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ORIGINAL RESEARCH ARTICLE

Distributional Cost-Effectiveness Analysis of Treatments for Non-Small Cell Lung Cancer: An Illustration of an Aggregate Analysis and its Key Drivers

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Abstract

Background and Objective Distributional cost-effectiveness analysis (DCEA) facilitates quantitative assessments of how health effects and costs are distributed among population subgroups, and of potential trade-offs between health maximisation and equity. Implementation of DCEA is currently explored by the National Institute for Health and Care Excellence (NICE) in England. Recent research conducted an aggregate DCEA on a selection of NICE appraisals; however, significant questions remain regarding the impact of the characteristics of the patient population (size, distribution by the equity measure of interest) and methodologic choices on DCEA outcomes. Cancer is the indication most appraised by NICE, and the relationship between lung cancer incidence and socioeconomic status is well established. We aimed to conduct an aggregate DCEA of two non-small cell lung cancer (NSCLC) treatments recommended by NICE, and identify key drivers of the analysis.

Methods Subgroups were defined according to socioeconomic deprivation. Data on health benefits, costs, and target populations were extracted from two NICE appraisals (atezolizumab versus docetaxel [second-line treatment following chemotherapy to represent a broad NSCLC population] and alectinib versus crizotinib [targeted first-line treatment to represent a rarer mutation-positive NSCLC population]). Data on disease incidence were derived from national statistics. Distributions of population health and health opportunity costs were taken from the literature. A societal welfare analysis was conducted to assess potential trade-offs between health maximisation and equity. Sensitivity analyses were conducted, varying a range of parameters.

Results At an opportunity cost threshold of £30,000 per quality-adjusted life-year (QALY), alectinib improved both health and equity, thereby increasing societal welfare. Second-line atezolizumab involved a trade-off between improving health equity and maximising health; it improved societal welfare at an opportunity cost threshold of £50,000/QALY. Increasing the value of the opportunity cost threshold improved the equity impact. The equity impact and societal welfare impact were small, driven by the size of the patient population and per-patient net health benefit. Other key drivers were the inequality aversion parameters and the distribution of patients by socioeconomic group; skewing the distribution to the most (least) deprived quintile improved (reduced) equity gains.

Conclusion Using two illustrative examples and varying model parameters to simulate alternative decision problems, this study suggests that key drivers of an aggregate DCEA are the opportunity cost threshold, the characteristics of the patient population, and the level of inequality aversion. These drivers raise important questions in terms of the implications for decision making. Further research is warranted to examine the value of the opportunity cost threshold, capture the public's views on unfair differences in health, and estimate robust distributional weights incorporating the public's preferences. Finally, guidance from health technology assessment organisations, such as NICE, is needed regarding methods for DCEA construction and how they would interpret and incorporate those results in their decision making.

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Key Points for Decision Makers

Distributional cost-effectiveness analysis (DCEA) facilitates a quantitative assessment of how health effects and costs are distributed among population subgroups, and of any ensuing trade-offs between health maximisation and equity, thereby supporting consideration of equity impact in the decision-making process.

Under the base-case assumptions, alectinib improved societal welfare. Second-line atezolizumab involved a trade-off between reduction of health inequalities and decreasing population health and had the potential to improve societal welfare under certain assumptions. Given the uncertainty about the true marginal cost per quality-adjusted life-year in the National Health Service (i.e., the health opportunity cost), which is central to the analysis, the basis for its value should be carefully examined. Other key drivers in the analysis were the characteristics of the patient population (size, distribution by deprivation) and level of inequality aversion.

Each of these drivers raises important questions in terms of the implications for decision making. Guidance from health technology assessment organisations, such as NICE, is warranted on methods for DCEA construction and how they will interpret and incorporate results into their decision making.

1 Introduction

Health inequities are unfair or avoidable variations in health status, or variations in access to healthcare services, among population subgroups defined by equity-relevant attributes (e.g., socioeconomic status, ethnicity income), also called 'social determinants of health' [1–3]. Health inequities have become a key policy focus of governments and healthcare systems, with the coronavirus disease 2019 (COVID-19) pandemic acting as a catalyst, as demonstrated by the growing body of literature on health equity [4–9].

There have been calls for health technology assessment (HTA) agencies to more systematically and more formally incorporate equity assessments in their decision-making processes [10]. Incorporation of equity considerations in HTA might have been limited to date because of issues such as lack of agreement on the definition of health equity and underlying value judgements about unfair variations in health, limitations in the methodologic approaches (such as lack of data [3] or absence of consensus on which methodologies to adopt). The National Institute for Health and Care Excellence (NICE) in England named the reduction of health inequities as one of six priorities in its strategy for the years 2021 through 2026 [11].

Numerous HTA agencies, including NICE, have an evaluation framework based on cost-effectiveness analysis (CEA) that allows quantifying and comparing the average incremental costs and health effects of interventions, with the aim of maximising population health. In healthcare systems with fixed short-term budgets, approving new interventions improve health for patients who benefit from those interventions. At the same time, such changes reduce health for other patients because of the loss of funding for already approved interventions (this is the health opportunity cost). Distributional cost-effectiveness analysis (DCEA) is an extension of CEA that aims to assess how health effects and costs are distributed across population subgroups, estimate the equity impact of adopting new interventions, and evaluate the potential trade-offs between population health maximisation and reducing unfair variations in health. Thus, DCEA can inform decision making by providing context about the extent and direction of health equity impacts. NICE is currently considering implementing DCEA as part of its HTA process [12].

To date, much of the research into the application of DCEA has focused on public health interventions [13–16]. However, public health interventions have many differences from the types of technologies routinely appraised by HTA programmes, such as the NICE single technology appraisal (STA) programme for new patent-protected medicines, including the size and characteristics of the populations targeted. Recent research applied the approach in its 'aggregate form' to a selection of NICE STAs [17]; nonetheless, important questions remain. It is unclear how key underlying parameters (e.g., the value of the opportunity cost threshold, the assumed level of aversion to inequity), and characteristics of the patient population (e.g., size, distribution by the equity measure of interest) affect the conclusions of a DCEA.

We sought to address this gap by illustrating the application of aggregate DCEA to two different treatments for non-small cell lung cancer (NSCLC) at different stages. Oncology was chosen because it is the disease area most appraised by NICE; since 2000, about 50% of NICE technology appraisals have been on cancer treatments [18, 19]. Additionally, previous research has established a link between lung cancer and socioeconomic deprivation [20].

