enable faster turnaround times. This not only reduces the burden on clinical staff by minimising the need for unnecessary scan reviews and MDT discussions but over time, also helps free up healthcare capacity. Additionally, miRNA testing may help shorten diagnostic delays in rare cases such as CNS GCT, where traditional diagnostic approaches are more limited.



1. *[Source: Guidelines for the Management of Testicular Cancer (West Midlands Expert Advisory Group), 2016]*

Understanding the GCT population

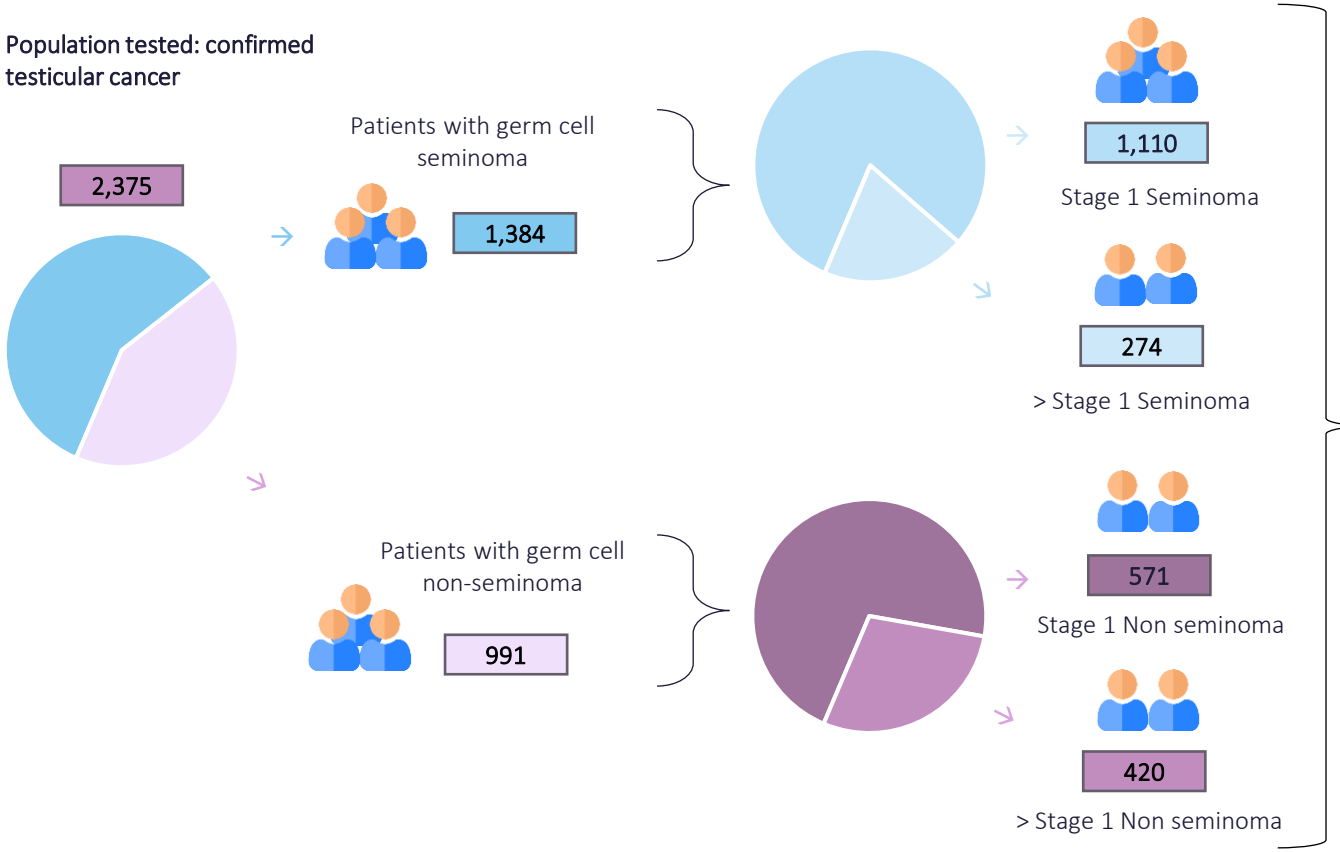
Between 2017 and 2019, roughly 2,500 new cases of germ cell tumours (GCT) were diagnosed annually in the UK, with testicular cancer accounting for 95% of these cases. Approximately 58% of these cases are split into seminoma, which are generally more predictable and easier to monitor, while 42% are non-seminoma, which requires more intensive follow-up as they can spread more quickly. The diagram below provides a further breakdown of tumour stages by seminoma and non-seminoma, which in turn, affects the frequency of scans required during the surveillance period.



1. *[Source: Cancer Research UK, 2017-2019]*
2. *95% of GCT cases are testicular cancer cases [Source: Rubero et al., 2021]*
3. *Breakdown in testicular GCT types [Source: Gandaglia et al., 2014]*

Tested population miRNA inclusion scenario

The tested population in this scenario includes 2,375 patients with confirmed testicular GCT cancer. Despite high survival rates, patients remain at risk of recurrence and late treatment effects, necessitating up to at least 5 years of follow-up. Current diagnostic procedures suggest a need for exploring alternatives to existing biomarkers and CT/MRI scans for monitoring during and after treatment.



Surveillance Period Post-Treatment*

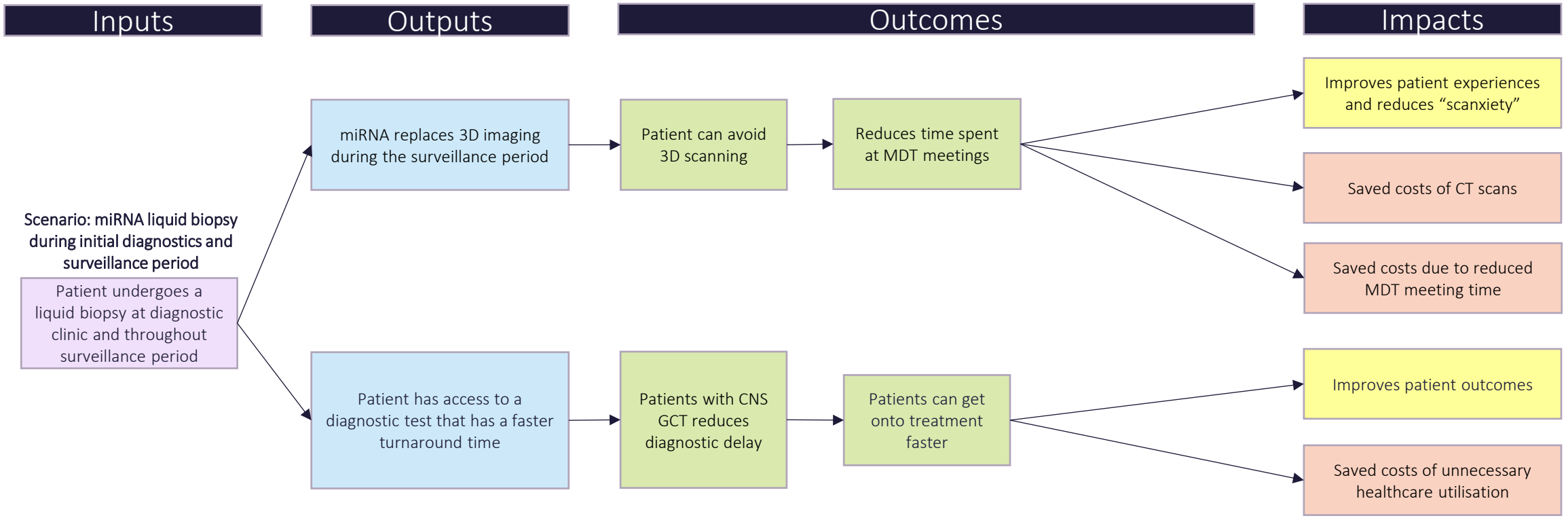
Post-treatment year	# of scans (stage 1 seminoma)	# of scans (stage 1+ seminoma)	# of scans (stage 1 non-seminoma)	# of scans (stage 1+ non-seminoma)
Year 1	1-2	1-2	2	2
Year 2	1	1-2	1	1-2
Year 3	1	1	0-1	0-1
Year 4	0-1	0-1	0	0-1
Year 5	0-1	0-1	0	0

*Number of scans during the surveillance period will vary depending on practice's 3D imaging resources and whether they utilise mainly CT scans or MRI scans

1. *miRNA outperforms traditional tumour markers [Source: Almstrup et al., 2020]*
2. *CT Scan surveillance schedule [Source: Guidelines for the Management of Testicular Cancer (West Midlands Expert Advisory Group), 2016]*
3. *MRI Scan surveillance schedule [Source: Anglian follow up schedule – clinical input]]*

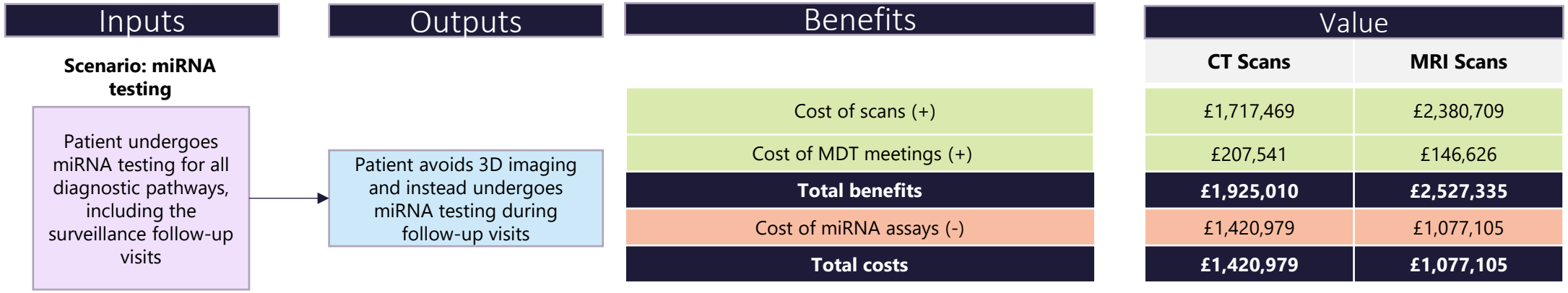
Understanding impact of inclusion scenario

The logic model below sets out how the impacts that miRNA testing on the GCT testicular cancer pathway can have on the healthcare system and individual patients.



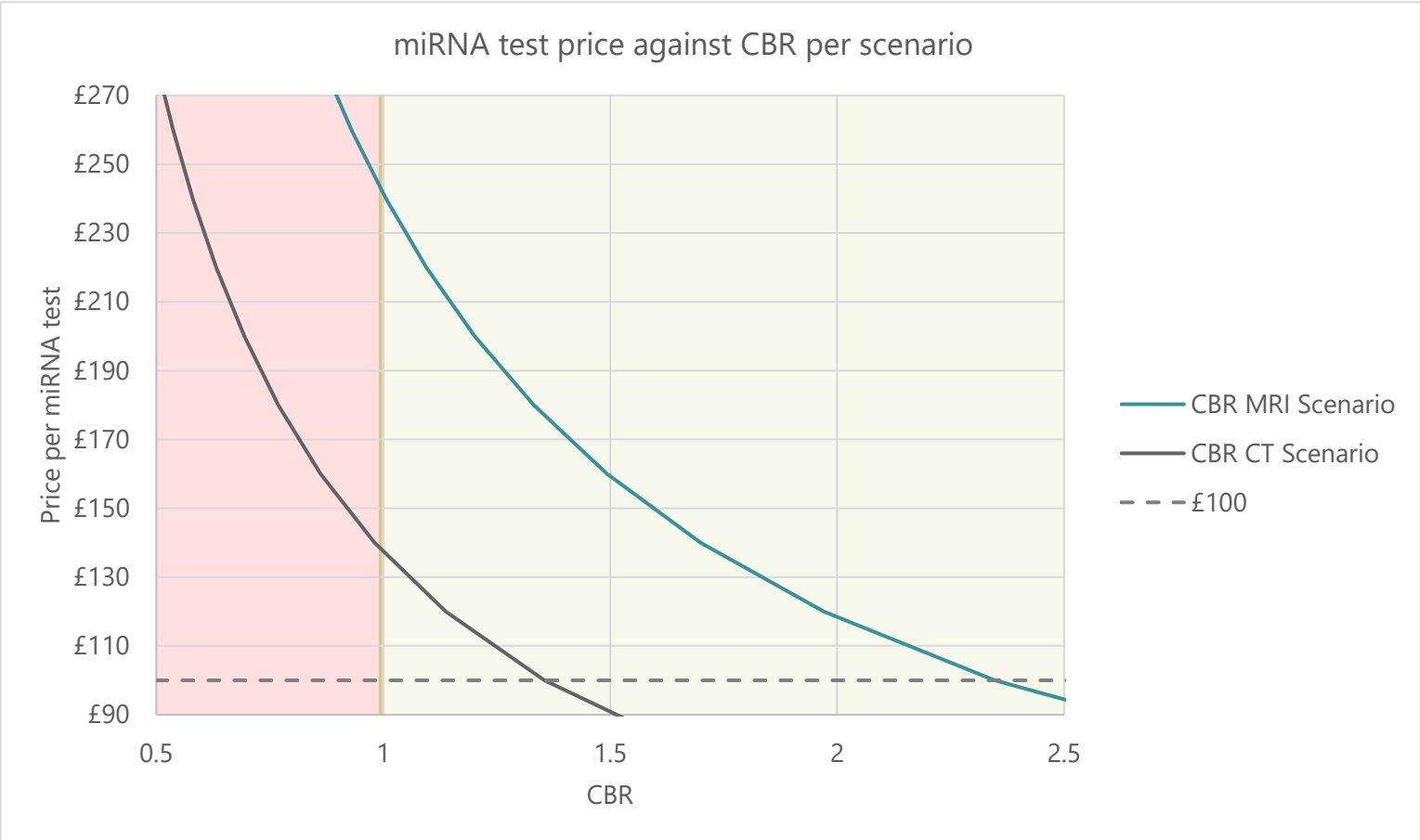
Estimating benefits of miRNA scenario

The estimated impacts of ctDNA testing on a population of around 2,375 patients are presented below. Overall, the benefits outweigh the costs with a benefit cost ratio of 1.35 in the CT scan scenario and 2.35 in the MRI scan scenario.



miRNA inclusion in surveillance scenario (+ 1 test at initial presentation)	Value	
	CT Scans	MRI Scans
Tested population	2,375	
Benefit cost ratio	1.35	2.35
Net impact	£504,031	£1,450,230

Sensitivity testing cost-neutral price scenarios



The chart illustrates how the cost of the miRNA test affects the benefit-cost ratio over a five-year post-treatment surveillance period for GCT patients.

Cost-neutrality is estimated to be achieved at approximately **£138** in CT scan scenario and **£241** in the MRI scan scenario. The difference between these scenarios reflects both the higher cost of MRI scans and the variation in the number of scans required, depending on the follow-up schedule. The vertical line at **£100** represents the current cost of the miRNA test (not including tube, transportation, and distribution costs).

