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Assessing the value of medicine for diverse patients: Implications of a QALY approach for health disparities

A study for the Alliance for Aging Research

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November 11, 2021

Executive Summary

Momentum and debate about the application of cost-effectiveness analysis to determine the value and prices of prescription drugs in the United States are growing. At the same time, it is universally acknowledged that addressing health disparities is critical to advancing health equity and improving patients' health outcomes. The US government has committed to addressing health disparities and there is broad agreement that each stakeholder in the health system has a role to play.[1] Access to and the use of, medicines play critical parts in either exacerbating or reducing differences in health outcomes among communities in the US.

Given the potential role of value assessment as a mechanism to affect access to medicine or feed into price determination in the US, the Alliance for Aging Research (Alliance) asked Charles River Associates (CRA) to examine the implications for health disparities of adopting cost-effectiveness analysis (CEA), including Quality-Adjusted Life Years (QALYs).[2] Specifically, CRA sought to explore the extent to which using value assessment methods in the determination of drug prices in the US could be achieved in parallel with advancing health equity among Black, Asian, Latinx, and Native American patients, with a focus on the older adults within those groups.[3]

As part of our approach, we selected two case study disease areas with strong evidence of racial and socioeconomic differences in the US: Alzheimer's disease and colorectal cancer.[4,5] We then evaluated the extent to which health technology assessment (HTA) agencies in Australia, Canada and England factor in equity and the differences in patient experience across racial and ethnic groups through their cost-effectiveness analyses. These countries were selected because of their well-established HTA agencies and similar methodological approach to value assessment, which is comparable to the methods used by the Institute for Clinical and Economic Review (ICER) in the US.

We find that QALY-based cost-effectiveness approaches fail to consistently consider differences in patient experience of the disease, including those resulting from access disparities, structural racism (which affects transportation, job type, living situation and exposure to environmental factors) and other social determinants of health. Although we find that some HTA agencies (e.g., the National Institute for Health and Care Excellence (NICE) in England, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, and

1 Executive Order on Advancing Racial Equity and Support for Underserved Communities Through the Federal Government, Executive Office of the President Joseph Biden, https://www.whitehouse.gov/briefing-room/presidential-actions/2021/01/20/executive-order-advancing-racial-equity-and-support-for-underserved-communities-through-the-federal-government/.

2 While this paper focuses on examples using the QALY, similar concerns exist with QALY-derived value assessment metrics, such as the equal-value of life-years gained (evLYG) measure, also developed by ICER.

3 For this study we use the terms "Black" and "Latinx" in defining racial groups; however, much of the literature referenced uses the terms "African American" and "Hispanic."

4 Alzheimer's Association, 2019 Alzheimer's Disease Facts and Figures, https://www.alz.org/media/Documents/alzheimers-facts-and-figures-2019-r.pdf; *Alzheimers Dement*. 2019;15(3):321-87.

5 US Cancer Statistics Working Group, US Cancer Statistics Data Visualizations Tool, based on 2020 submission data (1999–2018): US Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, www.cdc.gov/cancer/dataviz, released in June 2021.

the Canadian Agency for Drugs & Technologies in Health (CADTH) in Canada) do aim to consider health equity in principle, in practice, the consideration of disparities is limited and typically noted only as a contextual consideration. Similarly, ICER, a nongovernmental institution that entered into an agreement in 2017 with the US Department of Veterans Affairs Pharmacy Benefits Management Services office to support its use of QALY-based drug assessment reports, does not systematically consider impact on race and ethnic equity in value assessment. Further, because HTA agencies that use the QALY measure estimate the average value of a treatment for a population, they consistently fail to consider the differential impact of a treatment on specific racial and ethnic groups' perception of symptom and life expectancy improvement. We consider this issue in particular because there remain significant differences in income level, labor market participation, access to health coverage and other social determinants of health that affect a patient's experience of disease. For example, Black and Latinx persons are more likely to be employed in jobs that require physical labor, such as service, construction, or maintenance and they also tend to have lower incomes on average, due in part to persistent racism and unequal access to capital and education.[6,7,8] As a result, the value of a medicine is affected by occupation and the nature of the job, which will inevitably affect certain racial and ethnic groups. Determining the average value across a population may be accepted in a single-payer health system, but it is more problematic in the US's decentralized, pluralistic health system, where distinct payers establish formularies based on the specific needs of their patient populations.

Additionally, we find that cost-effectiveness analysis using the QALY to determine price and access reinforces existing racial bias and certain communities' unequal access to capital. We further find that these analyses often fail to consistently consider the full range of important nonclinical benefits. The benefits of medicines with respect to their impact on patients' health-related quality of life, labor market productivity, and ability to provide caregiving are rarely taken into account (or, if they are, they are not given sufficient weight). Given the differences in certain patients' experience of disease, including those resulting from access disparities, structural racism, differences in culture and social determinants of health, this again results in disparities between white and non-white populations.[9] Furthermore, it is well documented that disease onset for some conditions appears at younger ages and presents as more severe in certain racial and ethnic groups, so while the benefit of treatment is greater for those communities in comparison to the majority white population, traditional value assessment (i.e., QALYs) calculates the therapeutic as more expensive to society. As a result, the QALY and similar metrics are biased against those who likely already experience discrimination in US society.

When cost-effectiveness analysis is used to determine the price of a new drug, clinical trial data are relied on to demonstrate value. However, multiple published studies have found that

6 US Bureau of Labor Statistics, A Profile of the Working Poor 2018, July 2020, https://www.bls.gov/opub/reports/working-poor/2018/home.htm.

7 US Census Bureau, Current Population Survey, 1968 to 2021 Annual Social and Economic Supplements (CPS ASEC).

8 National Academies of Sciences, Engineering, and Medicine (2017). Communities in Action: Pathways to Health Equity (Chapter 5). Washington, DC: The National Academies Press, https://doi.org/10.17226/24624.

9 Friedman, E. M., Shih, R. A., Langa, K. M. & Hurd, M.D. (2015). US prevalence and predictors of informal caregiving for dementia. *Health Affairs* (Project Hope), 34(10), 1637–1641. https://doi.org/10.1377/hlthaff.2015.0510.

diverse groups are significantly underrepresented in clinical trial participants, so data commonly do not accurately reflect the diversity of the population that ultimately takes the medicine. On average, trials enroll a significantly higher percentage of whites than is reflected in the population.[10] Homogeneous trials can help to isolate the medicines' benefit, but this inadvertently puts non-white patients at risk. When trials are not diverse, the result is a diminished ability to identify effects that may disproportionately affect minority communities and a limited understanding of the efficacy of treatments.[11] The number of people enrolled in clinical trials is established to show a clinically meaningful effect size; testing on more or fewer people than are needed to show the clinical effect would be unethical. If clinical trial data were used to determine prices in the US, there would be an incentive to show as large of an effect size as possible beyond the minimum clinically meaningful effect. **This might create an even stronger motive to exclude enrollees who might not show as large a benefit (such as people with comorbid conditions) or to enroll more people than necessary for the purpose of showing a larger effect size.**[12] This effect would run counter to the efforts of the US Food and Drug Administration (FDA), the National Institutes of Health (NIH) and the US Department of Health and Human Services (HHS), as well as state organizations, to diversify clinical trials, make them efficient and collect information about minority and lower-socioeconomic-status patients in drug development.[13]

Our findings suggest several policy solutions to better assess the value of medicine without undue reliance on cost-effectiveness analysis:

- To support the assessment of new medicines in diverse patient populations, the NIH should develop **nationally representative, integrated longitudinal datasets** that can be used to examine the value of medicine to different racial and ethnic groups.
- Any form of cost-effectiveness analysis should involve a **systematic consideration of the impact of the new medicines by race and on health equity**. Congressional legislation could mandate the development of methods to better consider how new medicines could provide patient value and address health access and outcomes disparities. Organizations creating and implementing cost effectiveness approaches in the US, whether government-backed or private, should commit to assessment approaches that balance the consideration of clinical value for diverse populations and the impact on reducing inequities. Organizations such as the Patient Centered Outcomes Research Institute (PCORI) and the Innovation and Value Initiative are already developing methodologies that move away from considering the average value of a medicine across diverse populations to factor in the impact of health disparities on specific population groups.

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10 Nazha B., Mishra M., Pentz R. & Owonikoko T.K. (2019). Enrollment of racial minorities in clinical trials: Old problem assumes new urgency in the age of immunotherapy. *Am Soc Clin Oncol Educ* Book, 39:3-10, doi: 10.1200/EDBK_100021. Epub 2019 May 17. PMID: 31099618.