The primary aim of this study was to illustrate an aggregate DCEA from the perspective of England's National Health Service (NHS) for two NSCLC treatments recommended by NICE, defining population subgroups based on socioeconomic deprivation. A secondary aim was to identify key drivers of DCEAs by varying a range of model

Table 1 Drug-specific model inputs based on National Institute for Health and Care Excellence appraisal data

Input	Data	Source
Atezolizumab		
Incremental QALYs: atezolizumab (TA520)	0.746	NICE committee papers, company submission, company base case [22]
Incremental costs: atezolizumab (TA520)	£53,970	NICE committee papers, company submission, company base case [22]
Discounted incremental costs (hypothetical): atezolizumab (TA520)	£36,056	Calculated (assumption of 40% discount on drug costs)
Proportion of the patient population eligible to atezolizumab	14.79%	Calculated based on the resource impact report [27]
Alectinib		
Incremental QALYs: alectinib (TA536)	1.030	NICE committee papers, company submission, company base case [23]
Incremental costs: alectinib (TA536)	£70,229	NICE committee papers, company submission, company base case [23]
Discounted incremental costs (hypothetical): alectinib (TA536)	£25,169	Calculated (assumption of 31% discount on drug costs)
Proportion of the patient population eligible to alectinib	1.70%	Calculated based on the resource impact report [26]

NICE National Institute for Health and Care Excellence, *QALYs* quality-adjusted life-years, *TA* technology appraisal

parameters, including opportunity cost threshold, level of aversion to inequity, and distribution of patients by socioeconomic deprivation.

2 Methods

2.1 DCEA Approach

In DCEA, the post-decision health distribution is derived by adding the net health benefit (NHB) for a novel intervention to the baseline distribution of population health, thus allowing an assessment of changes in the distribution of the total population health and health inequities [6]. In this study, an aggregate DCEA method was adopted, estimating the NHB using average health gains and costs derived from a prior cost-effectiveness model [17].

2.2 Value Judgement About Unfair Differences in Health

The health inequity characteristic that forms the basis of this analysis is socioeconomic deprivation, measured by the Index of Multiple Deprivation (IMD) [21]. Small areas in England (about 1500 residents) are given a score, incorporating seven domains of deprivation (income, employment, education, health, crime, housing, and living environment). The analytic population is split into five equally sized groups. The first quintile (IMD1) represents the most deprived areas, and the fifth quintile (IMD5) represents the least deprived.

2.3 Choice of Technologies

We built on two NICE STAs in NSCLC: one for a general NSCLC population comparing atezolizumab with docetaxel in relapsed NSCLC after chemotherapy (TA520; 2018), and one for a rarer driver mutation of NSCLC comparing alectinib with crizotinib in first-line anaplastic lymphoma kinase-positive advanced NSCLC (TA536; 2018) [22, 23]. Atezolizumab met the NICE end-of-life criteria by which a technology can be approved at an incremental cost-effectiveness ratio (ICER) of up to £50,000/quality-adjusted life-year (QALY) gained. The two treatments were selected as illustrative case studies, given their differences in terms of population (general NCSLC versus a rarer NSCLC type) and other characteristics (e.g., end-of-life criteria/ICER), to examine the impact of these differences on the analyses.

2.4 Data Inputs

2.4.1 Costs and Quality-Adjusted Life-Years

Because the NICE committee's preferred ICERs were not explicitly reported, data on health benefits (expressed in expected QALYs gained) and costs were taken from the companies' base-case submissions for the intervention and the comparators (Table 1). The CEAs are briefly summarised in the electronic supplementary material [ESM] (A1, A2), and detailed descriptions have been reported elsewhere [22, 23].

Both drugs are subject to a confidential patient access scheme (PAS). In both appraisals, base-case results are presented without the PAS. The incremental costs represent the resources displaced to fund the new intervention,

Table 2 Population and disease distributional inputs

	IMD1 (most deprived)	IMD2	IMD3	IMD4	IMD5 (least deprived)	Source
Baseline distribution of health (QALE)	63.21	67.61	69.95	73.10	75.00	Love-Koh et al. [29]
Health opportunity costs distribution	26%	22%	22%	16%	14%	Love-Koh et al. [30]
Age-standardised lung cancer incidence rate per 100,000: Female	117.2	79.9	62.2	52.9	42.2	NCRAS [52]
Age-standardised lung cancer incidence rate per 100,000: Male	144.6	100.4	78.0	68.9	55.6	NCRAS [52]
Stage 3 or 4 diagnosis	70%	70%	70%	69%	69%	NCRAS [28]

IMD Index of Multiple Deprivation, *NCRAS* National Cancer Registration and Analysis Service, *QALE* quality-adjusted life expectancy

which can be converted on a health scale to estimate the foregone health resulting from this displacement. To avoid overestimating costs or health losses in the analysis, we applied hypothetical discounts to the drug costs to generate ICERs falling below the respective decision thresholds: £20,000–£30,0000/QALY for alectinib and £50,000/QALY for atezolizumab. In the NICE technology appraisal guidance for atezolizumab [22], the costs were disaggregated and drug costs were reported separately. We applied a hypothetical 40% discount to the drug costs to estimate the discounted total costs and ICER. In the NICE technology appraisal guidance for alectinib [23], costs were not disaggregated; as a result, we assumed the same proportion of drug costs and other costs as for atezolizumab and applied a 31% discount to the drug costs. Under these hypothetical assumptions, the implied ICERs would be £48,333/QALY for atezolizumab and £24,436/QALY for alectinib.

2.4.2 Patient Population

Data on the size of the population of England and distribution by sex-IMD subgroups were taken from the Office for National Statistics [24, 25]. Data on age-standardised lung cancer incidence rates and stage at diagnosis by IMD (based on 2019 diagnosis) reported by the National Cancer Registration and Analysis Service (Table 2) were combined with the proportion of patients who had NSCLC (88.5%). The proportion of patients eligible for treatment were derived from the data reported in the resource impact reports for each appraisal available on the NICE website (Table 1) [20, 26–28]. When scaling health gains and costs, all patients eligible for treatment were assumed to receive it. Detailed calculations are presented in the ESM (A3).

2.4.3 Baseline Distribution of Health and Opportunity Cost Distribution

The baseline distribution of population health was taken from a study by Love-Koh and colleagues (Table 2) [29], who estimated the distribution of quality-adjusted life expectancy (QALE) at birth by age-sex-IMD subgroups. We used the distribution of health opportunity costs estimated by Love-Koh et al. [30], who evaluated the QALY impact by IMD associated with a change in the NHS budget, based on differences in use of NHS resources by IMD subgroups (Table 2).

2.4.4 Health Opportunity Cost

In the base case, the opportunity cost threshold (representing the costs per QALY foregone as a result of displacing resources in the NHS) was set at the upper bound of the standard NICE threshold range, i.e. £30,000/QALY.

2.5 Analysis

2.5.1 Net Health Benefit

The distribution of health gains is derived by multiplying the per-patient incremental QALYs by the number of treated patients in each quintile. The total health opportunity cost is estimated by multiplying the per-patient incremental costs by the total number of treated patients and then dividing by the opportunity cost threshold to convert to a QALY scale. Subsequently, health opportunity costs are distributed between the five quintiles using the data from Love-Koh et al. [30], presented in Table 1, to derive the distribution of the health opportunity costs for the whole population. Finally, the NHB is calculated by subtracting the opportunity costs from the health gains. Calculation of the net incremental health benefit per quintile is illustrated in Eq. (1).