4

Advanced breast cancer

Structure of evaluation

The aim of this section of the report is to present a summary of the health economic results and accompanying materials that were developed during the evaluation of liquid biopsy ctDNA testing for late-stage advanced breast cancer patients. To do this, the following topics will be covered:

1) Background and summary of health economic results

2) Simplified diagnostic pathway, ctDNA inclusion scenario, and associated benefits

3) Relapsed advanced breast population, sub-types, and tested population

4) Understanding and estimating the impact of the inclusion scenario

Background

1. Clinical Background & Diagnostic Challenge

Advanced breast cancer is a common and recurrent malignancy managed within the NHS. In patients with oestrogen receptor-positive (ER+), HER2-negative disease, resistance to endocrine therapy often develops in the metastatic setting. This progression is frequently driven by mutations acquired through first-line (1L) treatment such as ESR1, with other genomic alterations like PIK3CA mutations emerging or becoming clinically relevant at relapse. Despite these mutations being actionable, genomic testing via tissue biopsy at the time of this evaluation was not routinely available in the second-line (2L) setting due to the absence of established pathways and capacity. This lack of infrastructure left patients without access to appropriate targeted therapies despite their eligibility.

2. Evaluated Scenario: ctDNA testing after 1L progression

This evaluation models the inclusion of ctDNA testing within the advanced treatment pathway for ER+ HER2-negative breast cancer patients, specifically after progression on prior endocrine therapy. Unlike other indications assessed in this report, the ctDNA testing pathway is introduced as a standalone genomic testing approach rather than being compared to an existing tissue-based diagnostic pathway. The aim of the scenario was to identify ESR1 and PIK3CA mutations using a single blood test, offering a non-invasive and accessible solution for molecular profiling once patients have already undergone 1L treatment.

The eligible population is estimated at 11,500 patients annually in the UK. This evaluation was initiated before NICE TA1036 which recommended the use of Elacestrant for ESR1-mutant disease. As a result, economic modelling was paused, and comparative benefits such as avoided biopsy costs, shorter diagnostic timelines, and reduced MDT burden were not assessed due to the absence of a viable tissue-based comparator. Recognising this narrower scope, the economics focuses specifically on assessing the trade-off between the QALY gains from targeted therapies enabled by ctDNA testing and the associated costs of delivering the test.

3. Forward View

The utility of ctDNA testing at the time of the evaluation lay in its ability to identify actionable mutations where no alternative testing infrastructure existed, increasing uptake for patients with eligibility for targeted treatments that could improve PFS and quality of life. With the recent approval of Elacestrant and addition of ESR1 testing on the test directory, an assessment of liquid biopsy ctDNA against the standard tissue biopsy pathway is warranted to fully evaluate the relative costs and benefits.

1. *[Source: Cancer Registration Statistics, 2022]*
2. *[Source: Lee & Pant, 2023]*

Summary of health economic results

Scenario: ctDNA for patients after 1L progression (Large panel/small panel)

Total benefit: £34.4m
Total cost: £20.5m/£9.7m

→

Net impact: +£13.9m/+£24.7m
Benefit Cost Ratio: 1.68/3.55

Quality of Life: increases in QOL due to better treatment access

- Through patients being able to access Elacesrtant for ESR1 mutations, and Alpelisib with Fulvestrant for PIK3CA, progression free survival is extended and quality of life whilst on treatment also increases
- When quantified at a willingness to pay threshold of £30,000 this amounts to **£34m in benefits**

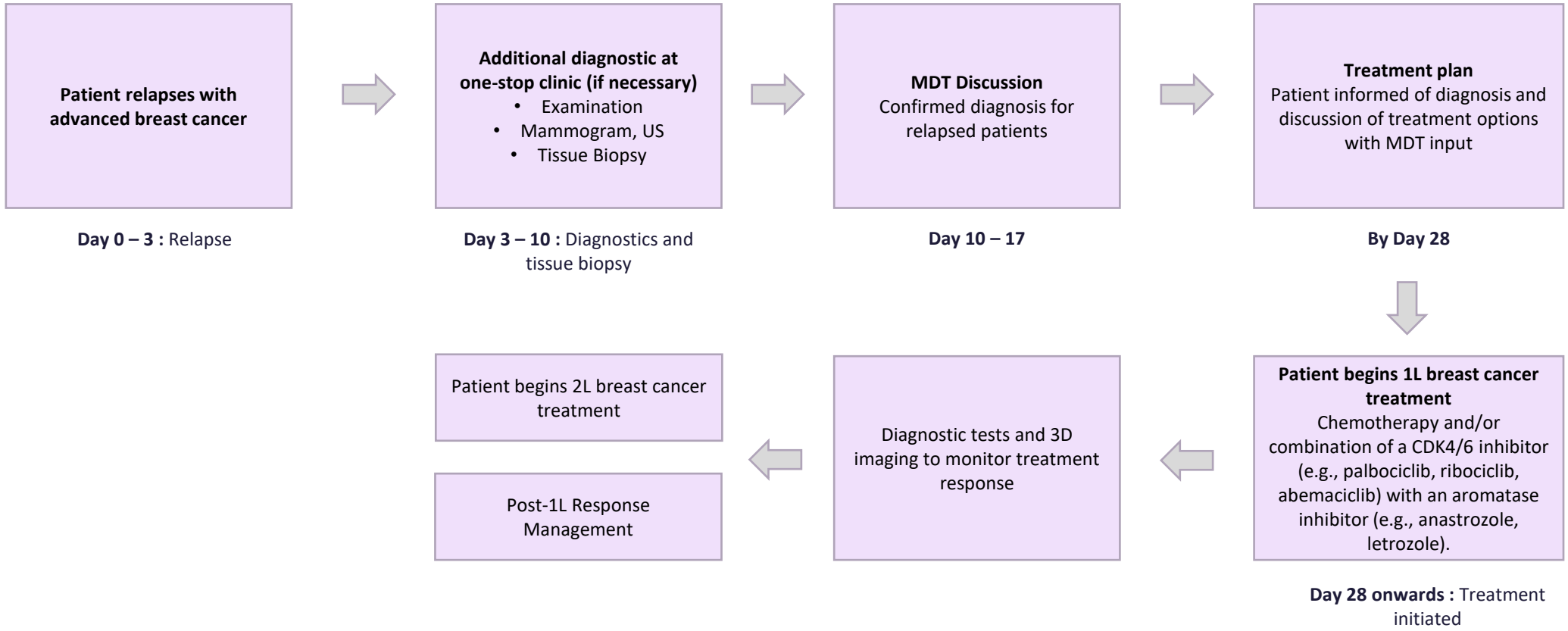
Summary of results:

This evaluation models the inclusion of ctDNA testing for patients with advanced breast cancer who progress following first-line (1L) aromatase inhibitor therapy. **The analysis generates an estimated net total benefit of £34.4 million against a total cost of £20.5 million (large panel) and £9.7 million (small panel), resulting in a net impact of £13.9 million or £24.7m and a benefit-cost ratio of 1.68 or 3.55.**

Unlike other indications such as HPB and CUP, **this methodology does not include broader system benefits**, such as reduced diagnostic loops or shorter diagnostic timelines. Instead, it focuses exclusively on quality-of-life improvements achieved through access to Elacestrant for ESR1 mutations and Alpelisib with Fulvestrant for PIK3CA mutations. The valuation of QALY gains is based on a willingness-to-pay (WTP) threshold of £30,000 per QALY, which aligns with standard NICE guidelines. At this threshold, the model estimates a total benefit of £34 million.

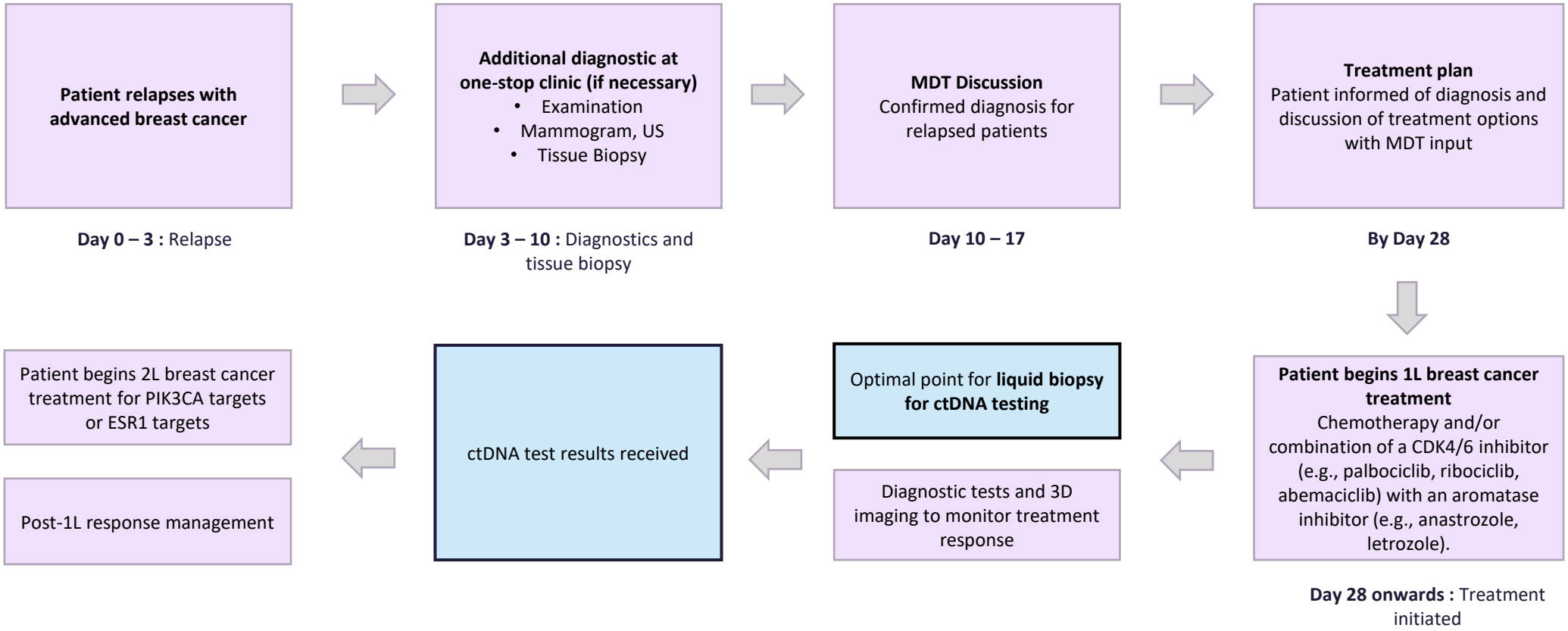
Simplified diagnostic pathway for advanced breast cancer

The diagram below shows a simplified diagnostic pathway (based on discussions with clinicians) for patients with suspected late stage relapsed advanced breast cancer. Patients relapse and are discussed at an MDT, usually beginning 1L treatment on a combination of CDK4/6 inhibitors with an aromatase inhibitor.



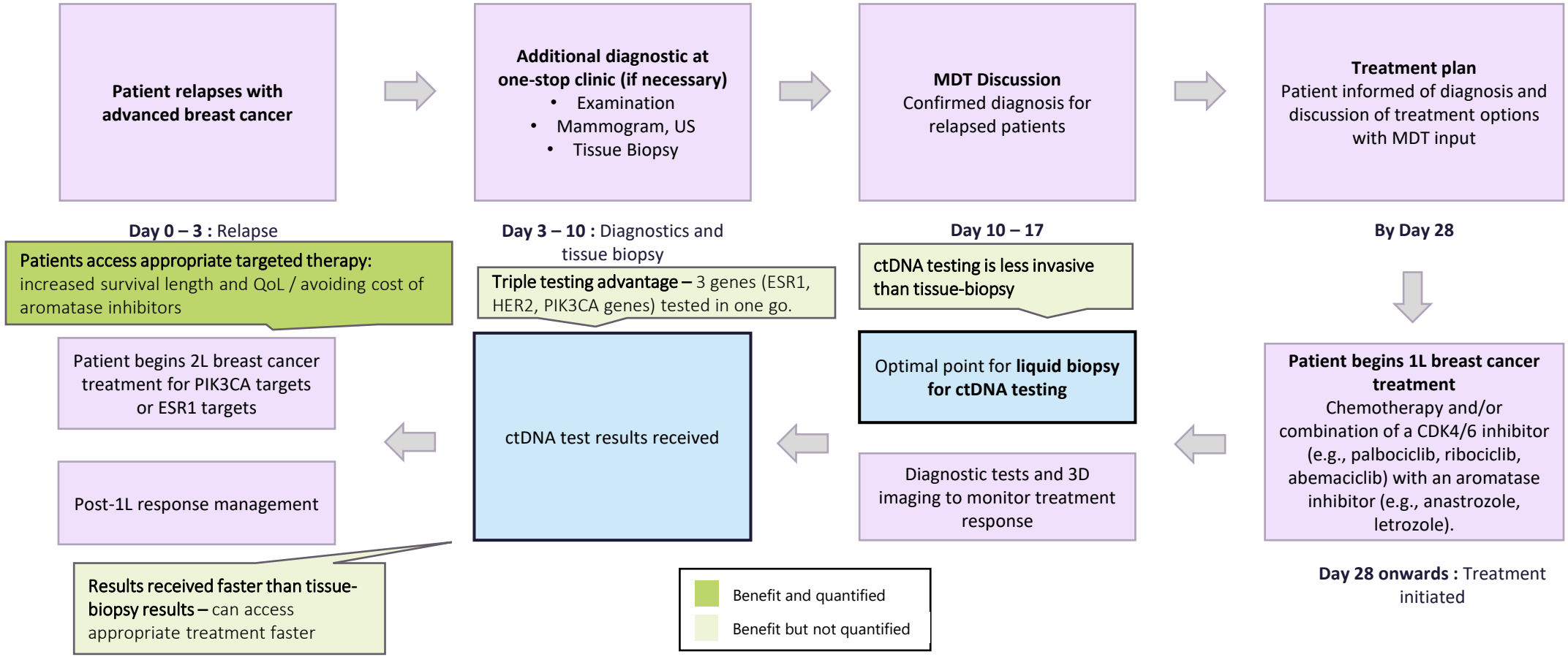
Inclusion scenario for ctDNA in the pathway

In the inclusion scenario, ctDNA testing is introduced after the conclusion of first-line (1L) treatment. At this point, patients may have developed an ESR1 mutation from 1L treatment, making them eligible for targeted therapies in the second-line (2L) setting. Additionally, PIK3CA alterations become clinically relevant at this stage, as they also have targeted treatment options available in the 2L. Currently, standard and recommended practices do not include tissue biopsy pathways at this stage. Moreover, previous tissue biopsies cannot be used for ESR1 testing because these mutations are acquired through therapy necessitating a more recent assessment such as through ctDNA testing.