11 Clark et al. (2019). Increasing diversity in clinical trials: Overcoming critical barriers, *Current Problems in Cardiology*, Vol. 44, No. 5, pp. 148–172, https://www.sciencedirect.com/science/article/pii/S0146280618301889?via percent3Dihub.

12 Cesana, B. M., Antonelli, P. (2016). Sample size calculations in clinical research should also be based on ethical principles. *Trials* 17, 149, https://doi.org/10.1186/s13063-016-1277-5.

13 US Food and Drug Administration Guidance, "Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry," November 2020, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial.

- An alternative approach to traditional value assessment that incorporates health inequities is needed. Approaches growing in popularity include multi-criteria decision analysis (MCDA) and the distributional cost-effectiveness analysis (DCEA) method. Further development of these metrics should focus on incorporating the range of outcomes important to distinct patient populations and include a focus on addressing health equity.
- To develop a more holistic and societal approach to value assessment, federal funding to develop diverse health economists in universities (e.g., through research grants) is needed. In addition, policy makers could establish standards and incentives to support the development and use of cross-functional research teams (social workers, economists, physicians) on state prescription drug affordability boards to conduct more nuanced assessments.

Background and objectives

Momentum and debate about the application of cost-effectiveness analysis to determine the value of a drug and ultimately its price in the US, as is done in many other countries, are growing. For example, this is seen in the following:

- **Increasing influence in US of Quality-Adjusted Life Year (QALY)–based cost-effective analysis (CEA)**: Private insurers have used QALY-based CEA as a consideration in their coverage and formulary determinations for a number of years. However, the US government has repeatedly rejected the use of QALY-based CEA by Medicare and Medicaid over the last fifty years due to concerns about discrimination and civil rights.[14] More recently, state Medicaid programs have expressed interest in using QALY and other QALY-derivative metrics developed by the Institute for Clinical and Economic Review (ICER).[15]
- **Inclusion of international reference pricing in the US House of Representatives' proposed Lower Drug Costs Now Act (H.R. 3)**: The international price index designated in H.R. 3 would establish a benchmark for prescription drug prices based on an index of prices from markets outside the US. Many of the included nations, such as the United Kingdom and Australia, use the QALY to assess the value of medications.[16]
- **The Biden administration's suggestion to develop a national health technology assessment (HTA) entity**: The administration is considering a national agency to advise public programs on medicine pricing and reimbursement issues. While a number of countries use QALY in their HTA, some do not, including Germany's Institute for Quality and Efficiency in Health Care (IQWiG). The US has organizations that collect patient outcomes data, but they are currently prohibited from advising government directly on

[14] National Council on Disability (2019). Quality-Adjusted Life Years and the Devaluation of Life with Disability, https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf.

[15] Pearson, S.D. & Emond, S.K. How Independent Assessment of Drug Value Can Help States, *ICER*, https://icer.org/news-insights/commentaries/how-independent-assessment-of-drug-value-can-help-states/.

[16] H.R.3 - Elijah E. Cummings Lower Drug Costs Now Act, 116th Congress (2019–2020), https://www.congress.gov/bill/116th-congress/house-bill/3.

pricing and reimbursement.[17] Nevertheless, in 2017 ICER entered into an agreement with the US Department of Veterans Affairs Pharmacy Benefits Management Services office to support its use of QALY-based drug assessment reports.

At the same time, it is universally acknowledged that addressing health disparities is critical to advancing health equity and patients' health outcomes.[18] The US government has committed to addressing health disparities and there is broad agreement that each stakeholder in the health system has a role to play.[19] Access to, and the use of, medicines have a critical part in either exacerbating or reducing differences in health outcomes among communities in the US.

Because of the potential role of value assessment (and the use of approaches such as the QALY) as a mechanism to grant or deny access to medicine or set prices, the Alliance for Aging Research ("Alliance") asked Charles River Associates (CRA) to examine the implications for health disparities of adopting QALY-based CEA in the US.[20] In so doing, CRA sought to explore the extent to which efforts to deploy value assessment methods in the US can be achieved in parallel to advancing health equity among Black, Asian, Latinx, and Native American patients and in particular older adults within those groups.[21]

Our approach

We adopted a three-step methodology to understand how CEA approaches could affect health disparities. We noted that some form of CEA is undertaken in the US by state prescription drug affordability boards, commercial payers, and ICER, although these groups generally lack the power that translates to substantial differences in access, which occur in markets outside the US. Therefore, given the growing influence of health technology assessment approaches by international agencies on CEA in the US, we sought to understand the extent to which HTA agencies in Australia, Canada and England factor in equity and the differences in patient experience across racial and ethnic groups through their cost-effectiveness analyses.[22]

Specifically, CRA considered the CEA approaches undertaken by the following agencies: **The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, the Canadian Agency for Drugs & Technologies in Health (CADTH) in Canada, and the National Institute for Health and Care Excellence (NICE) in England.**[23] These agencies rely on the

17 Kelly, C. (2020). Biden, Germany and Bringing a National Drug Pricing Negotiation Process to US, *Pink Sheet*, https://pharmaintelligence.informa.com/resources/product-content/biden-germany-and-bringing-a-national-drug-pricing-negotiation-process-to-us.

18 CDC, Reaching for Health Equity, https://www.cdc.gov/healthequity/features/reach-health-equity/index.html.

19 Executive Order on Advancing Racial Equity and Support for Underserved Communities Through the Federal Government, Executive Office of the President Joseph Biden, https://www.whitehouse.gov/briefing-room/presidential-actions/2021/01/20/executive-order-advancing-racial-equity-and-support-for-underserved-communities-through-the-federal-government/.

20 While this paper focuses on examples using the QALY, similar concerns exist with QALY-derived value assessment metrics such as the equal-value of life-years gained (evLYG) measure, also developed by ICER.

21 For this study we use the terms "Black" and "Latinx" in defining racial groups; however, much of the literature referenced uses the terms "African American" and "Hispanic."

22 Thokala, P. et al. (2020). HTA'd in the USA: A comparison of ICER in the United States with NICE in England and Wales. *Journal of Managed Care & Specialty Pharmacy*, 26:9, 1162–1170.

23 While NICE, CADTH, and PBAC do not use CEA to make formal reimbursement decisions, the agencies use the assessments to make recommendations that determine the availability of new medicines.

measurement of QALYs. These countries were selected because of their well-established HTA agencies and similar methodological approach to value assessment, which is comparable to the methods used by ICER in the US.

Second, we selected two study disease areas, **Alzheimer's disease (AD)** and **colorectal cancer (CRC)** where there is strong evidence of racial and socioeconomic differences in patient groups in the US.[24,25] Within each case study disease area, we have documented the differences in the burden of disease within racial groups in the US and evidence of health disparities and inequities faced by AD and CRC patients. Key words used in the literature review included "disparity," "inequity," "inequality," "access," "diagnosis," and "standard of treatment." Additional keywords were used to identify challenges faced by specific communities such as "Black," "Latinx," and "Native American." The review focused on academic articles, scientific and patient association publications and public agency reports from the last ten years.

Finally, we evaluated the extent to which HTA agencies in Australia, Canada, and England factor in the differences in patient experience across racial and ethnic groups through their CEA in these therapy areas. To do this, we reviewed the literature for assessments of drugs in our selected disease areas undertaken by NICE, CADTH, and the PBAC over the past ten years. We reviewed each drug's assessments for reference to consideration of subpopulations and diversity. Key words in our search included, but were not limited to, "race," "equity," diversity," "black," "Asian," and "ethnic minority." Where applicable, additional key words were used specific to the population and prevalent terminology used in a country, such as the acronym "BAME" in England and the term "indigenous" in Australia.

This review yielded insights into the extent to which NICE, CADTH and PBAC consider racial and ethnic groups in their assessment of new drugs in AD and CRC. Finally, we considered the implications of applying a typical QALY-based CEA approach to the US population.

Approach to testing if the QALY-based approach to CEA considers health disparities

The QALY metric aims to synthesize the perception of symptom and life expectancy improvement and inherently generalizes the perspectives of patient population groups. Challenges associated with the QALY-based approach and broad population-level CEA are well documented.[26,27,28] However, we wanted to investigate how the QALY metric accounts for health inequities and the impact of using QALY-based CEA on access disparities.