Equation 1. Aggregated incremental net health benefit per quintile

$$\Delta NHB_j = \Delta QALY \times n_j - \frac{N \times \Delta costs}{k} d_j \quad (1)$$

where ΔNHB_j is the aggregated incremental net health benefit in IMD quintile j; $\Delta QALY$ is the per-patient incremental health gain; n_j is the number of patients in quintile j, $N=\sum_j n_j$ is the total number of patients; $\Delta costs$ are the per-patient incremental costs; k is the opportunity cost threshold; and d_j is the proportion of opportunity costs accrued in quintile j.

2.5.2 Equity Impact and Trade-off Assessment

The results, aggregated at the population level, are presented on the equity-efficiency impact plane to assess potential trade-offs between health maximisation and reduction of health inequalities. A societal welfare analysis was conducted to assess any potential trade-off between health maximisation and health equity.

Inequity in the distribution was measured using the Atkinson index, which describes how social welfare is reduced by relative inequality in the distribution of health and is one of the most popular welfare-based measures of inequality [31, 32]. The Atkinson index, calculated as shown in Eq. (2), measures relative inequality by assessing proportional change in the distribution. Alternative value judgements about reducing health inequities versus improving total population health (i.e., willingness to forego a share of the population health to reduce health inequities, thereby increasing societal welfare) were captured by the Atkinson inequality aversion parameter (IAP). The greater the value of the IAP is, the greater the aversion to inequality is. In other words, higher IAP means a greater weight is given to health gains in the most deprived quintiles compared with health gains in the least deprived quintiles. Robson et al. [33] conducted a study to elicit the level of health inequality aversion between socioeconomic groups in England; they estimated an Atkinson IAP of 10.95 (95% confidence interval [CI] 10.95–10.95), which implies that health gains for the most deprived quintiles were weighted 6.95 times as highly as health gains in the least deprived quintiles.

Societal welfare was calculated by combining the Atkinson index with the mean level of health in the distribution. The equally distributed equivalent health (EDEH) of a distribution is the mean level of health per person that, if equally distributed across the population, would give the same level of societal welfare as the current unequal distribution. EDEH is an equity-weighted mean of the health distribution. An illustration of EDEH is presented in the ESM (A4). EDEH based on the Atkinson index was calculated using the formula detailed in Eq. (3). We were interested in health inequalities at the population level; therefore, we scaled the EDEH by multiplying it with the population size.

We calculated the population NHB and EDEH at baseline, after decision and the increment to evaluate changes in the health distribution. The health equity impact was expressed as the difference between the equity-weighted population health gains and overall population health gains (i.e., incremental population EDEH minus incremental population NHB). A positive equity impact suggests decreasing health inequities and a negative value indicates increased inequities. A positive change in population EDEH demonstrates an improvement in societal welfare (accounting for changes both in health and equity).

Equation 2. Atkinson index of inequality

$$A(\varepsilon) = 1 - \left(\frac{1}{N} \sum \left(\frac{h_i}{h} \right)^{1-\varepsilon} \right)^{\frac{1}{1-}} \varepsilon \tag{2}$$

where N *is* the population size; h is the mean health in the population; h_i is the health in quintile i; and ε is the Atkinson inequality aversion parameter.

Equation 3. Population EDEH based on the Atkinson societal welfare function

$$EDEH = N(1 - A(\varepsilon))h \tag{3}$$

where $A(\varepsilon)$ is the Atkinson index; N is the population size; and h is the mean health in the population.

2.5.3 Sensitivity Analysis

We conducted a range of scenario analyses, varying model parameters one by one to identify key drivers of the DCEA results. Where possible, input values for the scenarios were informed by literature; when this was not possible, extreme values were tested to identify switching points in the sign or direction of the societal welfare and equity impacts. Details of the model inputs for each scenario are presented in the ESM (A6).

2.5.3.1 Health Opportunity Costs Threshold To assess how the health equity impact changes with the value of the opportunity cost threshold, we conducted sensitivity analyses, setting it at £15,000/QALY, the value used by England's Department for Health and Social Care (DHSC), which is based on research by Claxton et al. on marginal productivity in the NHS [34, 35]. We also explored values of £20,000/QALY (the lower bound of the NICE threshold range), £25,000/QALY, £45,000/QALY, and £50,000/QALY, consistent with the former NICE end-of-life threshold, which incorporates equity concerns for disease severity. Thus, this value may not align with true marginal productivity in the NHS and was not chosen as the base-case for atezolizumab, despite being the decision threshold in NICE appraisals.

2.5.3.2 Atkinson Inequality Aversion Parameter The Atkinson IAP was varied from 0 to 20 to assess its impact

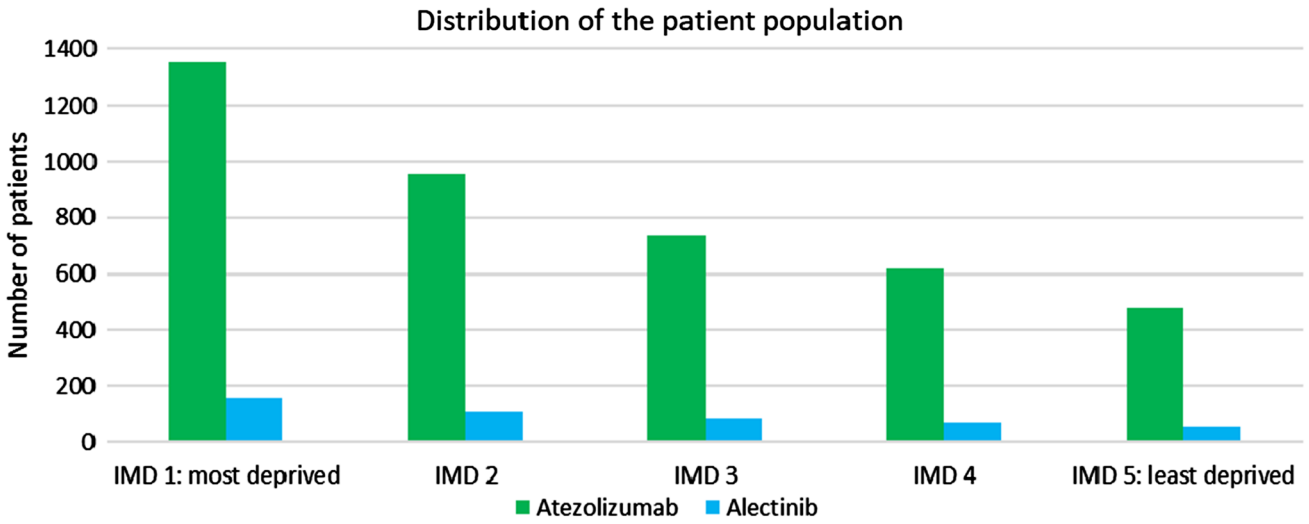

Fig. 1 Distribution of the patient population eligible to each treatment by index of multiple deprivation. *IMD* index of multiple deprivation

on health inequality and societal welfare at varying levels of concern for health inequality.