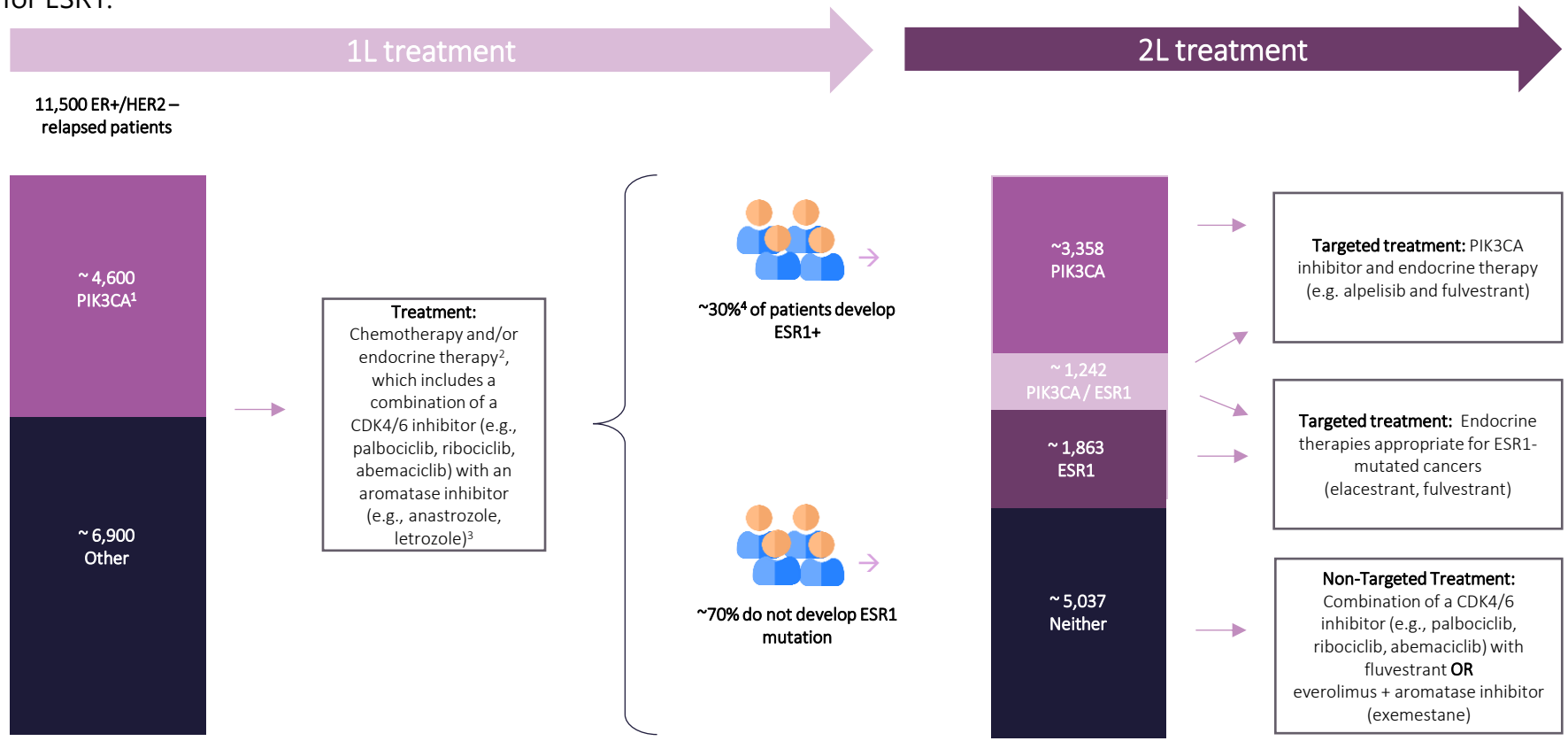
Inclusion scenario for ctDNA in the pathway

Integrating ctDNA testing after 1L treatment enables access to targeted therapies for ESR1 (Elacestrant) and PIK3CA (Alpelisib and Fulvestrant) mutations. Importantly, since no tissue biopsy pathway was stated to exist post-1L, an absence of genomic testing via tissue biopsy was assumed as the appropriate comparator. As a result, the traditional advantages ctDNA testing has over tissue biopsy such as being less invasive, causing few complications and being faster were not quantified. Future work could look to investigate these under a scenario where tissue biopsy and genomic testing are hypothetically assumed to exist post 1L.



Relapsed advanced breast cancer population and target populations

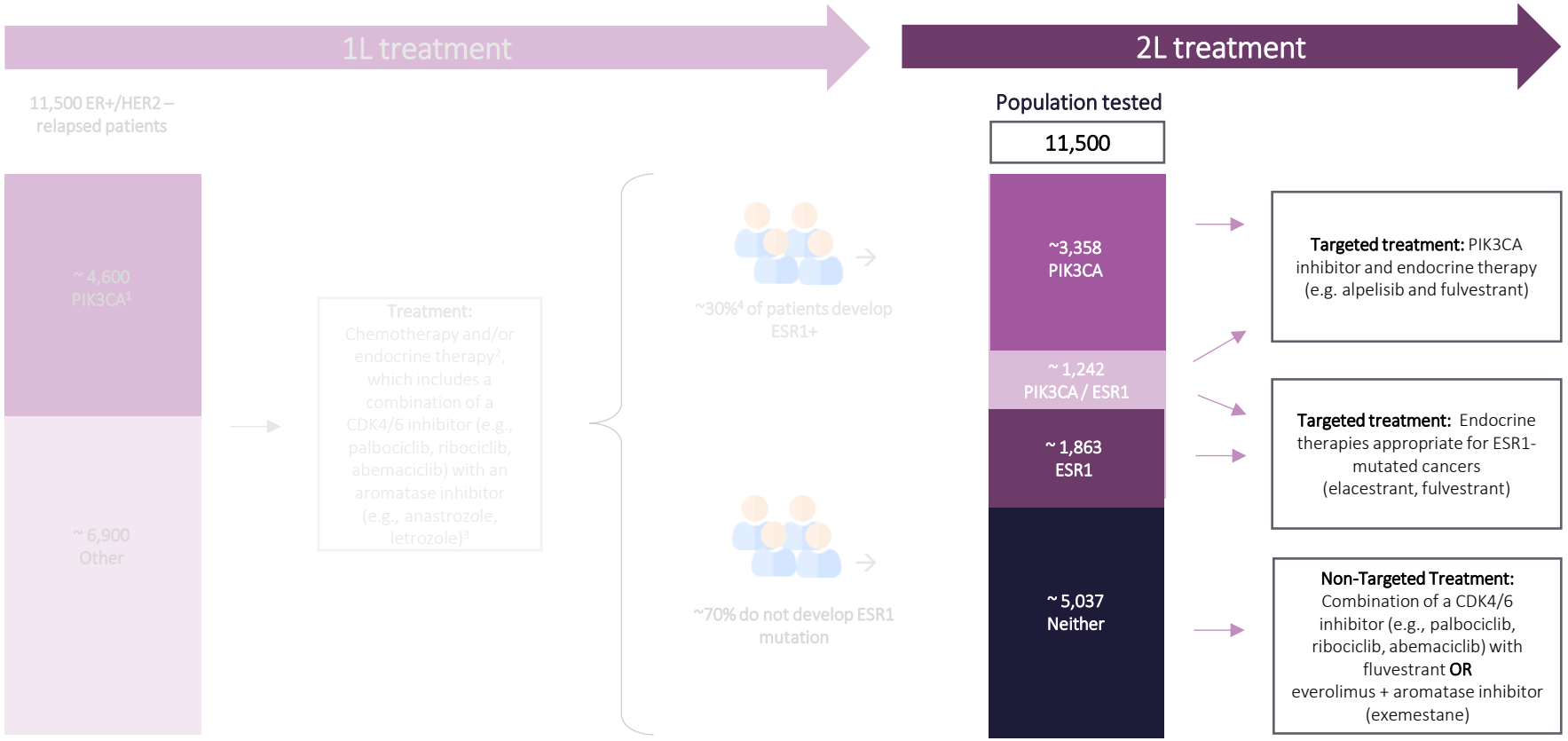
Approximately 11,500 patients relapse/present with ER+/HER2- advanced breast cancer annually, of which ~40% have a pre-existing PIK3CA mutation. After standard 1L treatment, which involves chemotherapy and endocrine therapy, ~30% develop an ESR1+ mutation and resistance to standard aromatase inhibitors. If patients progress after 1L, identifying these mutations through ctDNA testing is essential to guide appropriate 2L targeted treatments like Alpelisib for PIK3CA and Elacestrant for ESR1.



1. *40% of ER+/HER2- patients have a PIK3CA mutations [Source: NHS Wales Mutated Breast Cancer Document]*
2. *[Source: NICE clinical guidance on advanced breast cancer, 2009]*
3. *[Source: NICE TA11263 Final Scope Document]*
4. *[Source: Brett et al., 2021]*
5. *[Source: Jacobson, 2022]*

Tested population for ctDNA inclusion scenario

The modelling assumes all 11,500 ER+/HER2- relapsed patients undergo ctDNA testing following 1L treatment. While not all patients will progress to 2L, this approach provides an upper bound estimate of the potential benefit of incorporating ctDNA testing into the pathway to guide targeted 2L treatment decisions.



1. *40% of ER+/HER2- patients have a PIK3CA mutations [Source: NHS Wales Mutated Breast Cancer Document]*
2. *[Source: NICE clinical guidance on advanced breast cancer, 2009]*
3. *[Source: NICE TA11263 Final Scope Document]*
4. *[Source: Brett et al., 2021]*
5. *[Source: Jacobson, 2022]*

Estimating benefits of ctDNA scenario

The estimated impacts of ctDNA testing for approximately 11,500 patients annually are presented below. These estimates specifically assess the trade-off between the QALY gains from targeted therapies enabled by ctDNA testing and the associated costs of delivering the test. Additional scenarios and alternative modelling approaches are detailed in the appendix. Overall, significant QALY benefits are realised as patients' treatment options improve, with these benefits valued against testing costs through the benefit-cost ratio calculation.

Inputs	Outputs
Patient undergoes ctDNA testing after 1L treatment to evaluate treatment response	Patient accesses targeted treatments specific to ESR1 and PIK3CA mutations instead of standard 2L treatment

Benefits	Value	Lower Bound	Upper Bound
QALY benefits from targeted treatments (+)	£34,358,228	£34,358,228	£34,358,228
Total benefits	**£34,358,228**	**£34,358,228**	**£34,358,228**
Cost of ctDNA tests (LB: G360, UB: Small panel) (-)	£20,486,394	£20,486,394	£9,664,894
Total costs	**£20,486,394**	**£20,486,394**	**£9,664,894**

ctDNA during diagnostic pathway for relapse patients after 1L	Value	LB	UB
Tested population		**11,500**	
Benefit cost ratio (LB: G360, UB: Small panel)	**1.68**	**1.68**	**3.55**
Net impact	**£13,871,834**	**£13,871,834**	**£24,693,334**

5

Paediatric Cancer

Background

1. Clinical Background & Diagnostic Challenge

Paediatric cancers, including neuroblastoma, represent a challenging and diverse group of malignancies affecting children aged 0–14 years old. Neuroblastoma is one of the most common solid tumours in childhood, typically arising in nerve tissue and accounting for a substantial proportion of paediatric cancer-related deaths. Each year, approximately 100 new neuroblastoma cases are diagnosed in the UK.

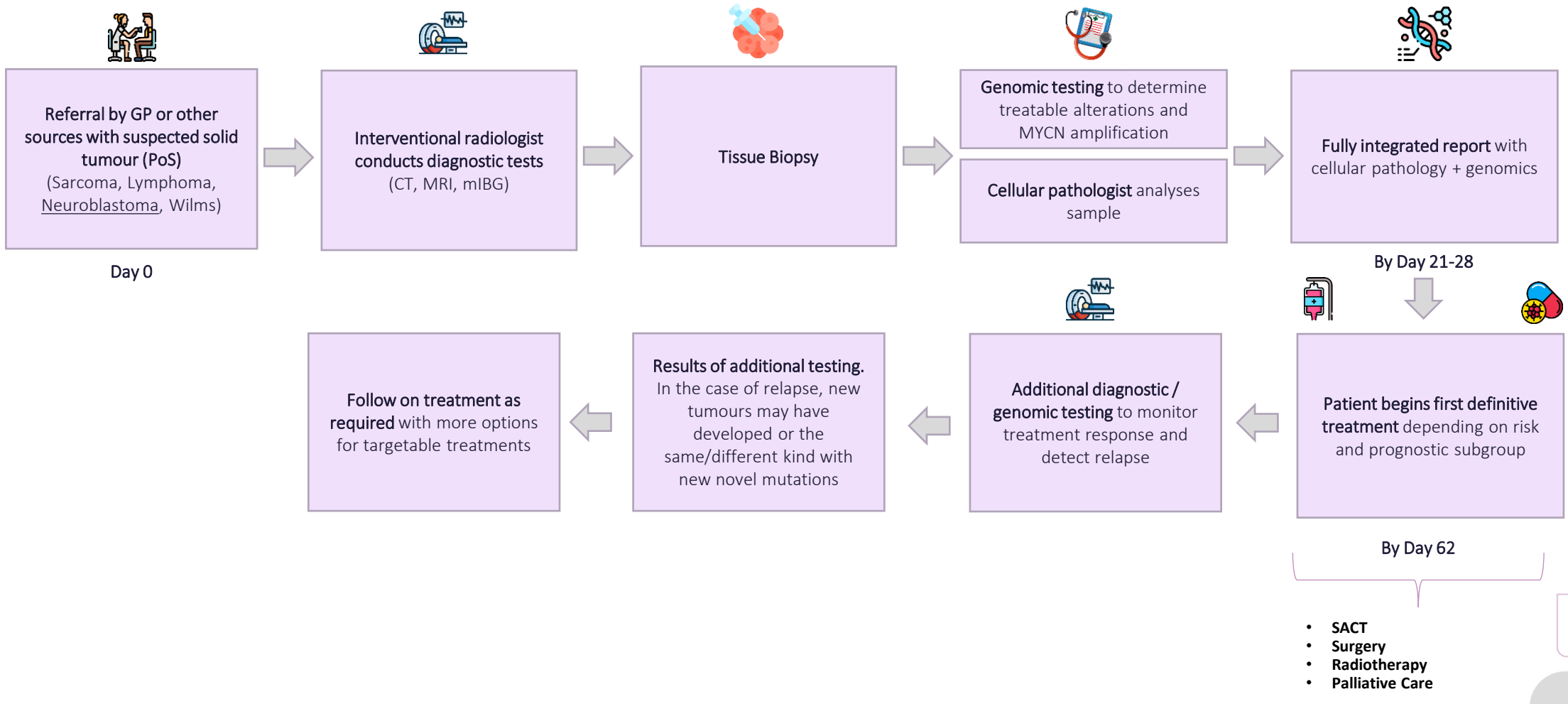
2. Evaluation of the Diagnostic Pathway

Initial assessments identified several potential inefficiencies in the paediatric cancer pathway, including the insensitivity of fine needle biopsies, inability to perform biopsies in complex paediatric cases, long turnaround times for genomics testing, and clinical risks and costs associated with invasive procedures. However, clinical feedback indicated that the potential benefits of ctDNA testing in this pathway were less clear than initially suggested, with aspects of the pathway being less well-defined. As such, further investigation and consultation with clinical stakeholders are needed to ensure a robust and meaningful evaluation before proceeding with inclusion scenario analysis.

Paediatric Cancer

Simplified diagnostic pathway for neuroblastoma (indicative)

The diagram below shows the initial simplified diagnostic pathway that was discussed during meetings to garner clinical input.



Paediatric Cancer

Inclusion scenario for ctDNA in the pathway (indicative)

Integrating ctDNA was initially thought to be able to be included during diagnosis.