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[24] Alzheimer's Association, 2019 Alzheimer's Disease Facts and Figures, https://www.alz.org/media/Documents/alzheimers-facts-and-figures-2019-r.pdf; *Alzheimers Dement*. 2019;15(3):321-87.

[25] US Cancer Statistics Working Group, U. Cancer Statistics Data Visualizations Tool, based on 2020 submission data (1999–2018): US Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, www.cdc.gov/cancer/dataviz, released in June 2021.

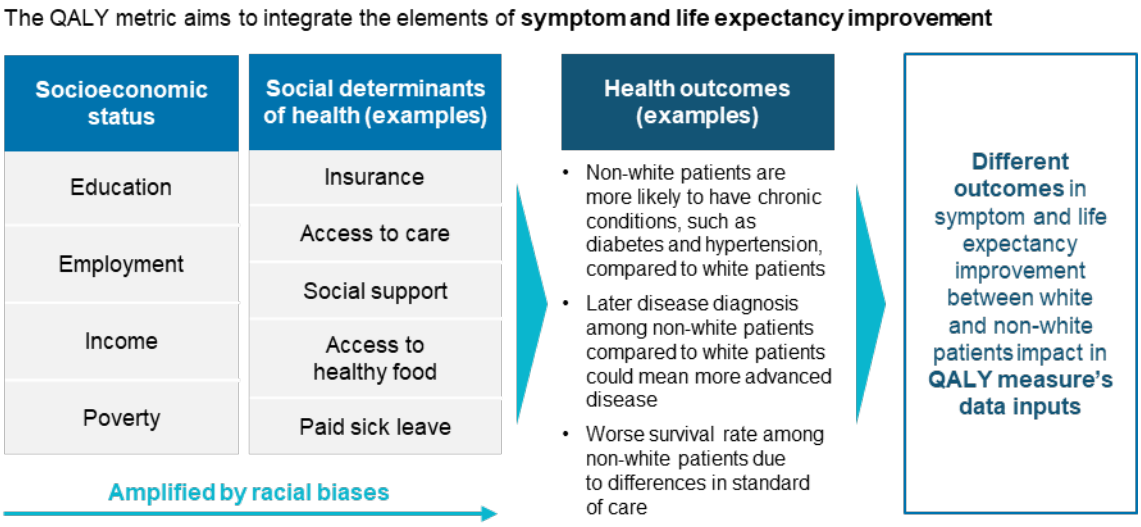
[26] Pettitt, D. A., Raza, S., Naughton, B., Roscoe, A., Ramakrishnan, A., Ali, A., Davies, B., Dopson, S., Hollander, G., Smith, J. A. & Brindley, D. A. (2016). The limitations of QALY: a literature review. *Journal of Stem Cell Research and Therapy*, 6(4), Article: 1000334.

[27] Caro, J. J., Brazier, J. E., Karnon, J. et al. (2019). Determining value in health technology assessment: Stay the course or tack away? *PharmacoEconomics* 37, 293–299, https://doi.org/10.1007/s40273-018-0742-2.

[28] Whitehead, S. J. & Ali, S. (2010). Health outcomes in economic evaluation: The QALY and utilities. *British Medical Bulletin,* 96: 5–21, DOI:10.1093/bmb/ldq033.

To achieve this, we considered the extent to which the QALY metric can effectively consider patients' experiences of diseases and account for health inequities. Triangulating the causes of health inequities—often a combination of socioeconomic factors reinforced by structural racism and previous policy decisions—is difficult.[29] Figure 1 illustrates our hypothesis: that differences in patients' experiences of disease and care can lead to different health outcomes, which would influence the QALY metric.

Figure 1: Summary of how socioeconomic status and the social determinants of health could filter into the QALY calculation



To test our hypothesis, we consider the calculation of the QALY in CEA.

An overview of CEA and how it is applied in practice

CEA use is growing in the US, but it is already prevalent in some form in many countries outside of the US and is used to support HTA decisions. This includes recommendations regarding access to medicine provided within the public health system and decision-making regarding the price of the medicine. The QALY is currently the main pillar of CEA and aims to capture the impact of medicine on a patient's health-related quality of life (HRQoL) and length of life. As a result, the QALY metric is often used to inform reimbursement and access decisions in international markets.[30]

[29] Rayleigh, V. & Holmes, J. (2021). The health of people from ethnic minority groups in England, *The Kings Fund*, https://www.kingsfund.org.uk/publications/health-people-ethnic-minority-groups-england.

[30] Whitehead, S. J. & Ali, S. (2010). Health outcomes in economic evaluation: the QALY and utilities. *British Medical Bulletin,* 96: 5–21 DOI:10.1093/bmb/ldq033.

BOX 1: Definitions

Health outcomes are the set of characteristics that describe the consequences of disease for an individual, including symptoms, level of function, participation in activities and social roles and health-related quality of life.[31] A common way to estimate the benefit of an intervention (critical to the CEA) is to quantify the impact of an intervention or disease on health outcomes.[32]

The **QALY** aims to describe both the quality and quantity of life gained from use of a new medicine.[33] QALY assessments assign a value, called a **health state preference value**, to the patient group for which a treatment is intended. These assessments are based on the perceived value of living with a given condition in comparison to being in "perfect health." Specifically, the QALY summarizes the effects of health interventions on mortality and morbidity into a single index, thereby producing a common "currency" to enable comparisons across different diseases and innovations.[34] The currency suggests that 1 QALY equates to one year in perfect health while 0 is death, so scores typically range from 0 to 1. There are cases where patients suggest their health state is worse than death (negative QALY) due to terminal disease or illness.[35]

It is important to note that health state preference values reflect the preferences and prejudices of the people who develop them and the people who are asked to rate them. For example—did the preference survey ask people who have the condition for their perspective, or did it ask people who have never had the condition or never even known anyone with the condition?

QALY Calculation*:* The QALY is calculated by multiplying the health state preference value by the time the patient is likely to spend in that state. By definition, QALYs attribute less value to treatments for populations that have fewer expected years of life left or shorter life spans relative to the total population. As an example, if a 30-year-old with cardiovascular disease and a 30-year-old with no comorbid conditions receive identical curative treatments for a fatal disease, the value of life gained for the healthier person is greater because they had a longer expected life but for the fatal disease.

QALY = (*HRQoL or utility value associated with a given state of health*) *x* (*time spent in health states*)

[31] Barnsbee, L., Barnett, A. G., Halton, K. & Nghiem, S. Chapter 24 - Cost-effectiveness, Editor(s): Shaun D. Gregory, Michael C. Stevens, John F. Fraser, Mechanical Circulatory and Respiratory Support, Academic Press, 2018, pages 749–772, https://www.sciencedirect.com/topics/medicine-and-dentistry/health-outcomes.

[32] Weinstein, M.C. et al. (2009). QALYs: The Basics, *Value in Health*, 1098-3015/09/S5 S5–S9.

[33] Weinstein, M.C. et al. (2009). QALYs: The Basics, *Value in Health*, 1098-3015/09/S5 S5–S9.

[34] Whitehead, S. J. & Ali, S. (2010). Health outcomes in economic evaluation: The QALY and utilities. *British Medical Bulletin,* 96: 5–21, DOI:10.1093/bmb/ldq033.

[35] Shaw, D. & Morton, A. (2020). Counting the cost of denying assisted dying. *Clinical Ethics*, 15(2):65-70, doi:10.1177/1477750920907996.

The CEA frequently performed by the HTA agencies is an approach used to estimate the costs and health gains of alternative interventions (treatments).[36] Specifically, CEA aims to quantify the gains or declines in population health resulting from a particular treatment during the time period in which patients are expected to be on the treatment. Gains are typically measured by QALY. The cost-effectiveness of an intervention may be expressed in cost per QALY.[37] If the cost per QALY is assessed as below a set **threshold**, then it is typically considered cost-effective.[38] This calculation is also known as the cost per QALY gained or the "incremental cost-effectiveness ratio":

Cost per QALY gained = *Net cost* (i*ntervention costs – averted medical and productivity costs*) */* n*et* h*ealth* o*utcomes* (o*utcomes with intervention – outcomes without intervention*)

While the concept of cost-effectiveness is relatively simple, what is included in the numerator and denominator can vary by assessment and disease.[39]

The cost-effectiveness threshold indicates the maximum investment a country or organization is normally willing to make to give a patient an additional QALY.[40] Some agencies publish strict thresholds, while in others this is established through how it is applied over time. Average threshold levels tend to vary across agencies and diseases. Critics of strict thresholds argue that the number is arbitrary, while critics of undefined thresholds claim the absence of a set amount adds an undesired degree of subjectivity to the assessment.