2.5.3.3 Distribution of the Patient Population Five scenario analyses were conducted to investigate the impact of the shape of the patient distribution. The base-case distribution was reversed and thus skewed toward the least deprived. Two distributions skewed toward the most deprived with varying gradients, and one with the patients distributed equally across the five quintiles, were also tested. Alectinib is indicated for the treatment of patients with anaplastic lymphoma kinase-positive NSCLC, who are less likely to have a history of smoking [23]. The distribution of non-smoker lung cancer patients by IMD may differ from that of patients with lung cancer in general. Based on the study by Rait and Horsfall [36] on the incidence of lung cancer in non-smokers in the UK, incidence by deprivation has a U-shaped distribution in men and is skewed toward the least deprived in women. However, the Rait and Horsfall study was based on the Townsend index rather than the IMD. Therefore, a U-shaped distribution was tested.

2.5.3.4 Gradient on the Incremental Quality-Adjusted Life-Years (QALYs) and Costs In the base case, the average incremental QALYs and costs taken from the NICE appraisals were applied to all IMD quintiles as described in Sect. 2.4 (Data Inputs). However, there is evidence from the literature that the distributions of costs and health benefits may not be uniform across IMD quintiles [37]. Indeed, an intervention may improve adherence to a larger extent in the most deprived quintiles of the population, who would therefore derive greater QALY gain and higher incremental costs than those who are less deprived. Conversely, patients in the least deprived quintiles may present at earlier stages of disease development and thus achieve greater health benefits. Two scenarios were conducted whereby a gradient was applied to favour the most deprived quintiles (e.g., multiplier applied to incremental QALYs, IMD1 = 1.2, IMD4 = 1.1, IMD3 = 1, IMD2 = 0.9, IMD5 = 0.8) and the least deprived (e.g., multiplier applied to incremental QALYs, IMD1 = 0.8, IMD4 = 0.9, IMD3 = 1, IMD2 = 1.1, IMD5 =1.2).

2.5.3.5 Discounted Drug Costs Different discounts were applied to drug costs to estimate the implied ICERs for alectinib and atezolizumab. Details of the scenario inputs and results are reported in the ESM (A6.6).

3 Results

3.1 Distribution of the Patient Population

We estimated that 4142 patients would be eligible for atezolizumab and 477 for alectinib, with 33% of eligible patients in the most deprived quintile (IMD1) compared with 12% in the least deprived quintile (IMD5) (Fig. 1).

3.2 Net Health Benefit

At an opportunity cost threshold of £30,000/QALY, the incremental population NHB was 91 QALYs gained for alectinib. Although atezolizumab produced incremental QALY gains, the NHB was negative (−1888), owing to the ICER being larger than the opportunity cost threshold (i.e., more health foregone with the displacement of resources than health gains accrued in the target population). At a £50,000/QALY threshold, atezolizumab became health improving. At

Table 3 Incremental population net health benefit

Opportunity cost threshold	ΔNHB atezolizumab	ΔNHB TA536 alectinib
£15,000/QALY	−6866	−309
£20,000/QALY	−4377	−109
£25,000/QALY	−2884	11
£30,000/QALY (base case)	−1888	91
£45,000/QALY	90	224
£50,000/QALY	103	251

Δ*NHB* incremental net health benefit, *QALY* quality-adjusted life-year

£15,000/QALY, both drugs reduced population health. The size of the NHB increased as the opportunity cost threshold was larger than the ICER, and decreased when it was smaller than the ICER (Table 3). Base-case results (health gains, opportunity costs, NHBs) disaggregated by IMD are presented in the ESM (A5).

3.3 Health Equity Impact

The mean baseline QALE per person was 69.72, equivalent to an EDEH of 68.32 at an Atkinson IAP of 10.95.

With alectinib, at an opportunity cost threshold of £30,000/QALY, the population incremental NHB was 91 QALYs, the population incremental EDEH was 162 QALYs, and the resulting health equity change was 71 QALYs (Table 4). Plotted on the equity-efficiency impact plane (Fig. 2), where the *x*-axis is the population health equity change and the *y*-axis is the incremental population NHB, alectinib was in the northeast quadrant, indicating improved population health and health equity.

With atezolizumab, at an opportunity cost threshold of £30,000/QALY, the population incremental NHB was −1888 QALYs, the population incremental EDEH was −1833 QALYs, and the resulting health equity change was 56 QALYs (Table 4). Plotted on the equity-efficiency impact plane, atezolizumab was in the southeast quadrant, suggesting a trade-off between decreasing population health and decreasing health inequities.

3.4 Sensitivity Analysis

3.4.1 Opportunity Cost Threshold and Atkinson Inequality Aversion Parameter

Figure 3 presents changes in the societal welfare impact for values of the Atkinson IAP between 0 (no equity weighting) and 20 (health gains for the most deprived quintile valued more highly), varying the opportunity cost threshold. Graphs showing the health equity impact are presented in the ESM (A6.2).

The incremental population NHB is the value of the intercept at a value of zero for Atkinson IAP (ε) [no equity weighting], giving us information on whether the intervention increases or decreases population health at the chosen value of the opportunity cost threshold. If the curve lies above the x-axis, societal welfare (incremental EDEH) is improved. The equity impact is the difference between a point on the curve and the intercept (i.e., incremental population EDEH minus incremental population NHB). Thus, the equity impact is positive and health inequities are reduced if the slope is positive.

For opportunity cost threshold values between £50,000/QALY and £25,000/QALY, which are above the ICER for alectinib (Table 1), alectinib improved societal welfare,

Table 4 Population equally distributed equivalent health impact at an opportunity cost threshold of £30,000 per quality-adjusted life-year

	TA520 atezolizumab	TA536 alectinib
Evaluating changes in population health (change in equity not included)		
Baseline population QALE ($QALE_b$*N) *(1)*	3,942,667,355 QALYs	3,942,667,355 QALYs
Post-decision population QALE ($QALE_p$*N) *(2)*	3,942,665,467 QALYs	3,942,667,446 QALYs
Incremental population QALE (ΔQALE*N) *(3)=(2)-(1)*	−1,888 QALYs	91 QALYs
Evaluating changes in equity-weighted health (changes in health and health equity both included)		
Baseline population EDEH (equity-weighted QALE) ($EDEH_b$*N) *(4)*	3,863,434,366 QALYs	3,863,434,366 QALYs
Post-decision population EDEH ($EDEH_p$*N) *(5)*	3,863,432,534 QALYs	3,863,434,528 QALYs
Incremental population EDEH (ΔEDEH*N) *(6)*	−1,833 QALYs	162 QALYs
Health equity impact		
Population equity impact (incremental EDEH – incremental QALE) *(6–3)*	56 QALYs	71 QALYs