1.) More patients can access more appropriate/effective treatment - ctDNA testing can be used when tissue biopsy is not feasible

2.) No need for genomic testing for those with positive test – eliminates associated costs

Referral by GP or other sources with suspected solid tumour (PoS)
(Sarcoma, Lymphoma, Neuroblastoma, Wilms)

Day 0

Interventional radiologist conducts diagnostic tests
(CT, MRI, mIBG)

1.) Optimal point for **liquid biopsy for ctDNA testing**

Tissue Biopsy

Genomic testing to determine treatable alterations and MYCN amplification

Cellular pathologist analyses sample

ctDNA results received for primary diagnosis

Fully integrated report with cellular pathology + genomics

By Day 21-28

Patient begins first definitive treatment depending on risk and prognostic subgroup

By Day 62

- **SACT**
- **Surgery**
- **Radiotherapy**
- **Palliative Care**

3. ctDNA Is less invasive than tissue biopsy – reduces costs of associated treatment and outcomes

2.) Optimal point for **liquid biopsy for ctDNA testing**

Additional testing to monitor treatment response and detect relapse

ctDNA results

Results of additional testing.

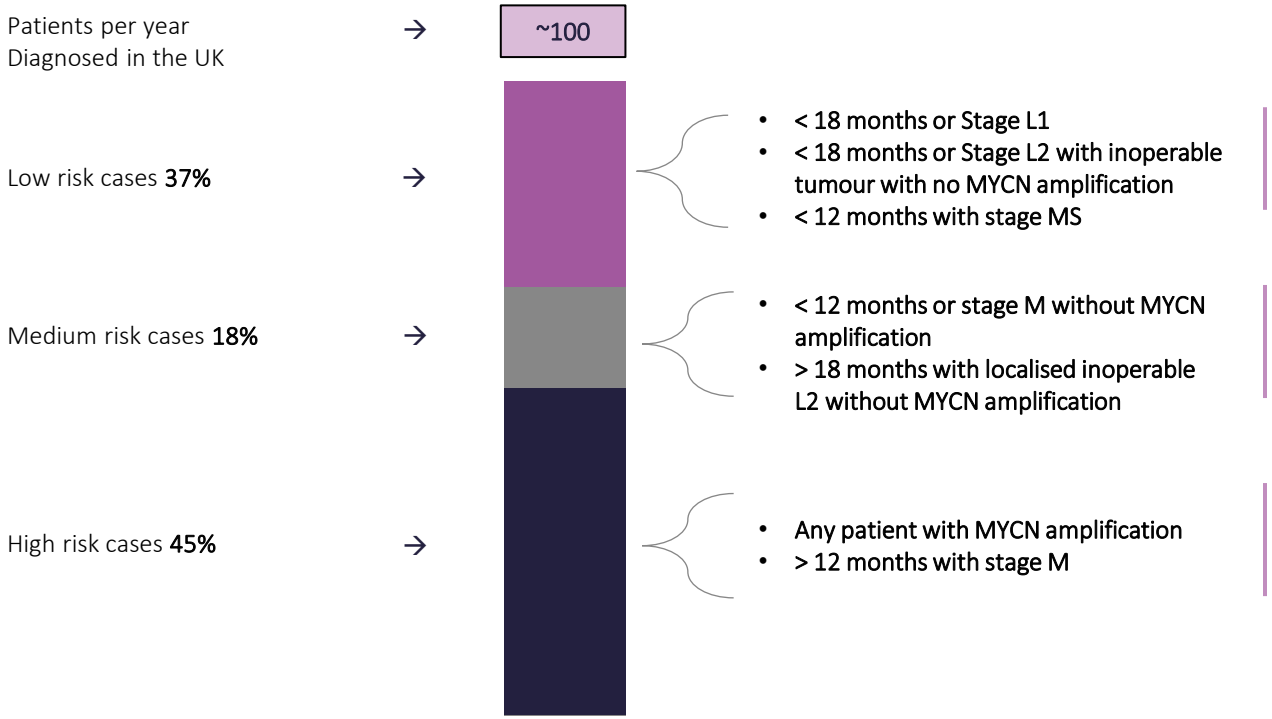
Follow on treatment as required with more options for targetable treatments

4.) Faster access to targeted therapy for patients with a targetable mutation in clinical trials and conventional treatment for non-targetable tumour

Paediatric Cancer

Understanding the neuroblastoma population (indicative)

Integrating ctDNA was initially thought to be able to be included during diagnosis.



Low-Risk: Observation or chemotherapy followed by surgery based on symptoms and genetic changes.

Intermediate-Risk: Chemotherapy, reassessment, potential surgery, radiotherapy, and 13-cis-retinoic acid.

High-Risk: Intensive chemotherapy, reassessment, surgery, high-dose chemotherapy, radiotherapy, and immunotherapy.

1. *[Source: Cancer Research UK]*
2. *[Source: Children's Neuroblastoma Cancer Foundation]*

Paediatric Cancer

Next steps for the pathway

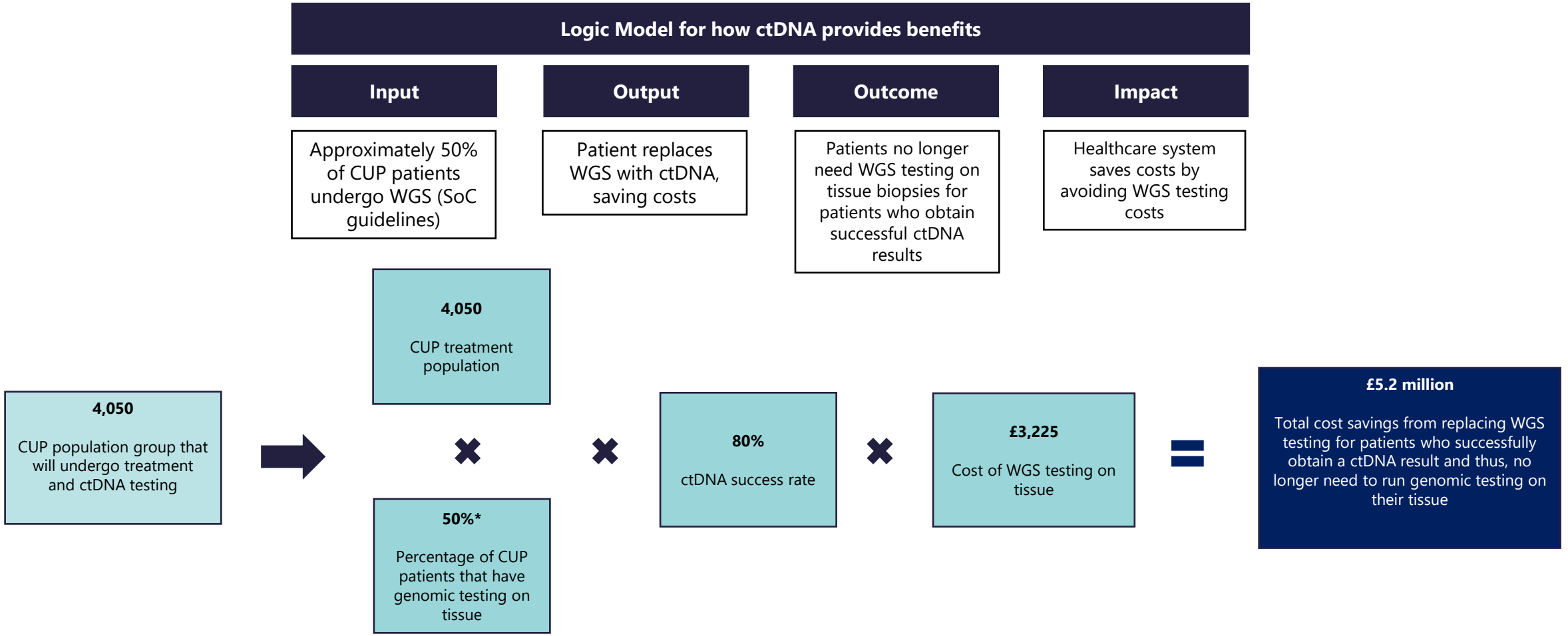
Below are some potential additional steps needed to investigate the full benefits of the pathway for further quantification

Typical benefits	Notes	Next steps
Avoided cost of genomic testing or other diagnostics procedures	• ctDNA was noted as not likely to replace tissue biopsies but may be able to reduce other scans and procedures such as mIGB	• Understanding the extent of the genomic testing that does currently occur on tissue to aid diagnosis and management would be key to exploring the potential benefits of using ctDNA testing instead. • Given the lack of targeted therapies currently in recommended practice, this may focus on risk stratification and diagnosis rather than specifically placing patients onto genomic treatments.
Avoided cost of repeated biopsy Avoided cost of complications of biopsy	• Little was noted around the number of repeat biopsies for these patients. It was understood however that fine needle aspirates are not used; radiologist do core samples which miss less treatable alterations. • Interventional radiologists were also able to build a relatively comprehensive diagnostic picture alone.	• Investigating current patients to understand if there are instances where repeated biopsy takes place. From initial research and engagement, it was understood that patients are often very advanced and can start treatment without a biopsy.
Reduced pathway length (healthcare resource)	• It was noted that there are relatively fast tissue biopsies and treatment times with patients often getting progressed quickly given how advanced they usually are. • There were also relatively few waiting lists due to low volumes. • It was noted that high risk patients often start treatment in < 2 weeks without biopsy.	• Understanding if there are any further instances in the pathway where bottlenecks and delay may be happening and then determining if ctDNA would be able to accelerate this.
QALY for getting onto targeted treatment Avoiding standard treatments	• Targeted treatments were also noted not to be used in current clinical practice although Lorlatinib was in trials at the time of the evaluation.	• Horizon scanning for changes in practice that use targeted treatments based on genomics should be carried out.

Appendix

A.) Cancer of unknown primary: costs & benefits

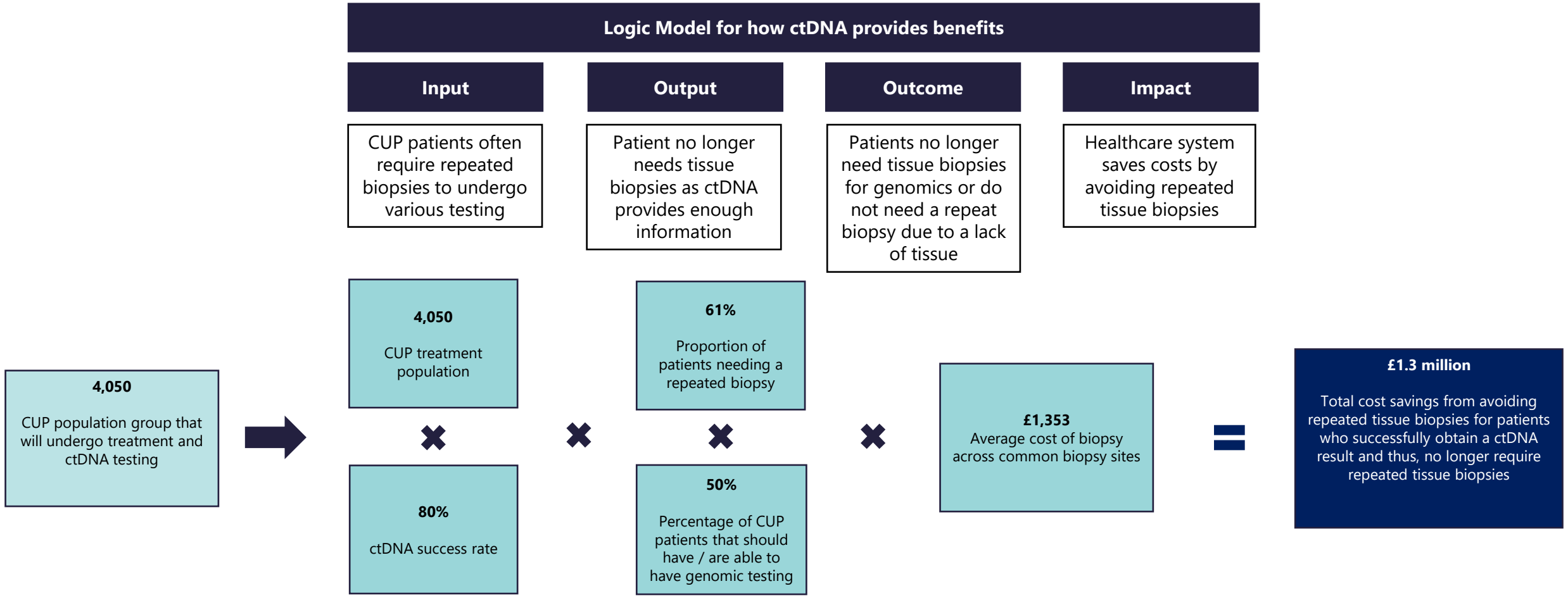
A1.1: Cost savings from tissue biopsies (WGS genomic testing)



* LB assumes 100% patients undergo NGS tissue testing while UB assumes 50/50 split for patients undergoing NGS and WGS tissue testing

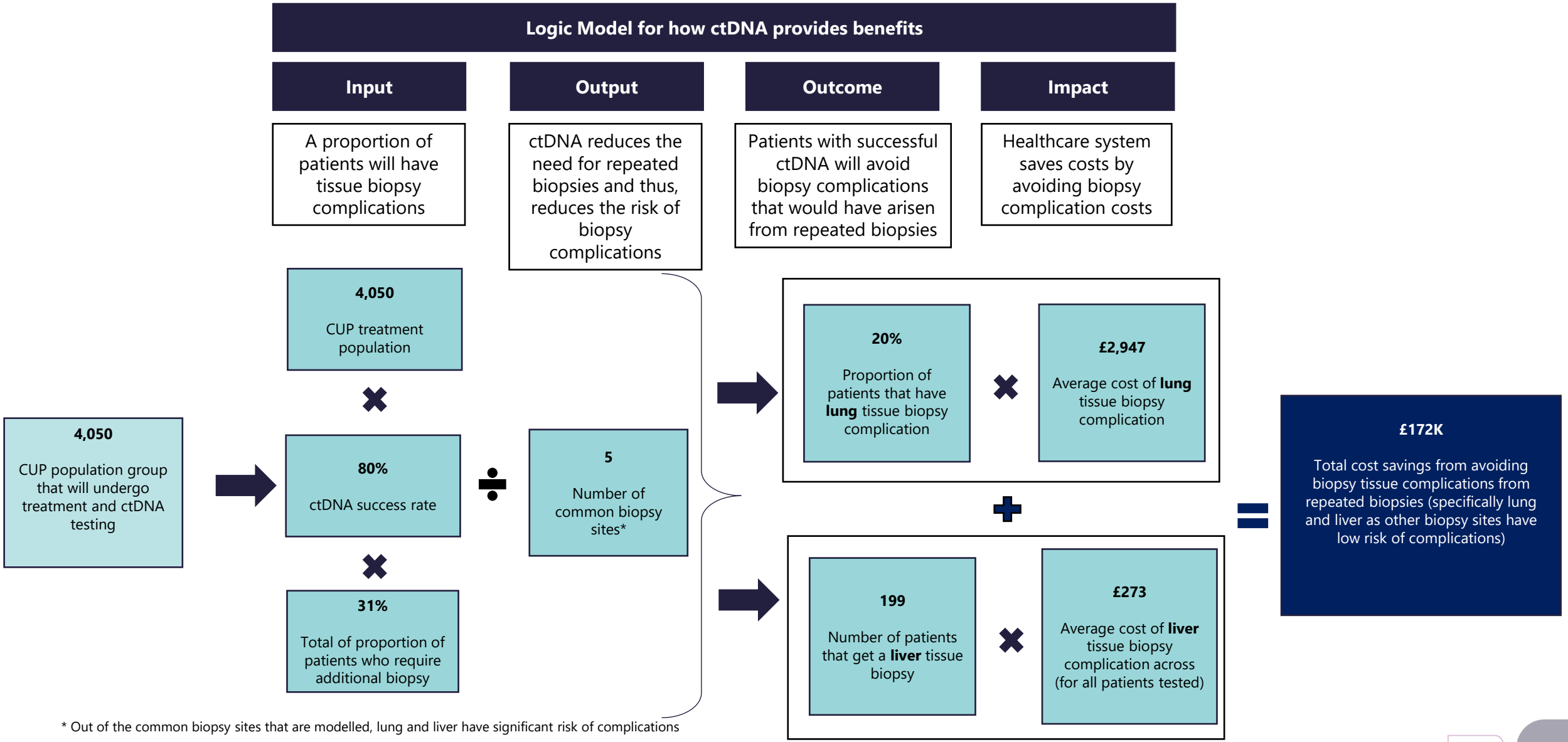
1. *WGS is included in the National Genomic Test Directory and is eligible for CUP patients [Source: NHS South East Genomics CUP]*
2. *CUPCOMP 2024 (awaiting publication) [Source: the Christie Foundation]*
3. *Health Economics in CUP Presentation [Source: Cook, 2023]*