Australia, Canada, and England each have national HTA agencies that advise on the cost-effectiveness of treatments. These agencies base decisions on cost-effectiveness thresholds under which a treatment would likely be recommended for reimbursement. Table 1 summarizes the approach to CEA taken by HTA agencies in Australia, Canada, and England.

36 WHO, Cost-effectiveness analysis for health interventions, https://www.who.int/heli/economics/costeffanalysis/en/.

37 Weinstein, M.C. et al. (2009). QALYs: The Basics, *Value in Health*, 1098-3015/09/S5 S5–S9.

38 CDC, Cost-Effectiveness Analysis, https://www.cdc.gov/policy/polaris/economics/cost-effectiveness/index.html#:~:text=Cost percent2Deffectiveness percent20analysis percent20is percent20a,gained percent20or percent20a percent20death percent20prevented.

39 CDC, Cost-Effectiveness Analysis, https://www.cdc.gov/policy/polaris/economics/cost-effectiveness/index.html#:~:text=Cost percent2Deffectiveness percent20analysis percent20is percent20a,gained percent20or percent20a percent20death percent20prevented.

40 Cameron, D., Ubels, J. & Norström, F. (2018). On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. *Global Health Action*, 11(1), 1447828, https://doi.org/10.1080/16549716.2018.1447828.

Table 1: HTA agencies and their use of cost-effectiveness assessments

Country	Agency	Cost-Effectiveness (CE) Recommendations and Threshold
Australia[41]	Pharmaceutical Benefits Advisory Committee (PBAC)	• No clear or defined threshold • Recommendations are acted on by the minister for health, who cannot list a drug on the Pharmaceutical Benefits Scheme unless the PBAC gives a positive recommendation
Canada[42]	Canadian Agency for Drugs and Technologies in Health (CADTH)	• CADTH does not formally state a CE threshold for new medicines • CAD $50,000 per QALY is often cited as a benchmark, but there is limited evidence to confirm accuracy of threshold • CADTH recommendation is non-binding
England[43,44]	National Institute for Health and Care Excellence (NICE)	• NICE typically uses a "standard" threshold for recommending treatments of between £20,000 and £30,000 per QALY • The NHS is legally obligated to fund treatments recommended by NICE's technology appraisals • Exceptions to the standard threshold include end-of-life technologies (£50,000 per QALY) and very rare diseases (£100,000 and £300,000 per QALY)

The HTA agencies in Australia, Canada and England use broadly similar methods to collect evidence that make up the QALY score. The most significant variation between how agencies assess CEA of a medicine is between diseases, given the differences in patient demographics, symptoms, outcomes, etc.[45] For example, depending on the disease, the data collected may be based on the perspective of whoever is reporting outcomes, e.g., the patient (experiencing the disease), the caregiver (caring for the patient experiencing disease), or a healthcare professional (monitoring or conducting a trial).[46] This suggests that the outcomes reported can inherently be more subjective (pain) or objective (number of strokes) in nature. In addition, the standard of acceptable evidence can vary for certain diseases such as those considered ultra- rare and are outlined by modified CEA frameworks.[47] Further, agencies typically accept higher cost-effectiveness thresholds oncology and end-of-life treatments.

41 Cameron, D., Ubels, J. & Norström, F. (2018). On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. *Global Health Action,* 11(1), 1447828, https://doi.org/10.1080/16549716.2018.1447828.

42 Paris, V. & A. Belloni (2013), Value in Pharmaceutical Pricing, OECD Health Working Papers, No. 63, *OECD Publishing*, https://doi.org/10.1787/5k43jc9v6knx-en.

43 NICE, Carrying NICE over the threshold, https://www.nice.org.uk/news/blog/carrying-nice-over-the-threshold.

44 Paulden, M. (2017). Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable? *Expert Review of Pharmacoeconomics & Outcomes Research*, 17:3, 239-242, DOI: 10.1080/14737167.2017.1330152.

45 Paris, V. & A. Belloni (2013). Value in Pharmaceutical Pricing, OECD Health Working Papers, No. 63, *OECD Publishing*, https://doi.org/10.1787/5k43jc9v6knx-en.

46 Weinstein, M.C. et al. (2009). QALYs: The Basics, *Value in Health*, 1098-3015/09/S5 S5–S9.

47 CADTH (2021) Health Technology Review: Drugs for Rare Diseases: A review of national and international Health Technology Assessment Agencies and public payers' decision-making processes. https://cadth.ca/sites/default/files/es/es0355-drugs-for-rare-diseases-pw.pdf

Another dimension is whether these outcomes can be measured directly or only indirectly. There is an extensive debate on the use of endpoints, such as overall survival, or surrogate endpoints, such as reduced cholesterol, that can be used to infer patient outcomes and the calculation of the overall benefit of an innovation.[48] The calculation is intended to be as robust as possible while also enabling the incorporation of clinically relevant outcomes. For the patient outcomes to be measured in a comparable way, these metrics are collected to quantify the "utility value" of an intervention, which is used to determine the potential QALY associated with a new medication.

To estimate the QALY, patients' perceptions of their HRQoL must be elicited. This evidence is typically collected during clinical trials or during a separate observational study. Generic preference-based measures such as a multi-attribute utility instrument (MAUI) survey is one common way of eliciting HRQoL from patients during clinical trials.[49] The most typically cited example of an MAUI is the EuroQol (EQ-5D), a questionnaire completed in relation to five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[50] Other forms of measuring patient perception of HRQoL include the Time Trade-Off (TTO) valuation technique, which presents patients with two alternative scenarios and asks which they would prefer and the Standard Gamble (SG) approach, which presents patients with the choice between remaining in a particular health state or taking a gamble of either being in full health or risking death.

Do HTA agencies consider differences in racial and ethnic groups?

In order to understand how disparities affect the QALY-based approach we assessed whether HTA agencies prioritize consideration of differences in racial and ethnic groups. Overall, we find little evidence of commentary in the literature about how these HTA agencies consider equitable access for specific groups.

Through our review of PBAC, CADTH, and NICE CEA guidelines, we find that consideration of racial and ethnic groups and access is not standard practice by these agencies (Table 2). While the agencies do appear to note that there may be differences between patient populations that would affect the CEA, there is no consideration of specific racial groups in the approach. In US-based CEA, there is some evidence which suggests a consideration of racial subpopulations, although it is limited.[51]

[48] Paris, V. & A. Belloni (2013), Value in Pharmaceutical Pricing, OECD Health Working Papers, No. 63, *OECD Publishing*, https://doi.org/10.1787/5k43jc9v6knx-en.

[49] Whitehead, S. J. & Ali, S. (2010). Health outcomes in economic evaluation: the QALY and utilities. *British Medical Bulletin,* 96: 5–21 DOI:10.1093/bmb/ldq033.

[50] Kennedy-Martin, M., Slaap, B., Herdman, M. et al. (2020). Which multi-attribute utility instruments are recommended for use in cost-utility analysis? A review of national health technology assessment (HTA) guidelines. *Eur J Health Econ,* 21, 1245–1257, https://doi.org/10.1007/s10198-020-01195-8.

[51] Of CEA published in 2014 in the US, only 19 percent reported patient subgroup results and only 4 percent reported on race or ethnicity specifically. Lavelle, T. A., Kent, D. M., Lundquist, C. M., Thorat, T., Cohen, J. T., Wong, J. B., Olchanski, N. & Neumann, P. J. (2018). Patient variability seldom assessed in cost-effectiveness studies, *Medical Decision Making: An International Journal of the Society for Medical Decision Making*, 38(4), 487–494. https://doi.org/10.1177/0272989X17746989.

Table 2: HTA agencies and their consideration of equitable access between racial and ethnic groups

Country	Agency	Consideration of racial and ethnic groups
Australia[52]	Pharmaceutical Benefits Advisory Committee (PBAC)	Guidelines for PBAC highlight that "a range of patient characteristics (e.g., age, sex, race)" are critical to understanding the evidence but do not state that specific races must be considered
Canada [53]	Canadian Agency for Drugs and Technologies in Health (CADTH)	CADTH considers data across subpopulations only if there is reason to believe there are different costs and outcomes associated with interventions across distinct subgroups. Otherwise, the CEA should be for the entire target population
England [54]	National Institute for Health and Care Excellence (NICE)	NICE states that an "additional QALY has the same weight regardless of the other characteristics of the people receiving the health benefit"

Drawing from case studies to determine the health equity implications of a QALY approach in the US

To understand the implications for health disparities of a QALY-based approach in the US, we considered the extent to which current CEA estimation methods sufficiently reflect the differences in patients' experience of disease. We use two case studies: colorectal cancer and Alzheimer's disease.