EDEH equally distributed equivalent health, $EDEH_b$ baseline equally distributed equivalent health per person, $EDEH_p$ post-decision equally distributed equivalent health per person, Δ*EDEH* difference in EDEH between post-decision and baseline, *N* population of England, *QALE* quality-adjusted life expectancy, $QALE_b$ baseline quality-adjusted life expectancy at birth per person, $QALE_p$ post-decision quality-adjusted life expectancy at birth per person, Δ*QALE* difference in QALE between post-decision and baseline, *TA* technology appraisal

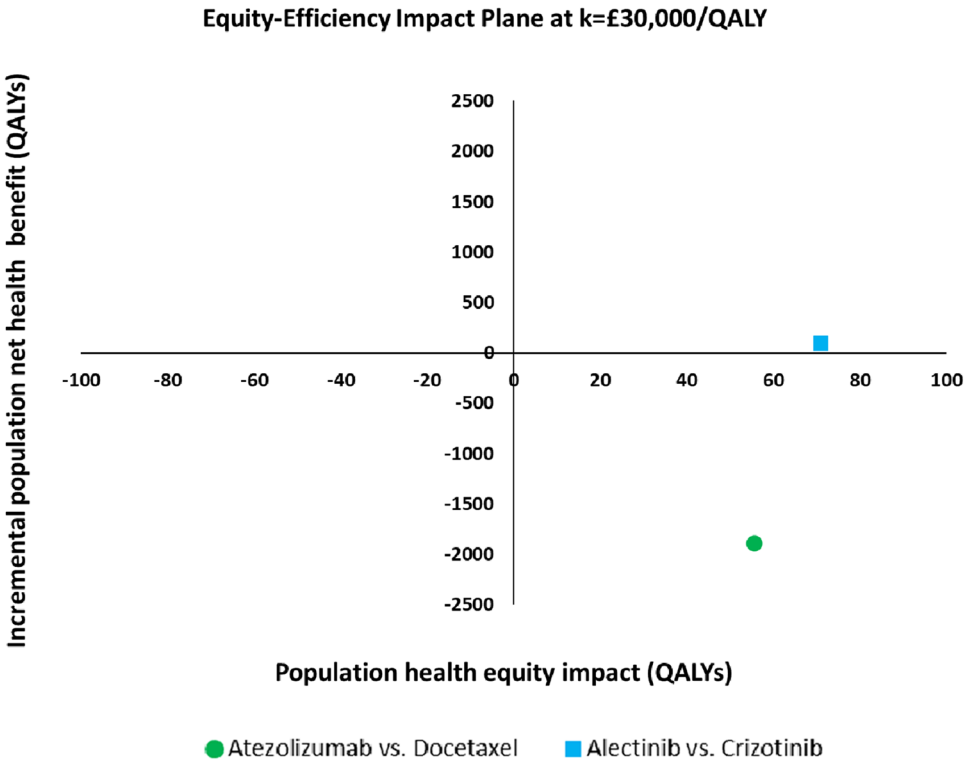

Fig. 2 Equity-efficiency impact plane. *EDEH* equally distributed equivalent health, *k* opportunity cost threshold, *NHB* net health benefit, *QALY* quality-adjusted life year. Population health equity impact is the incremental population EDEH minus the incremental population NHB

increasing total population health (positive intercept) and reducing health inequities (positive slope). Below £25,000/QALY, alectinib reduced total population health (negative intercept) but also reduced health inequities (positive slope), involving a trade-off, which did not favour alectinib (incremental EDEH negative) at £20,000/QALY or £15,000/QALY (Fig. 3a) for Atkinson IAP values between 0 and 20. At a £50,000/QALY threshold, atezolizumab increased total population health (positive intercept) and societal welfare (incremental EDEH positive, curve above the x-axis), and reduced health inequalities (positive slope) [Fig. 3b]. At a £45,000/QALY threshold, atezolizumab involved a trade-off between reducing population health (negative intercept) and reducing health inequities (positive slope). At an Atkinson IAP above 8, societal welfare improved, the reduction in health inequities compensated for health losses, and societal welfare increased as the Atkinson IAP increased (i.e., additional weight given to health gains in the least deprived quintiles). Below £25,000/QALY, societal welfare with atezolizumab was negative and decreased as the Atkinson IAP increased, highlighting that under this assumption, atezolizumab increased health inequities (negative slope) [Fig. 3b].

3.4.2 Distribution of the Patient Population

Figure 4 shows the impact on societal welfare at an opportunity cost threshold of £30,000/QALY and for a range of values of the Atkinson IAP (0–20).

For alectinib, reversing the base-case distribution so that it was skewed toward the least deprived resulted in a trade-off between increasing population health (positive intercept) and increasing health inequities (negative slope). For Atkinson IAP values between 0 and 6, societal welfare increased with alectinib, and the increase in total population health compensated for the increase in health inequalities. If the Atkinson IAP was greater than 6, social welfare decreased with alectinib due to increasing health inequalities. With a flat distribution and a distribution skewed toward the most deprived with a mild gradient (gradient 2), societal welfare increased but health inequities also increased. When the distribution was skewed toward the most deprived with a steep gradient, alectinib increased health and reduced inequities, as in the base-case. For the U-shaped distribution, societal welfare increased, although alectinib increased health inequities if the Atkinson IAP was less than 8 (negative slope), and decreased health inequities if the IAP was greater than 8 (positive slope) [Fig. 4a].