A1.2: Cost savings from repeated tissue biopsies



1. *Cost of biopsies [Source: NIHR Interactive Costing Tool]*
2. *Common sites of biopsy [Source: the Christie Foundation -- CUPCOMP]*
3. *39% had sufficient tissue for successful profiling (from the tissue before the CUP MDT) [Source: Huey et al., 2023]*

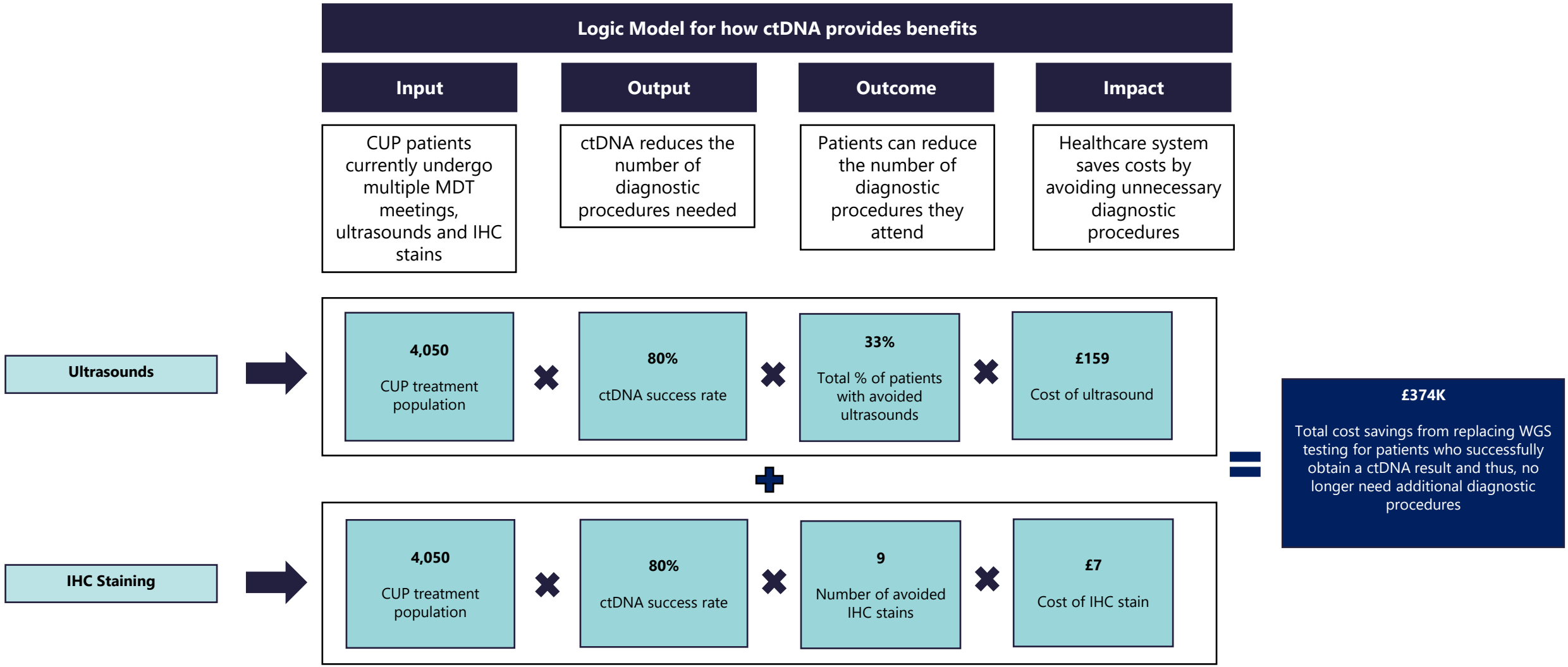
A1.3: Cost savings from tissue biopsy complications



* Out of the common biopsy sites that are modelled, lung and liver have significant risk of complications

1. *Biopsy complications among lung cancer patients [Source: Zhang et al., 2020]*
2. *[Source: National Cost Collection 2023/2024]*
3. *Complications surrounding liver biopsy [Source: Howlett et al., 2013]*

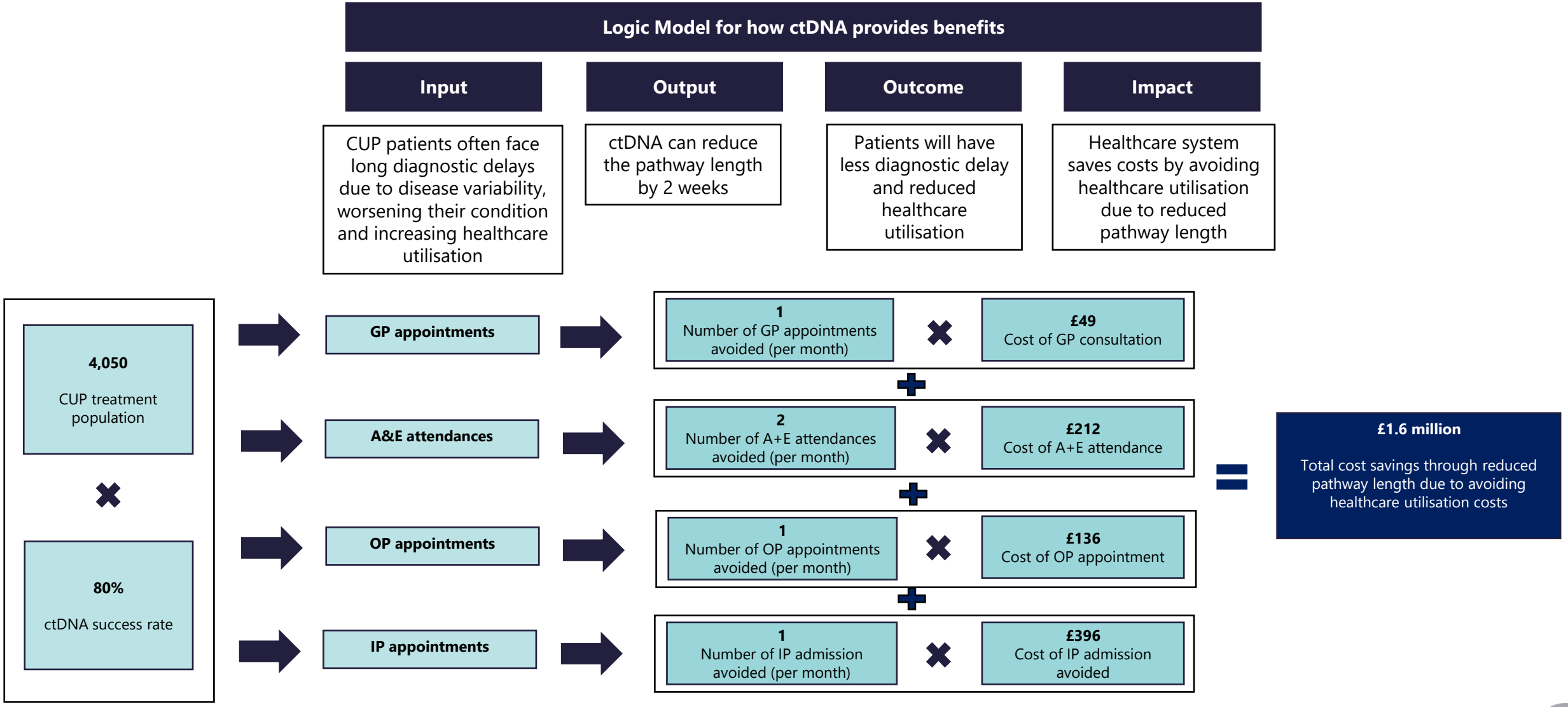
A2: Cost saving from other avoided diagnostic procedures



* LB and UB reflect variance in cost of ultrasound and number of IHC stains
** This model also assumes that IHC staining will get replaced by ctDNA, though this transition may not be immediately reflected in clinical practice

1. *Health Economics in CUP Presentation [Source: Cook, 2023]*
2. *[Source: National Cost Collection 2023/2024]*
3. *Avoided diagnostic procedures [Source: the Christie Foundation -- CUPCOMP]*

A3: Cost saving from reduced pathway length



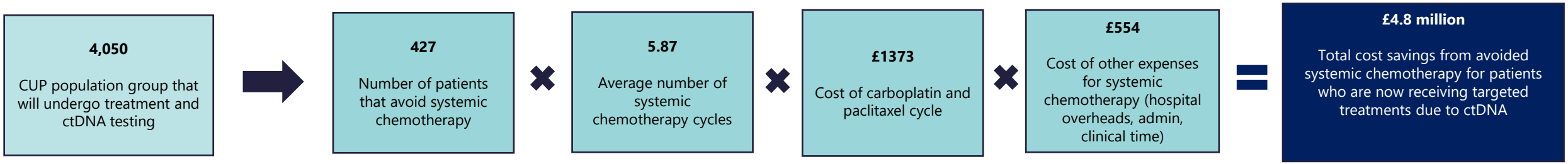
* Core scenario assumes ctDNA reduces pathway length by 2 weeks and LB assumes that ctDNA reduces the pathway length by 1 week

1. *[Source: National Cost Collection 2023/2024]*
2. *[Source: NHSE NSCLC Lung Pilot]*

A4.1: Cost saving from avoided mistreatment

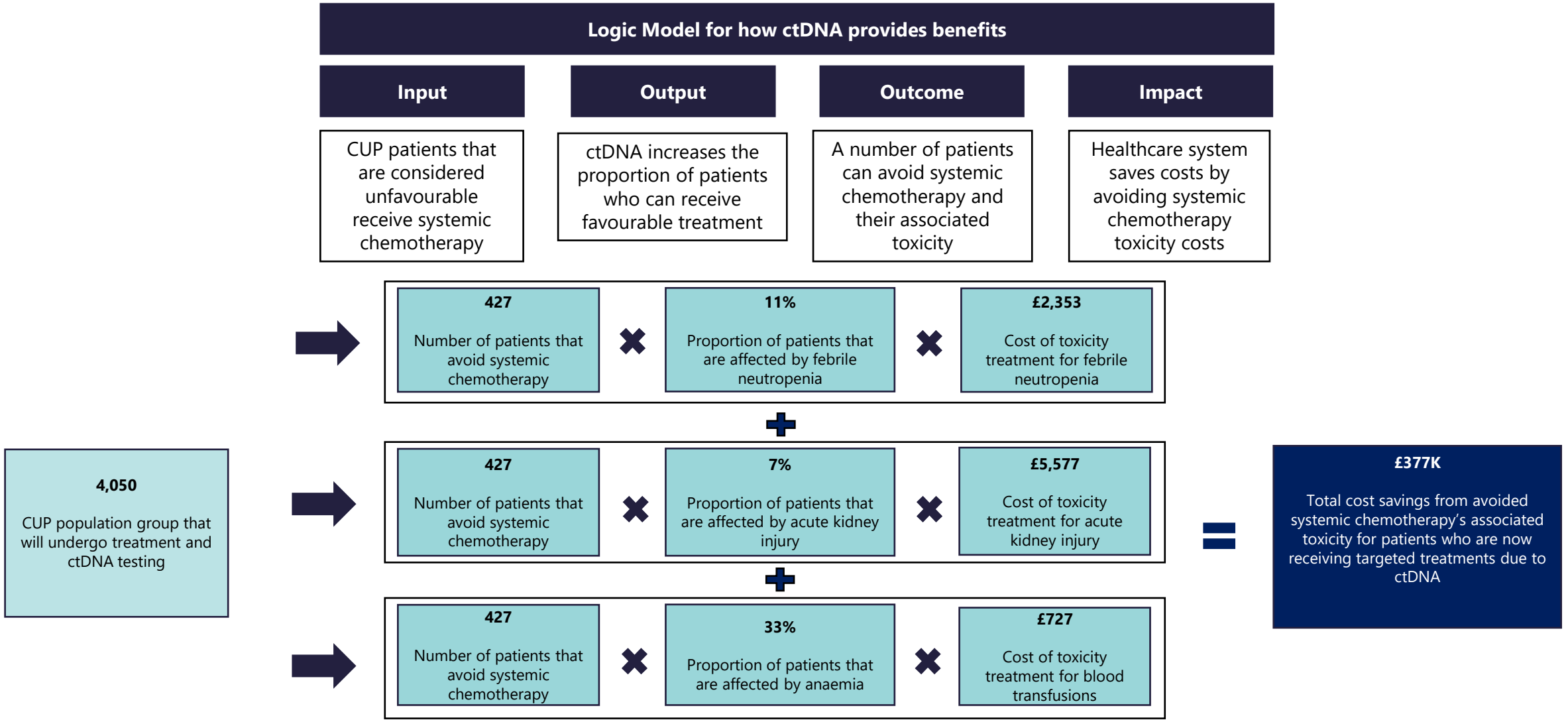
Logic Model for how ctDNA provides benefits

Input	Output	Outcome	Impact
CUP patients that are considered unfavourable receive systemic chemotherapy	ctDNA increases the proportion of patients who can receive favourable treatment	A number of patients can avoid systemic chemotherapy and receive targeted therapy instead	Healthcare system saves costs by avoiding systemic chemotherapy costs



1. *[Source: NICE clinical guidance on metastatic malignant disease of known primary origin, 2010]*
2. *[Source: National Cost Collection 2023/2024]*

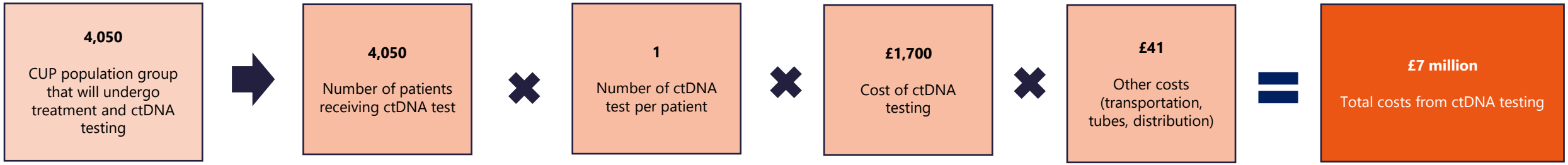
A4.2: Cost saving from avoided mistreatment and consequences