Case study: Colorectal cancer treatment

Background on colorectal cancer

Black Americans have the highest incidence rates of CRC of any ethnic group.[55] Specifically, CRC incidence is 45.7 in 100,000 among the Black population, 43.3 among Native Americans, 38.6 among non-Hispanic whites, 34.1 among Hispanics, and 30.0 among some Asian subpopulations.[56] Higher mortality rates are also observed among Black CRC patients (19.0 in 100,000 people), followed by Native Americans (15.8), non-Hispanic whites (13.8), Hispanics (11.1), and some Asian subpopulations (9.5).

52 PBAC, Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee, https://pbac.pbs.gov.au/information/about-the-guidelines.html.

53 CADTH, Guidelines for the Economic Evaluation of Health Technologies: Canada 4th Edition, https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.

54 NICE, Guidelines Manual, Assessing cost effectiveness, https://www.nice.org.uk/process/pmg6/chapter/assessing-cost-effectiveness.

55 Augustus, G. J. & Ellis, N. A. (2018). Colorectal cancer disparity in African Americans: Risk factors and carcinogenic mechanisms. *The American Journal of Pathology*, 188(2), 291–303, https://doi.org/10.1016/j.ajpath.2017.07.023.

56 Zavala, V.A., Bracci, P.M., Carethers, J.M. et al. (2021). Cancer health disparities in racial/ethnic minorities in the United States. *Br J Cancer*, 124, 315–332, https://doi.org/10.1038/s41416-020-01038-6.

It is clear from literature that multiple causes drive disparities in incidence and mortality. These factors include, but are not limited to, patient awareness of and unequal access to, screening; more advanced disease stage at diagnosis; differences in treatment patterns; and unique tumor biology.[57] Studies suggest that environmental risk factors account for the majority (65 percent) of the higher CRC risk, such as smoking, obesity, alcohol use, and vitamin D and selenium deficiency.[58] Table 3 summarizes the disparities in CRC patient outcomes in the US. Similar disparities to those described in Table 3 are evident in international markets.[59]

Table 3: Summary of health disparities in CRC among racial and ethnic groups

		Evidence of outcomes
Burden of disease	**Diagnosis**	• African Americans are more often diagnosed with CRC at an earlier age, with more advanced disease, and are more likely to have CRC in the proximal colon (associated with more aggressive tumor) • Median age at CRC diagnosis is 63 years for Black men and 64 years for Black women; for white men and women, it is 66 and 70, respectively
	Survival	• Lower 5-year survival for Black early-onset CRC patients (54.9 percent) compared to non-Hispanic white (68.1 percent) and Hispanic patients (62.9 percent) • CRC mortality among non-white patients is associated with higher rates of comorbidities: Cardiovascular disease and diabetes are associated with increased risk of death from CRC; under-treatment was associated with comorbidity profiles and may be a driver of worse CRC survival in these patients
	Treatment and care	• Several studies have found that African Americans are less likely than non-Hispanic whites to receive standard treatment and potentially curative treatment, such as surgery
	Direct healthcare costs	• Despite being less likely to receive treatment, non-Hispanic Blacks have been found to have higher CRC-attributable costs within different phases of care, particularly in the terminal phase of care • One study on CRC patients aged 18–64 years from 2004 to 2012 noted that insurance status and tumor characteristics accounted for 54 percent and 27 percent of excess deaths among African American patients respectively, suggesting that differences in care may contribute to differences in survival among young CRC patients
	Indirect healthcare costs	• The young-onset but late-stage diagnosis of CRC among non-white patients can disrupt early family and career goals. It can also require disproportionate informal caregiver support. This can have knock-on impacts on the lives of informal caregivers, as evidenced by a study that found that informal African American caregivers report more difficulty negotiating time away from work to fulfill caregiving responsibilities compared to white caregivers
	Mortality	• The mortality rate of African Americans is 35 percent higher than that of whites despite advances in treatment, improvements in the standard of care, and increased screening options. Advanced stage of disease at the time of diagnosis is a major contributing factor to the racial disparity in survival

Note: Please see Appendix for sources

[57] Jackson, C. S., Oman, M., Patel, A. M. & Vega, K. J. (2016). Health disparities in colorectal cancer among racial and ethnic minorities in the United States. *Journal of Gastrointestinal Oncology*, 7(Suppl 1), S32–S43, https://doi.org/10.3978/j.issn.2078-6891.2015.039.

[58] Jackson, C. S., Oman, M., Patel, A. M. & Vega, K. J. (2016). Health disparities in colorectal cancer among racial and ethnic minorities in the United States. *J Gastrointest Oncol*, 7(Suppl 1):S32-S43, doi: 10.3978/j.issn.2078-6891.2015.039.

[59] Fazil, Q. (2018) Cancer and black and minority. ethnic communities. *Race Equality Foundation.* http://raceequalityfoundation.org.uk/wp-content/uploads/2018/07/REF-Better-Health-471-1.pdf

Measuring the cost-effectiveness of CRC treatments: Examples from HTA agencies in Australia, Canada, and England

We reviewed NICE and PBAC assessments of bevacizumab and NICE, PBAC and CADTH assessments of cetuximab for the treatment of metastatic CRC.[60,61,62,63] Assessments were published by the HTA agencies between 2007 and 2013. The relevant outcomes typically reviewed were overall survival, progression-free survival, response rate, adverse reactions to treatment, and health-related quality of life.[64] Table 4 summarizes the typical approach to CEA of CRC innovation.

Table 4: Summary approach to CRC innovation cost-effectiveness assessment: Examples from Australia, Canada, and England

	Approach to cost-effectiveness assessment
Outcomes evidence collection and synthesis	• Evidence is drawn from data submitted by the manufacturer during Phase III clinical trial • HTA agencies capture the patient voice through inclusion of evidence submitted by patient experts. For example, patient groups noted that "very small increases in life expectancy [are beneficial] because this extra time allows them to put their affairs in order and help family and friends" • Notably, in England, the cost of CRC medicines can be reimbursed through the Cancer Drugs Fund, which provides access to medicines with the potential to be cost-effective with more data. Real-world evidence or longer-term overall survival data from an ongoing randomized clinical trials can be taken into account
Measurement of health benefits	• Health-related quality of life is generally estimated by applying different average utilities to pre-progression and post-progression disease states • Average utility values are estimated through a health utility index (such as EQ-5D) based on a questionnaire administered during the clinical trial and reference patients' lifetime. Notably, the response rate to these questionnaires can be low, with NICE highlighting that in one assessment for a CRC treatment, only 37 full responses (out of 42 patients who filled out the survey) were provided
Measurement of costs	• PBAC and NICE appear to consider the treatment administration costs to the health system, but there is no reference to capturing any further indirect costs that accrue to the patient. By contract, Canada's CADTH appears to factor in caregiver burden and travel costs. These were incorporated through patient advocacy group input into the HTA process. Notably, CADTH considers costs of treating adverse events and follow-up visit costs, in contrast to NICE

Note: Please see Appendix for sources

60 NICE (2007). Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer, Technology Appraisal guidance, https://www.nice.org.uk/guidance/ta118/chapter/4-Evidence-and-interpretation#cost-effectiveness.

61 PBS (2010) CETUXIMAB, solution for I.V. infusion, 100 mg in 20 mL and 500 mg in 100 mL, Erbitux® Public Summary Document, https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2010-07/pbac-psd-Cetuximab-july10.

62 PBS (2010). Bevacizumab, solution for intravenous infusion, 100 mg in 4 mL and 400 mg in 16 mL, Avastin® Public Summary Document, https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2010-11/Bevacizumab_AVASTIN_Roche_PSD_2010-11_6-2_FINAL.pdf.

63 pCODR (2013). Final Recommendation for Cetuximab (Erbitux) for Metastatic Colorectal Cancer, https://www.cadth.ca/sites/default/files/pcodr/pcodr-erbitux-mcrc-fn-rec.pdf.

64 NICE (2007). Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer, Technology Appraisal guidance, https://www.nice.org.uk/guidance/ta118/chapter/4-Evidence-and-interpretation#cost-effectiveness.