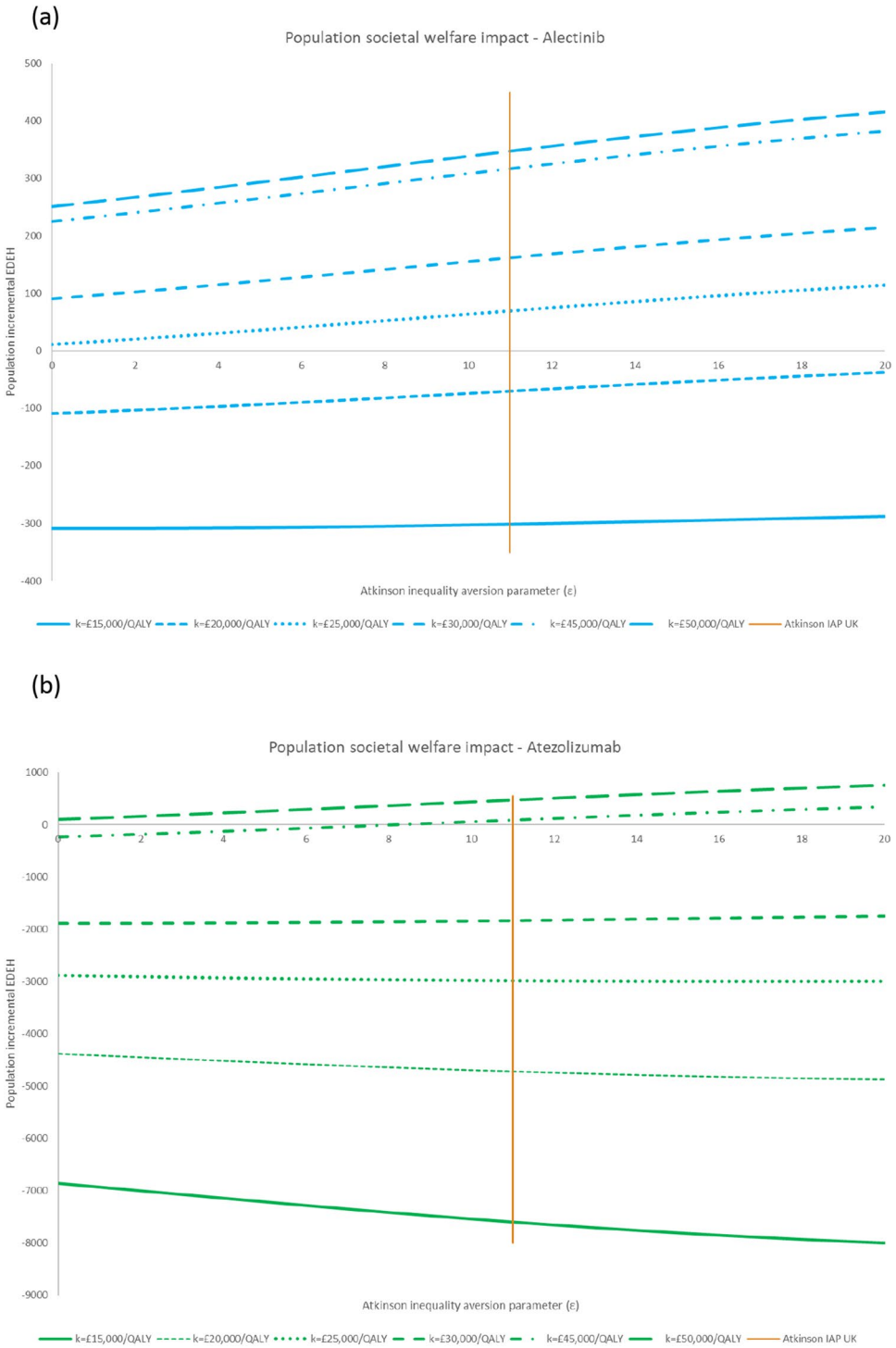

Fig. 3 Effect of the opportunity-cost threshold and Atkinson inequality aversion parameter on societal welfare with (**a**) alectinib and (**b**) atezolizumab. *EDEH* equally distributed equivalent health, *IAP* inequality aversion parameter, *k* opportunity cost threshold, *QALY* quality-adjusted life year

For atezolizumab, in all scenarios, the incremental societal welfare was negative; as the share of patients in the least deprived quintiles increased, health inequities also increased with the Atkinson IAP (steeper slope) [Fig. 4b].

3.4.3 Gradient on the Incremental Health Benefits and Costs

We conducted exploratory sensitivity analyses, incorporating gradients on the incremental costs and health benefits

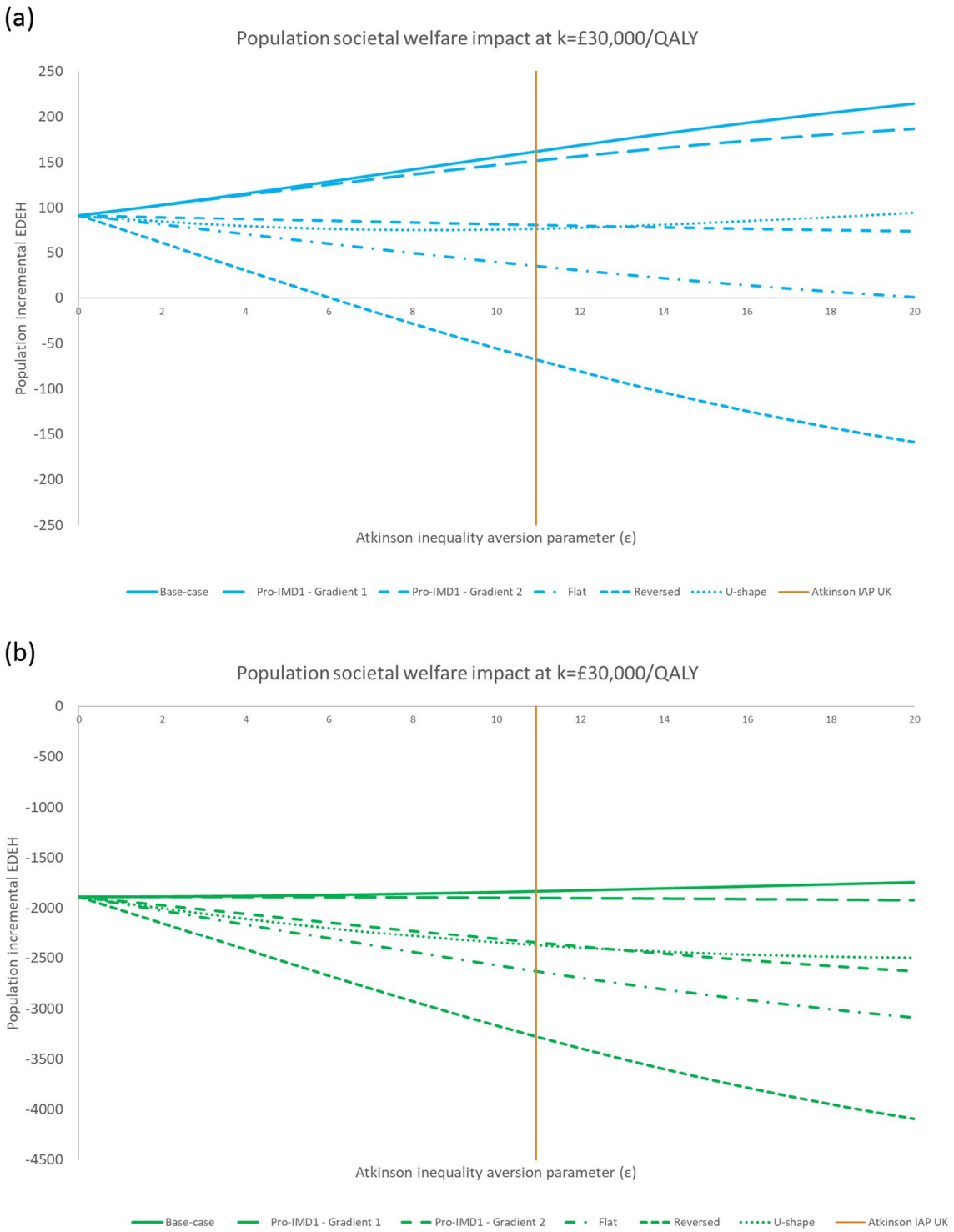

Fig. 4 Effect of the shape of the patient distribution and Atkinson inequality aversion parameter on societal welfare with (**a**) alectinib and (**b**) atezolizumab. *EDEH* equally distributed equivalent health, *IAP* inequality aversion parameter, *IMD* index of multiple deprivation, *k* opportunity cost threshold, *QALY* quality-adjusted life year