1. *Febrile neutropenia as systemic chemotherapy toxicity [Source: Greco et al., 2000]*
2. *Cost of treating febrile neutropenia [Source: Schelenz et al., 2012]*
3. *[Source: National Cost Collection 2023/2024]*
4. *Acute Kidney Injury [Source: Kitchlu et al., 2018]*
5. *Anaemia and blood transfusions [Source: Barrett-Lee et al., 2000]*

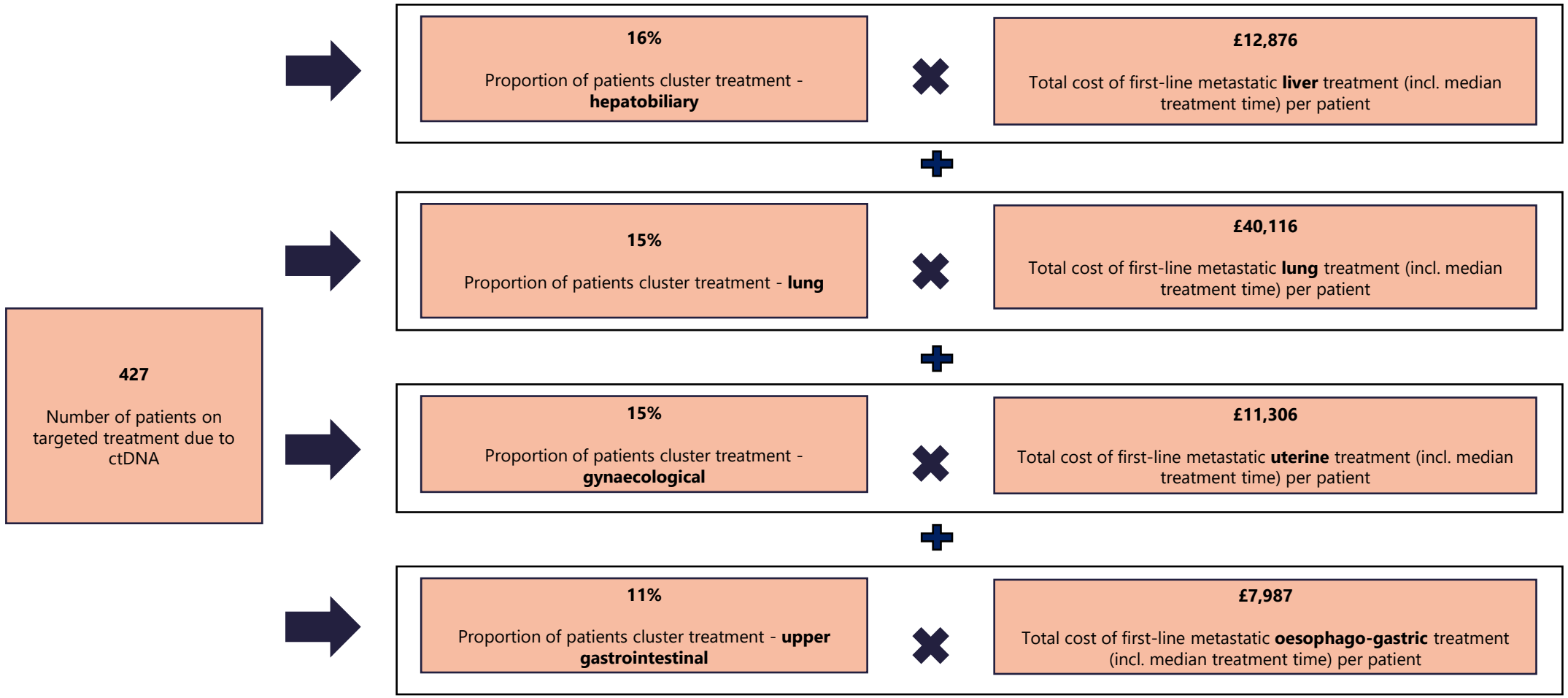
C1: Costs associated with ctDNA testing

The logic model below sets out the breakdown of the calculation to quantify ctDNA testing costs.



C2: Costs associated with receiving favourable treatment

The logic model below sets out the breakdown of the calculation to quantify patients that are receiving favourable treatment, due to ctDNA, and their costs. The total cost is taken from the cost of the treatment multiplied by the median treatment time, as evidenced in research literature.

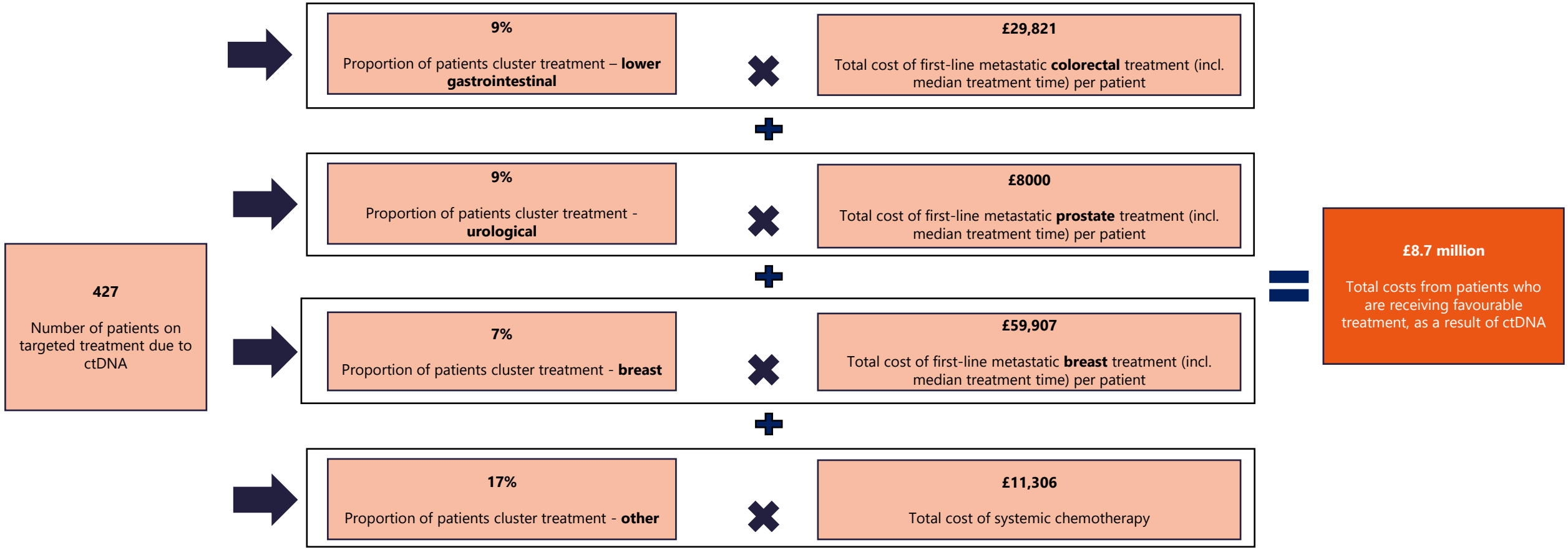


* This calculation continues on the next slide

1. *Costs of favourable treatment came from NICE guidelines and British National Formulary (BNF)*
2. *Cost of hepatocellular carcinoma to the national health service in England [Source: Cullen et al., 2023]*
3. *Carboplatin/Paclitaxel Induction in Ovarian Cancer [Source: Boyd and Muggia, 2018]*
4. *First-line nivolumab plus chemotherapy for advanced gastric, gastroesophageal junction, and esophageal adenocarcinoma [Source: Janjigian et al., 2024]*

C2 (continued): Costs associated with receiving favourable treatment

The logic model below sets out the breakdown of the calculation to quantify patients that are receiving favourable treatment, due to ctDNA, and their costs. The total cost is taken from the cost of the treatment multiplied by the median treatment time, as evidenced in research literature.

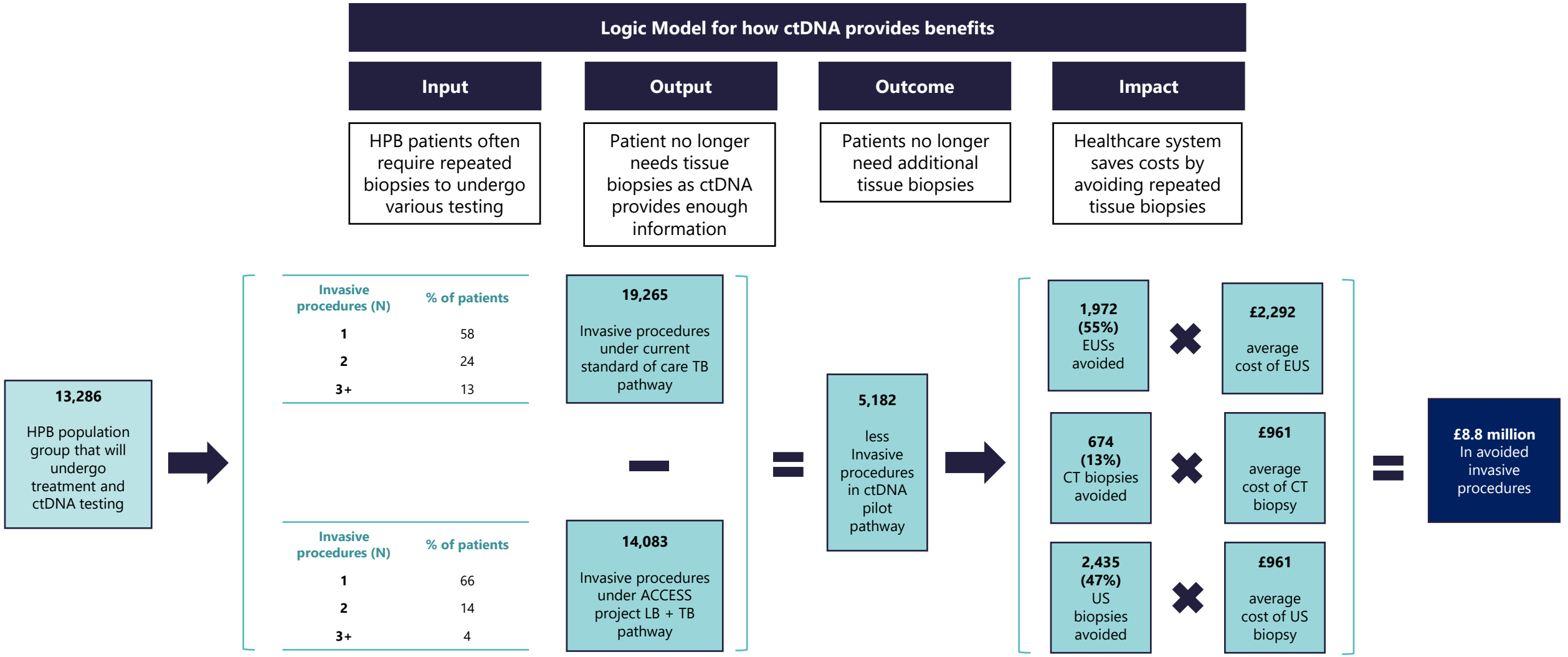


* Since "Other" is unknown, it has been assumed that the costs of their treatment is equivalent to systemic chemotherapy

1. *Costs of favourable treatment came from NICE guidelines and British National Formulary (BNF)*
2. *Progression-Free survival CDK4/7 inhibitors plus endocrine therapy in metastatic breast cancer [Source: Piezzo et al., 2020]*
3. *Clinical effectiveness and cost-effectiveness for previously untreated metastatic colorectal cancer [Source: Crathorne and Varley-Campbell, 2017]*

B.) Hepato-pancreato-biliary (HPB): costs & benefits

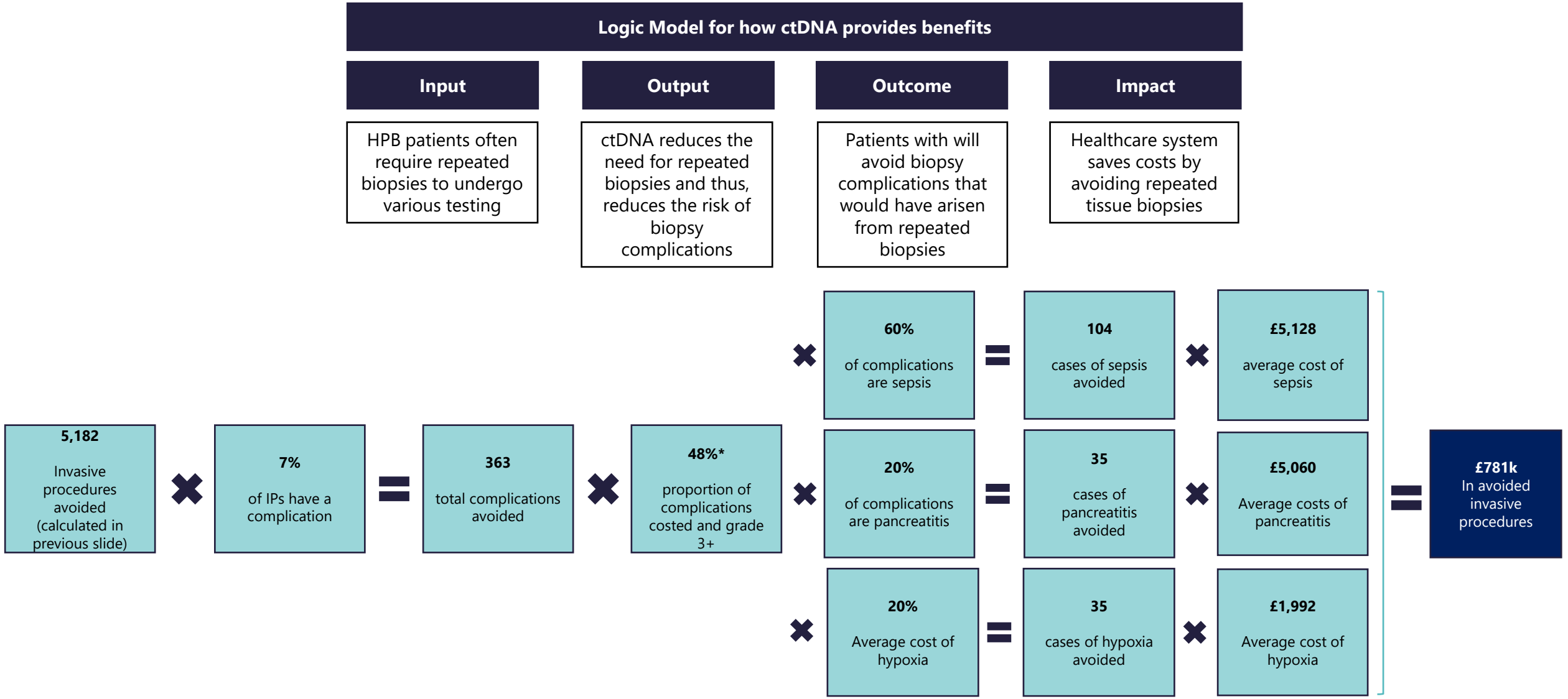
A1.1: Cost savings from avoided invasive procedures (new)



1. *[Source: NIHR SBRI liquid biopsy HE report]*
2. *[Source: RMH historical data]*
3. *[Source: NHS 2023/24 National Cost Collection data]*