Implications of using a QALY-based approach to assess the value of CRC medicines

Outcomes evidence collection and synthesis

The evidence used in the estimation of the QALY metric was collected during Phase III clinical trials. This can create an issue for different patient groups, as any racial underrepresentation in CRC trials can affect the ultimate assessment of the value of medicine.[65] The findings described above demonstrate the fact that non-white patients are typically diagnosed with a more advanced stage of CRC compared to white patients and typically accrue higher health costs. However, *evidence from the FDA suggests that 73 percent of all cancer trial participants were* white, 14 percent were Asian, 5 percent were Black or African American and 6 percent were Hispanic.[66] This is despite the fact that the racial distribution in the general US population is roughly 60 percent non-Hispanic white, 19 percent Hispanic or Latino, 13 percent Black or African American and 6 percent Asian.[67] Although evidence assessing the racial representativeness of CRC patients specifically in clinical trials is limited, one study has shown that Black, Hispanic, and Asian/Pacific Islanders were less likely than white patients to enroll in colorectal cancer trials.[68] There is no evidence that skewed race data is adjusted for in CEA.

Inclusion and exclusion criteria can inadvertently lead to a nonrepresentative sample. For example, inclusion criteria for one CRC treatment included “life expectancy of >3 months.” Exclusion criteria included use of anticoagulants, chronic treatment with aspirin, significant impairment of renal function, and other factors that disproportionately exclude minority populations, who tend to have higher rates of high blood pressure, diabetes, obesity and heart disease, and higher risk of kidney disease.[69,70] As a result, non-white patients who have a greater likelihood of underlying health conditions or advanced stages of disease are more likely to be excluded from clinical research and therefore consideration in value assessment.

We find evidence that non-white patients are more likely to be diagnosed at an advanced stage of CRC and that time of diagnosis is a major contributing factor to the racial disparity in survival. However, in England, the population of the Phase III trial for one CRC treatment was noted by NICE to be relatively younger than the UK NHS population of CRC patients.[71]

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65 National Minority Quality Forum, Traditional Value Assessment Methods Fail Communities of Color and Exacerbate Health Inequities, https://static1.squarespace.com/static/5be307ae5b409bfaa68b1724/t/5f58fbb6eaffbe1bb7c24416/1599667126706/Disparities+and+Value+Assesssment+White+Paper.pdf.

66 FDA 2020 Drug Trials Snapshots Summary Report, https://www.fda.gov/media/145718/download**.** The percentage of non-Hispanic and Unknown/Unreported ethnicity makes up 100 percent of the ethnicity category.

67 US Census Bureau, Population Estimates, July 1, 2019, https://www.census.gov/quickfacts/fact/table/US/PST045219.

68 Murthy, V. H., Krumholz, H. M. & Gross, C. P. (2004). Participation in cancer clinical trials: Race-, sex-, and age-based Disparities. *JAMA*, 291(22):2720–2726, doi:10.1001/jama.291.22.2720.

69 A Study to Evaluate Avastin in Combination with Standard Chemotherapy to Treat Colorectal Cancer, https://clinicaltrials.gov/ct2/show/NCT00109070.

70 National Kidney Foundation, Race, Ethnicity, & Kidney Disease, https://www.kidney.org/atoz/content/minorities-KD.

71 NICE, Final appraisal determination: Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer, https://www.nice.org.uk/guidance/ta212/documents/colorectal-cancer-metastatic-bevacizumab-final-appraisal-determination3.

Overrepresentation of younger patients may skew the valuation of CRC innovation. Additionally, if the intervention extends the life of the patient for more years but with significant health care costs and/or progressive disease, this may cause the treatment to be perceived as less effective.

There are many reasons for seeking homogeneity in clinical trials, such as isolating the medicines' benefit. However, the result is a lower likelihood of identifying effects that may disproportionately affect racial and ethnic communities and a more limited understanding of the efficacy of treatments. This is likely to exacerbate the inequitable distribution of benefits and risks from new medicines.[72] While real-world studies may mitigate this problem, identifying effects that may disproportionately affect racial and ethnic communities in Phase IV trials for CRC is dependent on equitable racial representation in real-world evidence studies and the collection of race information, both of which are currently limited.

Measurement of health benefits

The QALY metric generalizes patient population preferences. However, there is significant evidence of the differences between racial and ethnic groups in cancer patients' HRQoL.[73,74] Specifically, we find evidence of significant disparities in diagnosis, care, and survival among non-white CRC patients. These differences feed into patients' assessment of their HRQoL, which may result in a skewed QALY assessment, which could either *undervalue* or *overvalue* new CRC medicines. For example:

- Non-white CRC patients are typically diagnosed at an earlier age relative to white patients. As described in Box 1, the QALY calculation attributes greater value to treatments for populations with more life years left. Therefore, more representative inclusion of non-white CRC patients could lead to a higher valuation of new medicines.
- Poor HRQoL has been found to be associated with worse survival rates among Black and Hispanic CRC patients.[75] Greater consideration of non-white CRC patients in CEA may lead to a lower valuation of new medicines, given the increased inclusion of patients with lower likelihood of post-progression survival.

Measurement of costs

We find evidence that direct and indirect health costs of disease are higher among non-white patients than white patients. [76] This means if average costs are taken into account, this will under-estimate the value to non-white communities. In practice, HTA agencies do not

[72] Ford, J. G. et al. (2007). Barriers to recruiting underrepresented populations to cancer clinical trials: A systematic review. *Cancer,* 112(2), p.228–242, https://doi.org/10.1002/cncr.23157.

[73] Rao, D., Debb, S., Blitz, D., Choi, S. W. & Cella, D. (2008). Racial/ethnic differences in the health-related quality of life of cancer patients. *Journal of Pain and Symptom Management*, 36(5), 488–496, https://doi.org/10.1016/j.jpainsymman.2007.11.012.

[74] Janz, N. K., Mujahid, M. S., Hawley, S. T., Griggs, J. J., Alderman, A., Hamilton, A. S., Graff, J. & Katz, S. J. (2009). Racial/ethnic differences in quality of life after diagnosis of breast cancer. *Journal of Cancer Survivorship*: Research and Practice, 3(4), 212–222. https://doi.org/10.1007/s11764-009-0097-y.

[75] University of Texas M. D. Anderson Cancer Center. (2017, March 27). Minority colorectal cancer patients report higher burden of poor quality-of-life than whites. *ScienceDaily*, www.sciencedaily.com/releases/2017/03/170327143651.htm.

[76] Tramontano, A. C., Chen, Y., Watson, T. R., Eckel, A., Hur, C., Kong, C. Y. (2020). Racial/ethnic disparities in colorectal cancer treatment utilization and phase-specific costs, 2000–2014. *PLoS ONE* 15(4): e0231599, https://doi.org/10.1371/journal.pone.0231599.

systematically incorporate indirect healthcare costs, such as travel costs and opportunity costs to family members and informal caregivers (e.g., from missing work), this is even more problematic for non-white communities. Specifically, a failure to systematically capture indirect health costs, such as the cost of informal caregiving, may undervalue the benefit of the innovation for communities that accrue higher indirect health costs. On the other hand, if the new medicine can significantly reduce or avert overall medical costs, more equitable consideration of non-white patients in CEA may positively improve the QALY metric.

Case study: Alzheimer's disease treatment

Background on Alzheimer's disease

Nearly twice as many Black Americans as non-Hispanic whites have AD (19 percent vs. 10 percent).[77] The incidence of dementia in American Indian/Alaska Native was 22.2 per 1,000 people; in white patients, 19.3 per 1,000.[78] Hispanics also have a higher prevalence of AD compared with whites (14 percent vs. 10 percent), although variation among Hispanic subgroups is likely. Asian Americans have the lowest incidence and prevalence of AD, though heterogeneity may exist within specific Asian American subgroups.

Studies that account for health and socioeconomic factors find smaller racial and ethnic differences in dementia compared to studies that do not control for social determinants of health. This suggests that the large difference in risk of AD between Black and Latinx populations compared to white populations could be explained by disparities in health-related behaviors and socioeconomic risk factors.[79] Social and environmental disparities, including lower levels of quality of education, higher rates of poverty, and greater exposure to adversity and discrimination, increase rates of chronic conditions and risk for dementia in Black and Latinx populations. There is evidence that genetic risk factors may differ by race, but these are not considered significant enough to account for the large differences in prevalence and incidence between racial groups. Table 5 summarizes the health disparities experienced by specific groups of AD patients in the US. We find evidence that similar disparities in health outcomes are also experienced by AD patients in international markets.[80]

[77] Alzheimer's Association 2021. Alzheimer's Disease Facts and Figures, https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf.