instead of a uniform distribution, as in the base-case. As expected, this had an impact on the incremental population NHBs, which increased when more health gains and fewer costs were accrued in the more deprived quintiles and decreased when more health gains and fewer costs were accrued in the least deprived quintiles. Applying

gradients in the distribution of the incremental NHBs had a larger effect on the equity impact than the gradients in the incremental costs. Details of the scenario inputs and results are presented in the ESM (A6.4, A6.5).

3.4.4 Discount on Drug Costs

We also conducted a scenario analysis applying different discounts on the incremental drug costs. The direction of societal welfare and equity impacts was unchanged and only their sizes were impacted. The results are reported in the ESM (A6.6).

4 Discussion

The illustrative examples of applying an aggregate DCEA approach presented here reveal key drivers of the analysis, building on the work conducted by Love-Koh and colleagues [17]. Beyond the health benefits and incremental costs of the intervention, other key drivers in the analysis were the value of the health opportunity cost threshold, characteristics of the patient population (size, distribution), and level of inequality aversion. Each of these drivers raises important questions in terms of the implications for decision making that have not yet been addressed by HTA bodies, such as NICE.

Any intervention for a disease that is more prevalent in the most deprived quintiles of the population will be more likely to show an equity improvement, although this will be context-specific, depending on the size of the ICER relative to the opportunity cost threshold and how skewed the distribution is. As demonstrated in scenario analyses, shifting from a steep pro-IMD1 gradient to a mild gradient resulted in a negative equity impact. When the distribution has a U shape, the health equity impact may vary depending on the level of aversion for inequities, as measured by a parameter such as the Atkinson IAP. Incorporating an assessment of health inequities in the decision-making process for funding new interventions may incentivise pharmaceutical companies to invest in research and development under these circumstances, thereby improving societal welfare. In the case of diseases with a patient distribution skewed toward the least deprived (such as breast cancer, cutaneous melanoma, or prostate cancer [38]), it is unclear whether the analysis results could have negative implications on reimbursement decisions or price negotiations.

The size of the equity impact is driven by the size of the per-patient NHB, as well as the size and distribution of the target population. The results were sensitive to the distribution of the patient population despite the small number of patients. The small population in the analysis resulted in very small changes in health equity and societal welfare, which could be interpreted as neutral. Although the equity impact of a single intervention or for one indication may be small, the overall societal impact could be great when aggregated across all NICE recommendations. Decision makers may need to consider below what threshold (positive or negative) would the equity impact be regarded as null or acceptable, or the threshold above which further investigation (e.g., full DCEA) would be warranted.

Devlin and Parkin conducted an analysis of recommendations made by NICE from its inception in 1999 to 2002 [39], finding a median threshold somewhat above the £30,000/QALY upper bound suggested in the NICE guidelines. To assess whether this finding still held true, we reviewed the 67 NICE STAs published over the 12 months preceding our search (July 2021–June 2022)[1]. Among the 67 NICE STAs we reviewed, 61 treatments were recommended and the company base-case ICER was available for 37 (including the PAS, when applicable). The ICER was above £15,000/QALY for 28 appraisals (76%) [data on file]. Recognising the limitations of this exploratory analysis, the evidence suggests that the average threshold at which technologies are recommended by NICE is above £15,000/QALY. Love-Koh and colleagues [17] found that the societal welfare impact aggregated over 27 interventions was positive. However, eight (30%) of the selected interventions were dominant, and nine (33%) had an ICER below that of the chosen opportunity cost threshold (£12,936/QALY). Additionally, the study included a disproportionately low number of oncology appraisals, which are frequently assessed under end-of-life criteria, and for which the ICER can be as high as £50,000/QALY. Hence, the study sample reported by Love-Koh et al. may not be fully representative of NICE appraisals [17]. Any drug approved at an ICER above the opportunity cost threshold will reduce overall population health. In this case, our analysis illustrated that although the intervention may have a positive equity impact, it may also have a negative societal welfare impact; in other words, the reduction of health inequities is not worth the total population health losses. These findings are consistent with the results reported by Love-Koh et al. [17], suggesting that this may be generalisable across interventions and disease areas. Therefore, if the analysis conducted by Love-Koh et al. was replicated with

[1] We reviewed the 67 NICE STAs published over the last 12 months (July 2021–June 2022). When multiple ICERs were reported against different comparators or for subgroups, we used the average value. The ICER was below £15,000/QALY or the technology dominated the comparator for nine appraisals (24%), between £15,000 and £30,000/QALY for 15 appraisals (41%) and between £30,000 and £50,000/QALY for 13 (35%) appraisals (data on file). Additionally, we used the company submission base-case ICER, which has been reported to be lower than that of the Evidence Review Group (Versoza et al. [40]); hence, the distribution could be even more skewed towards higher ICERs.

a representative sample of appraisals [17], it may result in a negative aggregate societal welfare impact. The inconsistency between the cost effectiveness and opportunity cost thresholds is likely to result in numerous interventions showing a negative societal welfare impact, with the direction of the aggregate impact being uncertain. To prevent this, it would be preferable if the two thresholds were explicitly aligned.

There is uncertainty regarding the true value of opportunity cost in the NHS. The DHSC uses a £15,000/QALY threshold based on research by Claxton et al. on marginal productivity in the NHS [34, 35]. NICE has not adopted this £15,000/QALY threshold and it is below its standard cost-effectiveness threshold of £20,000–£30,000/QALY [35], which is not empirically based. Alternative approaches focusing on the societal value of a QALY produced a wide range of estimates and found no compelling evidence for changing the NICE threshold [40, 41]. The basis for the assumed value of the opportunity cost threshold should be examined carefully.