**It is assumed that the 27% reduction between the ACESS and standard of care pathway in total invasive procedures applies to all 3 procedures types of procedures.*

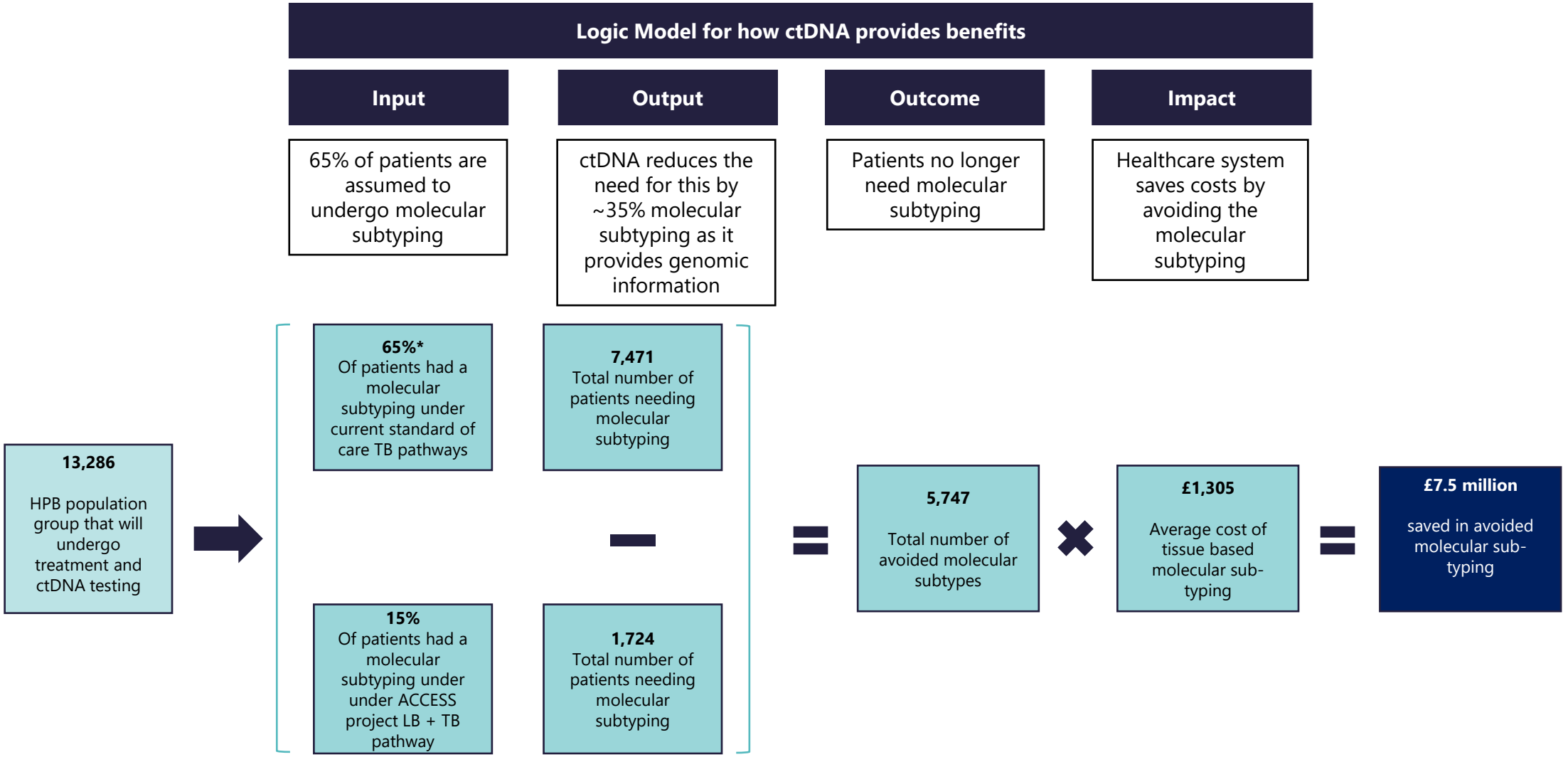
A1.2: Cost savings from tissue biopsy complications



1. *[Source: NIHR SBRI liquid biopsy HE report]*
2. *[Source: RMH historical data]*
3. *[Source: NHS 2023/24 National Cost Collection data]*

** The 48% is a combined percentage of the total percentage of compliations that are grade 3 (76%) and the percentage of complications that are sepsis, pancreatitis or hypoxia (63%)*

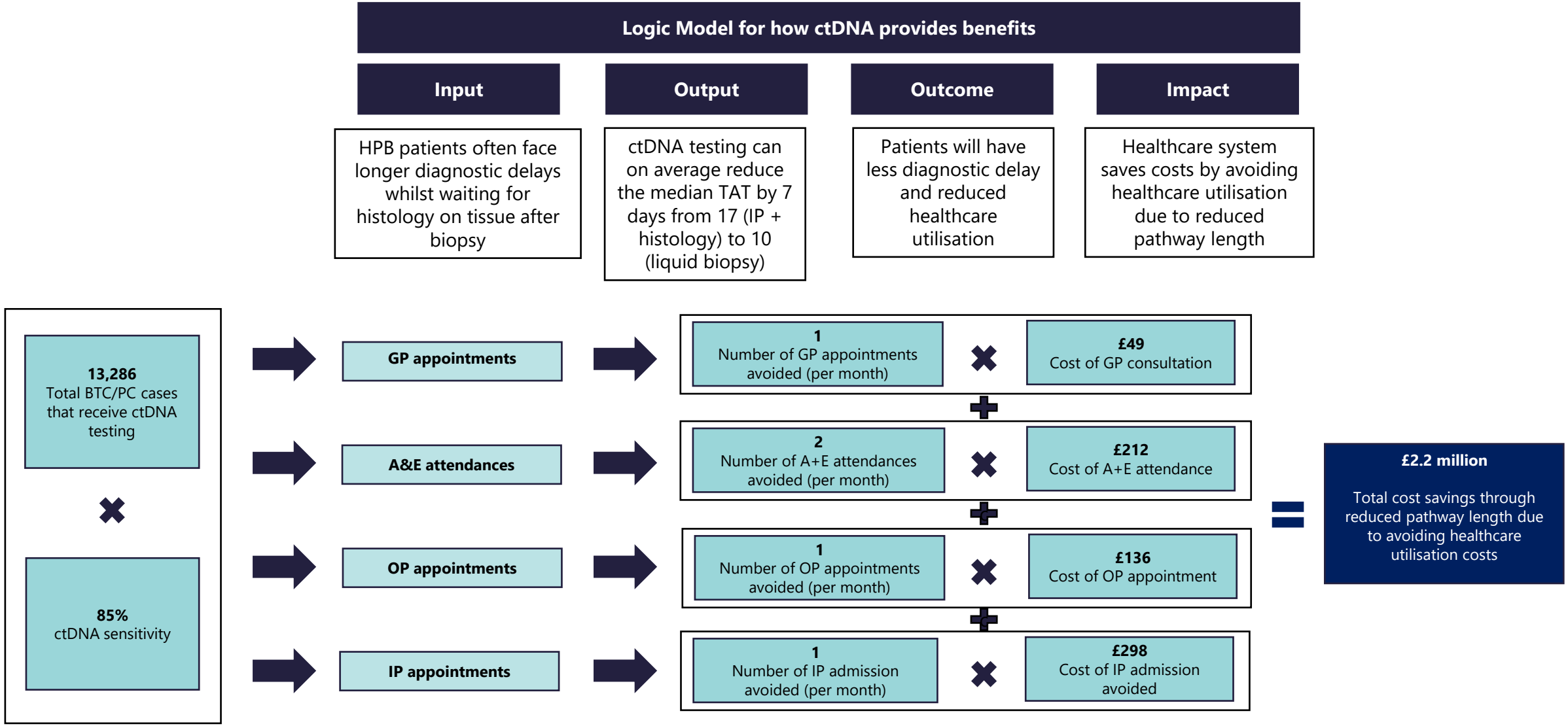
A1.3: Cost savings from genomic testing/molecular profiling



1. *[Source: NIHR SBRI liquid biopsy HE report]*

**Baseline tissue NGS uptake is set at 65 %. Historic trial data stated 50%, a more recent clinical estimate was 80 %, the baseline value represented the average.*

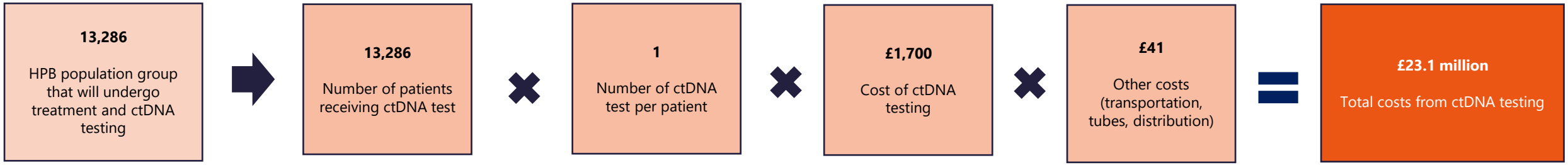
A3: Cost saving from reduced pathway length



1. *[Source: National Cost Collection 2023/2024]*

C1: Costs associated with ctDNA testing

The logic model below sets out the breakdown of the calculation to quantify ctDNA testing costs.

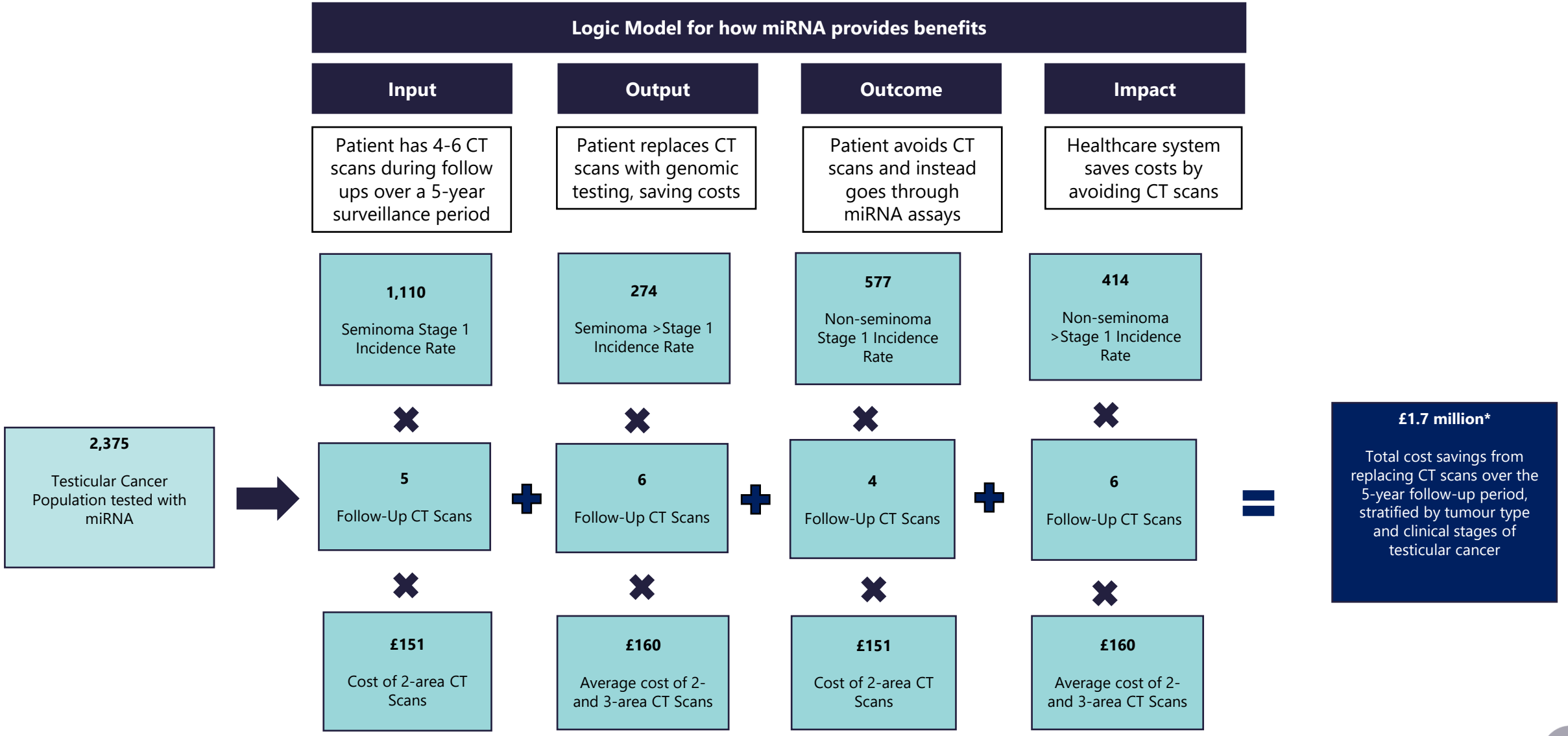


1. *[Source: NIHR SBRI liquid biopsy HE report]*

C.) Germ cell tumour: costs & benefits

C.1) CT Scan Calculations

A1: Saved cost associated with replacing CT scans during surveillance follow-ups



* Benefits and costs in this instance are discounted

1. *Different number of scans during 5-year surveillance period [Source: NHS Guidelines for Testicular Cancer]*
2. *Cost of CT scans refer to scans with contrast and varies by 2 area or 3 area [Source: National Cost Collection Data Publication: National Schedule 2022/2023]*

A2: Saved cost associated with reducing MDT meeting time during surveillance follow-ups

Logic Model for how miRNA provides benefits

Input	Output	Outcome	Impact
Patient has an average of 5.25 follow up visits during surveillance period, in which each visit requires an MDT meeting	Including miRNA and replacing CT scans reduces the amount of time during MDT meeting case discussions	MDT meeting case discussion time will be reduced as miRNA makes diagnosis of relapse more straightforward	Healthcare system becomes more efficient by reducing MDT meeting time and creates more time for other clinical staffing needs