[78] Mayeda, E.R. et al. (2016). Inequalities in dementia incidence between six racial and ethnic groups over 14 years, *Alzheimer's Association*, 12(3), pp.216–224, https://doi.org/10.1016/j.jalz.2015.12.007.

[79] Chin, A. L., Negash, S. & Hamilton, R. (2011). Diversity and disparity in dementia: The impact of ethnoracial differences in Alzheimer disease. *Alzheimer Disease and Associated Disorders*, 25(3), 187–195, https://doi.org/10.1097/WAD.0b013e318211c6c9.

[80] Pham, T. M., Petersen, I., Walters, K., Raine, R., Manthorpe, J., Mukadam, N., & Cooper, C. (2018). Trends in dementia diagnosis rates in UK ethnic groups: analysis of UK primary care data. *Clinical epidemiology*, 10, 949–960. https://doi.org/10.2147/CLEP.S152647

Table 5: Summary of health disparities in AD among racial and ethnic groups

		Evidence of outcomes
Burden of disease	**Diagnosis**	• 14 percent of adults with AD are likely to be African American, compared with 12 percent Hispanics and 10 percent non-Hispanic whites. While African Americans are almost two times more likely than whites to have Alzheimer's and other dementias, they are only 34 percent more likely to have a diagnosis. Hispanics are only 18 percent more likely to be diagnosed, suggesting that non-white patients are often unaware that they have the disease • Associated with higher dementia risk are chronic health conditions such as cardiovascular disease and diabetes, which are more prevalent among non-white patients compared to white patients. Native Americans are more likely to present with depression, diabetes, hypertension, and heart disease than whites • African Americans and Hispanics are typically diagnosed in the later stages of the disease
	Survival	• Evidence suggests that African Americans are more likely to present with an earlier age of onset and exhibit greater severity of symptoms at the time of presentation
	Treatment and care	• African Americans are less likely than non-Hispanic whites to receive innovative Alzheimer's treatments, such as acetylcholinesterase inhibitors or memantine • One study has found that ethnic minority Medicare beneficiaries are 30 percent less likely to receive dementia treatment than non-Hispanic whites
	Direct healthcare costs	• In 2014, average per-person Medicare payments for African Americans with Alzheimer's and other dementias were 35 percent higher than those for whites with Alzheimer's and other dementias. Medicare payments for Hispanics with Alzheimer's and other dementias were 7 percent higher than those for their white counterparts. This is linked to their later stage of diagnosis • Studies demonstrate that non-white AD patients experience significant and disproportionate direct and indirect healthcare costs. For example, one study suggests that while African Americans make up only 14 percent of the US population, they bear a third of the costs of AD and other dementias. Families in non-white communities can expect between $41,000 and $56,000 annually in dementia-related costs, which exceeds the median household income for Latinx and African American communities ($40,785 and $39,715, respectively)
	Indirect healthcare costs	• Caregiving represents a significant proportion of the economic costs of AD, making up more than 60 percent of AD costs for African Americans. Similarly, Latinx family caregivers tend to be in more intensive caregiving situations, with 63 percent in high-burden situations compared to 51 percent of non-Latinx caregivers • Generally, elders from racial and ethnic communities are more likely to receive care from family and friends and less likely to rely on formal care compared with non-Hispanic whites. As a result of this and other factors such as insurance status, poverty level, and level of impairment, minorities were 40 percent less likely to enter a long-term facility than whites in the US, potentially placing even greater burden on non-white caregivers
	Mortality	• Evidence points to longer survival among racial and ethnic subpopulations compared with white patients

Note: Please see Appendix for sources

Measuring the cost-effectiveness of AD treatments: Examples from HTA agencies in Australia, Canada, and England

We reviewed PBAC, CADTH, and NICE assessments of donepezil, galantamine, rivastigmine and memantine for the treatment of AD.[81,82,83,84] Assessments were published by the HTA agencies between 2001 and 2012.[85] When assessing AD drugs, HTA agencies typically rely on evidence from randomized control trials that measure outcomes using clinical scales for cognition and functioning.[86] For example, *c*ognitive, functional, and clinical endpoints are typically used in clinical investigation of AD medicines in England, Australia, and Canada. Table 6 summarizes the typical approach to CEA of AD innovation.

Table 6: Summary approach to AD innovation cost-effectiveness assessment: Examples from Australia, Canada, and England

	Approach to cost-effectiveness assessment
Outcomes evidence collection and synthesis	• Cognitive endpoints include neuropsychological states identified through a questionnaire-based test (such as the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). Global effects include a broad measure of patient function rating patient's clinical and behavior metrics Functional endpoints are typically caregiver-based scores that assess ability to perform day-to-day activities (for example, measured by the Activities of Daily Living scale (ADL)). Behavioral and mood endpoints assess functions such as delusions, hallucinations, agitation/aggression, and anxiety
Measurement of health benefits	• Health-related quality of life is assessed through the EQ-5D measure and evaluates mobility, self-care, mood, daily activities, and pain. Surveys are completed during AD Phase III trials. In England, NICE accepts health-related quality of life as reported by patients and by carers as proxy responses • In England, no other economic benefits (e.g. cost offsets to hospital care) have typically been assessed for AD treatments. By contrast, in Australia and Canada, time delay to patients entering long-term care facilities and the potential impact on patient health care expenditures are considered for AD treatment
Measurement of costs	• In England, NHS and personal social services costs are typically included in the HTA assessment, along with costs to the individual and their family. The impact on carers of the patient entering long-term care facilities was not covered. NICE does consider informal caregiver utility. However, variation in informal caregiver utility according to the severity of AD patients appears to be estimated • In Canada, non-healthcare resources, such as patient's time (treatment time and loss of productivity), caregiver time, and out-of-pocket costs (including travel expenses, childcare, etc.) are not systematically incorporated and must be reported separately

Note: Please see Appendix for sources

81 Dekker M. J. H. J., Bouvy, J. C., O'Rourke, D., Thompson, R., Makady, A., Jonsson, P. & Gispen-de Wied, C. C. (2019). Alignment of European regulatory and health technology assessments: A review of licensed products for Alzheimer's disease. *Front. Med.* 6:73, doi: 10.3389/fmed.2019.00073.

82 NICE, Technology appraisal guidance: Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease, https://www.nice.org.uk/guidance/ta217.

83 Canadian Coordinating Office for Health Technology Assessment, Drug Treatments for Alzheimer's Disease: Efficacy, Outcome Measurements and Cost-Effectiveness, https://www.cadth.ca/sites/default/files/pdf/217_alzheimers_ov_e.pdf.

84 Report to the PBAC - Review of Pharmaceutical Benefits Scheme anti-dementia drugs to treat Alzheimer's Disease, https://www.pbs.gov.au/info/reviews/anti-dementia-report.

85 International agencies' assessments of aducanumab had not yet been published at the time of this study.

86 Bauer, A., Wittenberg, R., Ly, A., Gustavssond, A., Bexelius, C., Tochel, C., Knapp, M., Nelson, M. & Sudlow, C. L. M. (2020). Valuing Alzheimer's disease drugs: A health technology assessment perspective on outcomes. *International Journal of Technology Assessment in Health Care*, 1–7, https://doi.org/10.1017/S0266462320000574.

Implications of using a QALY-based approach to assess the value of AD innovation

Outcomes evidence collection and synthesis

A QALY-based approach is reliant on evidence informed by the clinical trial population. However, the current demographic makeup of AD clinical trials does not represent the true demographic nature of the disease because it fails to reflect the greater prevalence of AD among Black, Hispanic, and Native American patients compared to white patients. Specifically, while white people make up 60 percent of the US population, on average they account for 77 percent of NIH-funded AD research participants. Black patients make up 14 percent of AD trial participants and Hispanics represent 5 percent of trial participants.[87] As with other minorities, indigenous populations in the US are also poorly represented in clinical trials.[88] The race breakdowns of new AD medicine trials indicate similar disproportionate consideration of patients and we do not see any adjustment for skewed race data in CEA approaches. For example, in the Phase III trial for aducanumab, Asian patients (the only indicator of a non-white patient specified) represented roughly 10 percent of the trial population.[89]

Limited diversity of participants in AD trials has been linked to barriers to trial recruitment strategies as well as screening and eligibility criteria.[90] Overall, representation of racial and ethnic groups in AD clinical trials indicates that outcomes associated with non-white AD patients (linked to earlier age of onset, greater severity and higher healthcare costs) are given too little weight by the QALY measure.