A few important questions remain unanswered, including how decision makers will interpret the results of DCEAs. For example, what is the decision makers' and public's willingness to pay to improve equity? How much redistribution of healthcare resources are decision makers prepared to accept to improve equity? Measures of inequity aversion provide some information on societal preferences, but it is unclear whether these preferences would translate directly to decision-making policies. In addition, decision makers and society also have other important equity concerns [42]. For example, the NICE process incorporates a decision modifier with QALY weighting for severe diseases (i.e., the rule of rescue) [43] and previously had an end-of-life criterion increasing the value of the cost-effectiveness threshold to £50,000/QALY [44]. Equity concerns for current disease severity tend to prioritise care for older patients with late-stage disease, who tend to have lived a long life and have higher socioeconomic status. Equity concerns for reducing health inequality tend to prioritise care for children and the working-age population with early-stage disease, for whom untreated disease could result in below-average lifetime health and societal status [45]. How would an HTA body, such as NICE, reconcile these two possibly conflicting equity concerns in its decision-making processes?

We assessed health inequalities between socioeconomic subgroups. However, the factors that matter most to the general public in resource allocation decisions are not fully clear. Gu et al. conducted a systematic literature review of studies that elicited stated preferences from the general public [46]. They concluded that people prioritise younger and more severely ill patients and those with lower socioeconomic status, and that patients with self-induced illnesses tend to be attributed lower priority. There is an ongoing debate about healthcare prioritisation and personal responsibility for health; this discourse is complex, given how social determinants of health affect individuals' health behaviours [47]. For example, it is well-documented that lower socioeconomic status is a risk factor for smoking and, consequently, lung cancer [48, 49]. Furthermore, in their review, Gu et al. found considerable heterogeneity between elicitation methods and study findings. Hence, caution is warranted when interpreting results or basing policy on such preference weights. Healthcare prioritisation is inevitable, and further research is required to better characterise the public's views on unfair differences in health and to estimate robust distributional weights incorporating these prioritisation preferences.

Our study has several limitations. We presented illustrative examples of applying an aggregate DCEA approach based on data available in NICE documents. We used the ICER presented in the company's NICE submission, which differs from the ICER considered by the NICE Committee to make their recommendation. It also did not incorporate the actual PAS for the interventions or comparators; hence, we applied hypothetical discounts instead and estimated the share of drug costs for alectinib based on that of atezolizumab. Thus, the analysis provides a ballpark estimate of the size and direction of the impact on equity and societal welfare, which could be larger, smaller, or in the other direction depending on the actual PAS for the intervention and comparators, as well as the ICER considered in the decision making. Our research complements the work of Love-Koh and colleagues, which included a disproportionately low number of cancer appraisals (2 of 27) [17]. However, the study focused on lung cancer and included only two treatments; therefore, it is not a representative sample of oncology treatments assessed by NICE and it does not provide an estimate of the overall equity impact of (lung) cancer treatments recommended by NICE.

In our analysis, we assumed that all eligible patients received treatment. However, this may not hold true in clinical practice, with uptake varying across IMD quintiles, as has been observed across many interventions (e.g., cancer screening, diabetes complications screening). A CEA of COVID-19 vaccines highlighted that the value for money of vaccines may depend more on how well they are distributed and less on their clinical efficacy [50]. Yang et al. conducted DCEAs on two public health interventions in the UK—smoking cessation and alcohol brief intervention—to investigate the impact of incorporating or ignoring gradients in the underlying cost-effectiveness model and DCEA-specific inputs [31]. They found that setting uptake rates to the highest level observed across all quintiles had a strong positive impact on both improving population health and reducing inequalities in both case studies. These studies suggest that access to treatment is an important mediating factor

to improve population health and reduce health inequities. To inform the design of policies aimed at improving the uptake of interventions, more research should be conducted to better understand barriers affecting access to treatment, as patient's choice alone may not explain the differences observed between patient groups [51].

The 'staircase of inequality' is a framework used in DCEA to identify the stages of a health programme where inequalities may result in costs and health effects varying between equity-relevant subgroups of patients [6]. We applied an aggregate DCEA approach, incorporating distributional impacts only in the estimation of the eligible population. The aggregate DCEA approach is informative, providing a starting point for deliberations about equity concerns. Future research could explore applying a full DCEA that incorporates various sources of inequalities where relevant on the continuum of the staircase. To illustrate the potential impact of incorporating gradients in parameters driving differences in health gains and costs between subgroups (e.g., differences in access and uptake between IMD quintiles), we conducted scenarios applying linear gradients (although other shapes, such as a U shape, could be possible) in the incremental health benefits and costs rather than a uniform distribution as in the base case. These scenarios show how this may alter the size and direction of the equity impact. Yang et al. found that ignoring gradients in the model inputs had significant effects on the size and direction of the health benefit and health equity impacts [31]. However, no trend could be identified regarding the gradient in an input and the associated impact on the model results nor conclusions generalised from one setting to another. In a context where differences in costs or outcomes are anticipated or observed between IMD subgroups, these findings highlight the importance of identifying the parameters driving these differences. A full DCEA may also be valuable if the size or direction of an equity impact assessed using an aggregate approach may be of concern to decision makers.

Areas of future research to explore the uncertainty in model parameters, which was not examined in this study, have been detailed in the ESM.

DCEAs are data-intensive. This may lead to relying on assumptions or a tendency to ignore gradients in model inputs to address data gaps, possibly resulting in uncertainty in the estimates. Furthermore, introducing additional analyses into the evidence requirements of HTA bodies would increase the burden for those submitting and those appraising the evidence. Nonetheless, distributionally sensitive economic evaluations allow a more comprehensive valuation of interventions, which is informative to decision makers such as NICE, and governments that have a stated objective to reduce health inequities. Therefore, efforts should be made to collect data (e.g., epidemiology, efficacy, uptake, adherence, costs) more consistently and with more granularity (i.e., disaggregated by relevant equity attributes [e.g., IMD, smoking status]) to increase the quality and quantity of DCEAs and to inform decision making [3].

5 Conclusion

This study presents an example of applying an aggregate DCEA method to estimate equity impacts of new interventions using interventions recommended by NICE in NSCLC. We conducted scenario analyses varying a range of model parameters to test various assumptions and simulate alternative disease areas and decision contexts. The opportunity cost threshold was identified as a key driver of the analysis. Other key drivers were the characteristics of the patient population (size, distribution by deprivation) and the level of inequality aversion. Each of these drivers raises important questions in terms of the implications for decision making. Given the uncertainty about the true marginal cost per QALY in the NHS, the basis for its value should be carefully examined. Further characterisation of the public's views on unfair differences in health and estimation of robust distributional weights incorporating these prioritisation preferences should be conducted. Finally, guidance from HTA organisations, such as NICE, is needed regarding methods for DCEA construction and how such organisations will interpret and incorporate results into their decision making.

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Declarations

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Ethics approval Not applicable.

Consent Not applicable.

Code availability Please contact the corresponding author for any requests for any study materials including codes.

Author contributions AM: Study conception and design, data analysis and interpretation, drafting of the manuscript. LL: Study conception and design, data analysis and interpretation, critical revision of the paper for important intellectual content, supervision. SR: Critical revi-

sion of the paper for important intellectual content, obtaining funding, supervision. MG, LG, SP: Critical revision of the paper for important intellectual content.

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