2,375
Population with testicular cancer tested with miRNA

×

£62
Cost of MDT meeting case discussion

×

30%
Assuming 30% reduction in MDT meeting case time as a result of miRNA

×

5.25
Average number of scans that each patient receives during the follow-up visits over 5 years

=

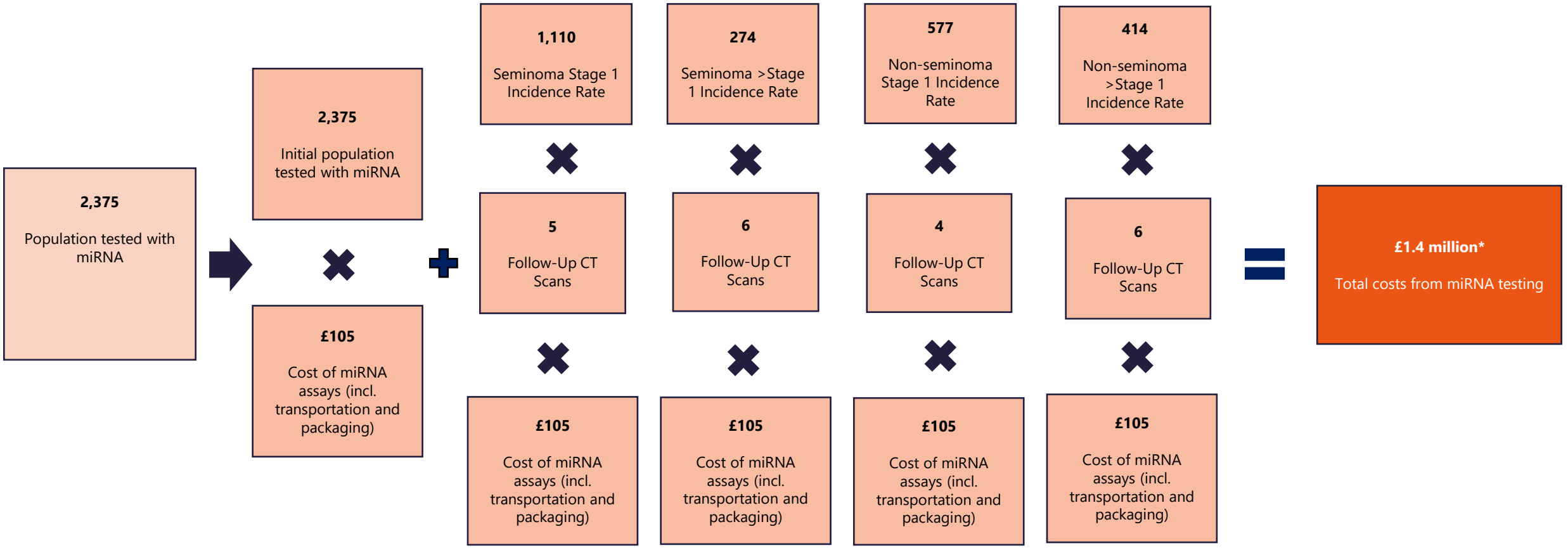
£208K*
Estimated cost benefit from reducing MDT meeting time

* Benefits and costs in this instance are discounted

1. *[Source: Neves et al., 2019]*

C1: Costs associated with miRNA testing (CT Scan)

The logic model below sets out the breakdown of the calculation to quantify miRNA testing costs to replace CT scans

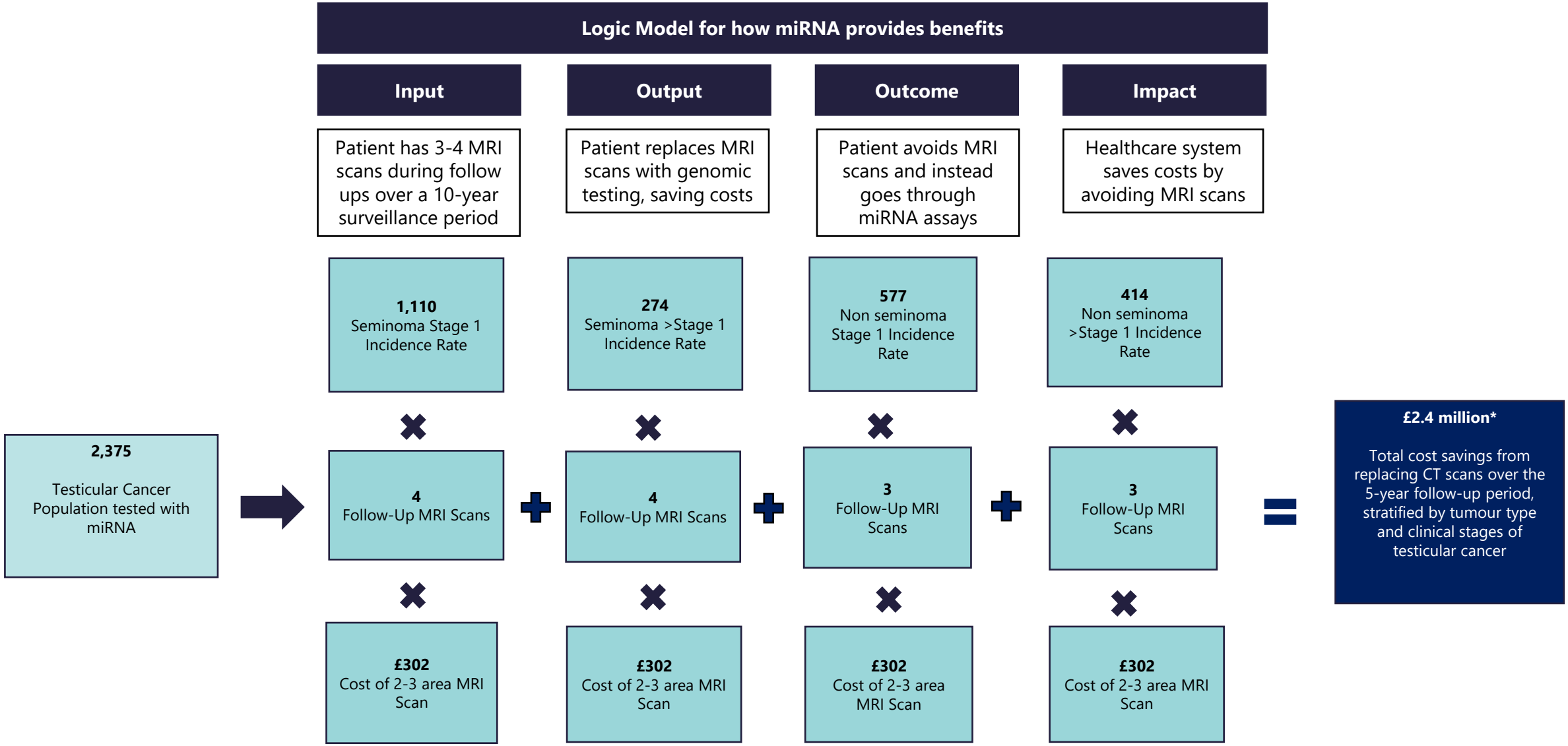


* Benefits and costs in this instance are discounted

1. *[Source: Guidelines for the Management of Testicular Cancer (West Midlands Expert Advisory Group), 2016]*

C.2) MRI Scan Calculations

A1: Saved cost associated with replacing MRI scans during surveillance follow-ups



* Benefits and costs in this instance are discounted

1. *Different number of scans during 10-year surveillance period [Source: Anglian Follow Up Schedule shared by clinician]*
2. *Cost of MRI scans refer to scans with contrast [Source: National Cost Collection Data Publication: National Schedule 2022/2023]*

A2: Saved cost associated with reducing MDT meeting time during surveillance follow-ups

Logic Model for how miRNA provides benefits

Input	Output	Outcome	Impact
Patient has an average of 5.25 follow up visits during surveillance period, in which each visit requires an MDT meeting	Including miRNA and replacing CT scans reduces the amount of time during MDT meeting case discussions	MDT meeting case discussion time will be reduced as miRNA makes diagnosis of relapse more straightforward	Healthcare system becomes more efficient by reducing MDT meeting time and creates more time for other clinical staffing needs

2,375
Population with testicular cancer tested with miRNA

×

£62
Cost of MDT meeting case discussion

×

30%
Assuming 30% reduction in MDT meeting case time as a result of miRNA

×

3.5
Average number of scans that each patient receives during the follow-up visits over 5 years

=

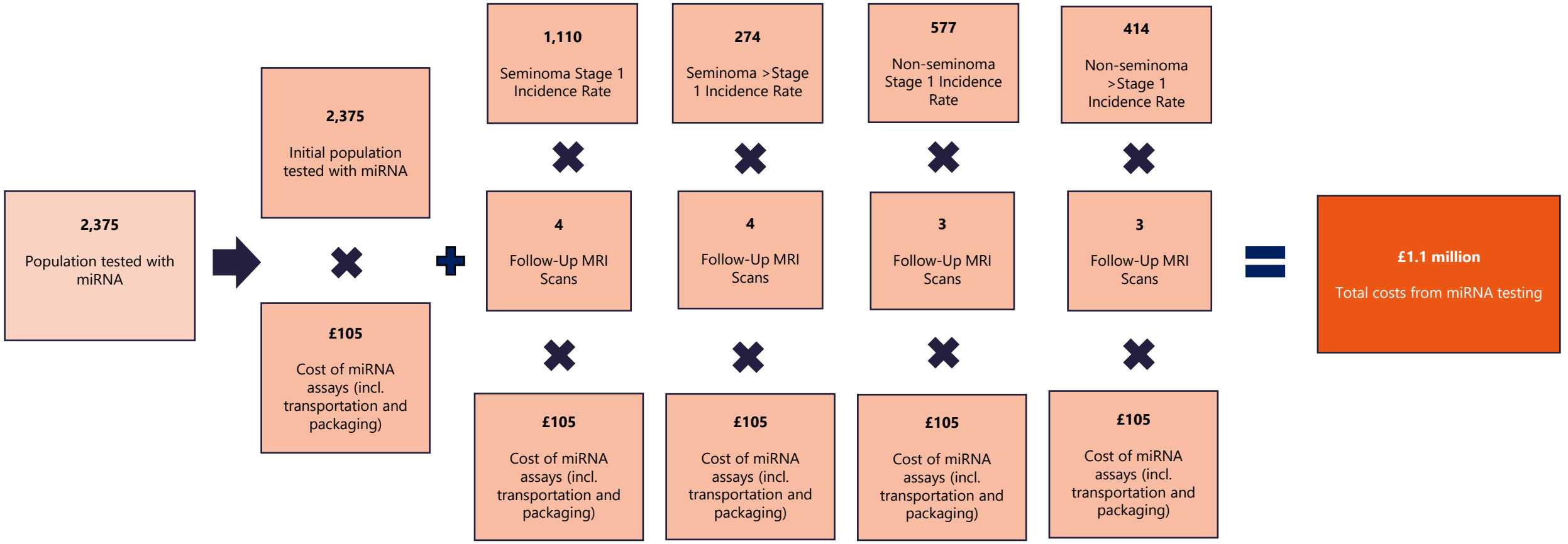
£147K*
Estimated cost benefit from reducing MDT meeting time

* Benefits and costs in this instance are discounted

1. *[Source: Neves et al., 2019]*

C1: Costs associated with miRNA testing (MRI)

The logic model below sets out the breakdown of the calculation to quantify miRNA testing costs to replace MRI scans.

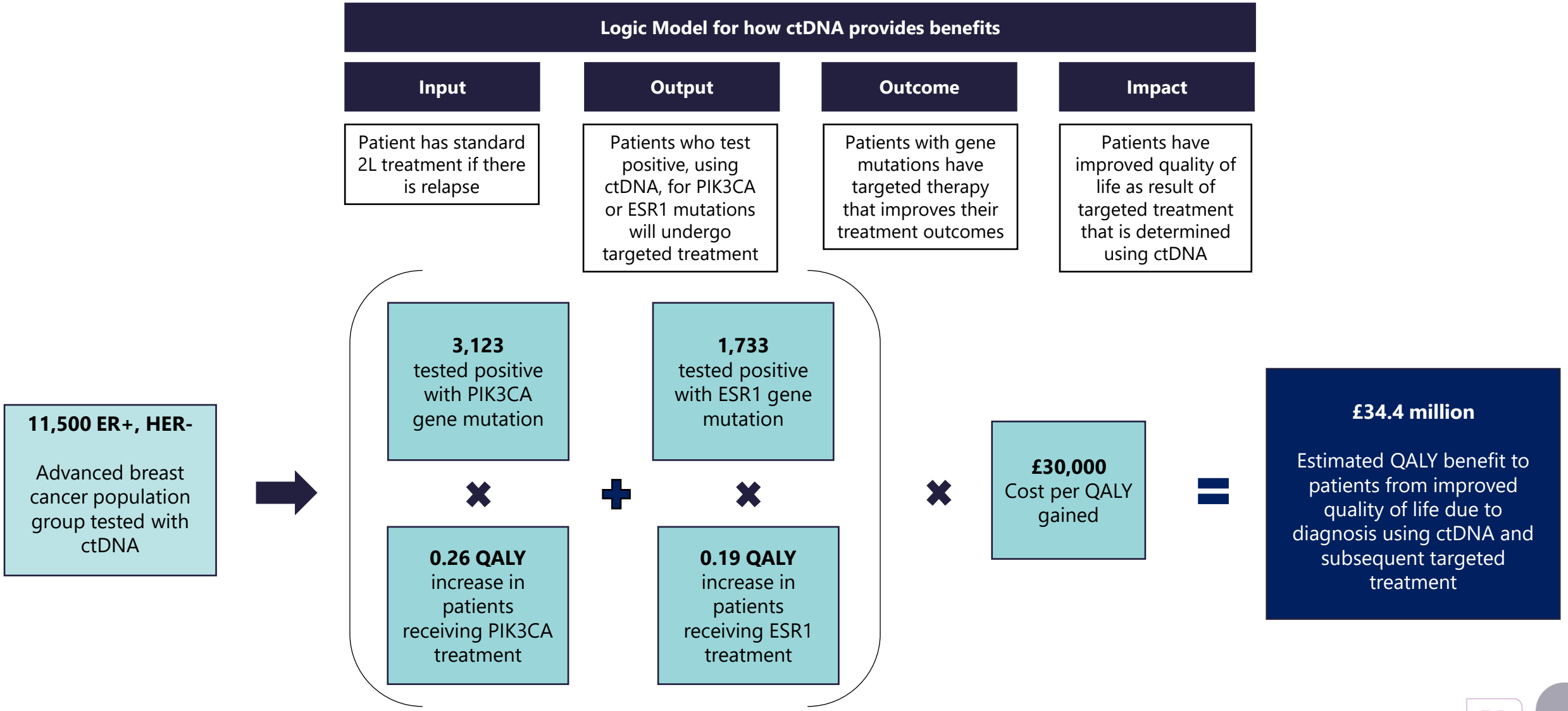


* Benefits and costs in this instance are discounted

1. *Different number of scans during 10-year surveillance period [Source: Anglian Follow Up Schedule shared by clinician]*

D.) Advanced breast cancer: costs & benefits

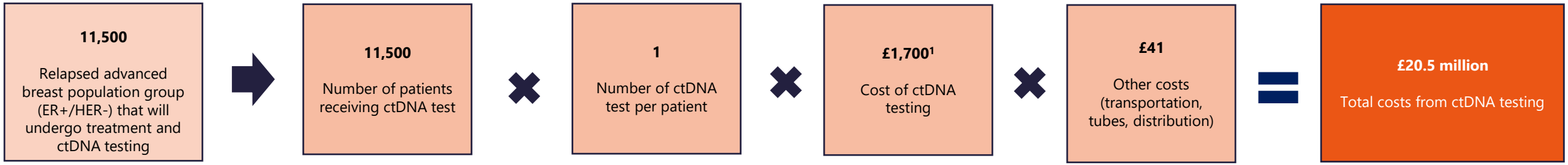
A2: Improved quality of life due to ctDNA testing



1. *[Source: Office for Health Improvement and Disparities Guidance for Cost Utility Analysis, 2020]*
2. *[Source: NICE TA816 Final Appraisal Document]*
3. *[Source: Zeng et al., 2023]*

C1: Costs associated with ctDNA testing

The logic model below sets out the breakdown of the calculation to quantify ctDNA testing costs.



1. *This cost was estimated at £800 for the small panel scenario.*

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In delivering this vision, we understand the importance of maintaining the confidentiality of our clients' proposals, plans and data. To support this we have a range of internal procedures and regular internal audits to make sure these are being followed. We ask in return that our proprietary analysis, approaches, insights, and methodologies are protected by our clients.