In addition, health outcomes data that are informed by categorical scores and based on clinical and cognitive tests are subject to variation by patient background and context. Furthermore, insofar as the standardized tests are not reflective of cultural or linguistic differences, their outcomes may be biased as well.[91]

Measurement of health benefits

Given evidence of AD patients' HRQoL to inform the QALY metric is collected during clinical trials, the value assessment of new AD medicines using a QALY metric could be skewed (both upward and downward) if population groups with a higher burden of the disease are equitably assessed:

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87 *UsAgainstAlzheimer's* (2020). A Vision for Equity in Alzheimer's Research in 2020, https://www.usagainstalzheimers.org/blog/vision-equity-alzheimers-research-2020.

88 Olson, N. L. & Albensi, B.C. (2020). Race- and sex-based disparities in Alzheimer's disease clinical trial enrollment in the United States and Canada: An Indigenous perspective, *Journal of Alzheimer's Disease Reports,* 4(1) pp. 325–344.

89 Biogen Investors Report, EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients with Early Alzheimer's Disease, https://investors.biogen.com/static-files/8e58afa4-ba37-4250-9a78-2ecfb63b1dcb.

90 Raman, R., Quiroz, Y. T., Langford, O. et al. (2021). Disparities by race and ethnicity among adults recruited for a preclinical Alzheimer disease Trial. *JAMA Netw Open,* 4(7) e2114364, doi:10.1001/jamanetworkopen.2021.14364.

91 Ramírez, M., Ford, M. E., Stewart, A. L., & Teresi, J. A. (2005). Measurement issues in health disparities research. *Health services research*, 40(5 Pt 2), 1640–1657. https://doi.org/10.1111/j.1475-6773.2005.00450.x

- The evidence highlighted above demonstrates that non-white patients are typically diagnosed with a more advanced stage of AD compared to white patients. Equitable representation of non-white patients' perceptions of health benefits could improve the value assessment of AD innovation and *increase* the estimate of cost-effectiveness of new AD treatment, since patients with a higher burden of disease may assign a higher value to new innovative medicines.[92]
- At the same time, equitable consideration of non-white patients in CEA could also decrease the value assessment of new AD medicines. Based on the evidence described above, chronic disease comorbidities and the socioeconomic factors that could diminish the quality of a patient's physical environment and access to care disproportionately affect non-white patients. This could feed into patients' perception of HRQoL and thus the QALY metric. Specifically, comorbidities, including hypertension, diabetes, and depression, among patients with AD are negatively associated with HRQoL.[93,94] The value of a new AD medicine may be *underestimated* if many reporting patients suffer from comorbidities.

Measurement of costs

Caring for a person at home with AD puts more of the burden of care on the family.[95] We find evidence of non-white racial groups with AD relying more heavily on informal caregivers than white AD patients do. Relative to non-white families, white families are more likely to use a long-term care facility for an elderly relative with AD, which could shift the cost of care outside the family to Medicaid or long-term care insurance. In line with previous studies, we also find that HTA agencies fail to consistently incorporate indirect healthcare costs and the costs to family members and informal caregivers when considering AD innovation.[96] However, failure to consider the differences in cost burden across racial groups may undervalue the benefit of medicine that has the potential to alleviate the cost burden of disease.

Conclusions and recommendations

The use of CEA is increasing in prevalence in the US as a method for payers and budget decision-makers to prioritize access to medicines. Given the growing debate on prescription drug prices in the US, there may be further integration of CEA methods into access decisions. In other countries, HTA agencies measure the cost-effectiveness of new medicines and often

92 McPhail S. M. (2016). Multimorbidity in chronic disease: impact on health care resources and costs. *Risk management and healthcare policy*, 9, 143–156, https://doi.org/10.2147/RMHP.S97248.

93 Nelis, S. M., Wu, Y. T., Matthews, F. E., Martyr, A., Quinn, C., Rippon, I., Rusted, J., Thom, J. M., Kopelman, M. D., Hindle, J. V., Jones, R. W. & Clare, L. (2019). The impact of co-morbidity on the quality of life of people with dementia: Findings from the IDEAL study. *Age Ageing*, 48(3):361-367, doi: 10.1093/ageing/afy155.

94 Barbe, C., Jolly, D., Morrone, I., Wolak-Thierry, A., Dramé, M., Novella, J. L. & Mahmoudi, R. (2018). Factors associated with quality of life in patients with Alzheimer's disease. *BMC Geriatrics*, 18(1), 159, https://doi.org/10.1186/s12877-018-0855-7.

95 Pyenson, B. et al. (2021). Assessing the Value of Therapies in Alzheimer's Disease, *Millman*, https://www.agingresearch.org/app/uploads/2021/05/Assessing-the-Value-of-Therapies-in-Alzheimer percentE2 percent80 percent99s-Disease_FINAL.pdf.

96 Bauer, A., Wittenberg, R., Ly, A., Gustavssond, A., Bexelius, C., Tochel, C., Knapp, M., Nelson, M. & Sudlow, C. L. M. (2020). Valuing Alzheimer's disease drugs: A health technology assessment perspective on outcomes. *International Journal of Technology Assessment in Health Care*, 1–7, https://doi.org/10.1017/S0266462320000574.

rely on the QALY as a metric of value. This is despite the significant documentation by academics and healthcare professionals that points to the limitations of this approach.[97,98,99]

Our study further highlights the potential role that the use of the QALY in the value assessment of new medicines may have in affecting access and health inequities in the US. Specifically, we find the following:

1) QALY-based CEA fails to consistently consider differences in patient experience of the disease, including those resulting from access disparities, structural racism, and social determinants of health

Our case studies highlight that the health utility measures that feed into the QALY metric are typically derived from evidence which over-represents white populations relative to incidence of the disease. We find that although major HTA agencies such as NICE, PBAC, and CADTH aim to consider health equity in principle (see Table 2), in practice, consideration of disparities is limited and typically only noted as a contextual consideration. This is the case for diseases where there is evidence of a clear difference across racial groups.

We further find that CEA often fails to consistently consider the full range of important nonclinical benefits. The benefits of medicines with respect to their impact on patients' health-related quality of life, labor market productivity and ability to provide caregiving are rarely taken into account (or if they are, they are not given sufficient weight). Given the differences in certain patients' experience of disease, including those resulting from access disparities,, differences in culture, and social determinants of health, this exacerbates disparities between white and non-white populations.[100] Furthermore, our case study assessment highlights that the age of disease onset can be earlier but the disease is diagnosed at a more severe stage in certain racial and ethnic groups (due to disparities in access to healthcare), so while the benefit of treatment is greater for those communities in comparison to the majority white population, traditional value assessment (i.e., QALYs) calculates the therapeutic as more expensive to society. As a result, the QALY and similar metrics are biased against those who likely already experience discrimination in US society.

ICER's approach to health equity is similarly limited: The organization states that "when judged feasible" ICER may explore the impact of new medicines on "disparities in life expectancies across different populations through scenario analyses methods."[101] But in its review of aducanumab, ICER concluded that the "impact [of the medicine] on health inequities is unclear" since certain populations "were not well represented in the clinical trials of

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97 Pettitt, D. A., Raza, S., Naughton, B., Roscoe, A., Ramakrishnan, A., Ali, A., Davies, B., Dopson, S., Hollander, G., Smith, J. A. & Brindley, D. A. (2016). The limitations of QALY: A literature review. *Journal of Stem Cell Research and Therapy*, 6(4), Article: 1000334.

98 Caro, J. J., Brazier, J. E., Karnon, J. et al. (2019). Determining Value in Health Technology Assessment: Stay the Course or Tack Away?, *PharmacoEconomics*, 37, 293–299, https://doi.org/10.1007/s40273-018-0742-2.

99 Whitehead, S. J. & Ali, S. (2010). Health outcomes in economic evaluation: The QALY and utilities, *British Medical Bulletin,* 96: 5–21, DOI:10.1093/bmb/ldq033.

100 Friedman, E. M., Shih, R. A., Langa, K. M. & Hurd, M. D. (2015). US prevalence and predictors of informal caregiving for dementia. *Health Affairs (Project Hope),* 34(10), 1637–1641, https://doi.org/10.1377/hlthaff.2015.0510.

101 ICER (2020). 2020-2023 Value Assessment Framework, https://icer.org/wp-content/uploads/2020/10/ICER_2020_2023_VAF_102220.pdf.

aducanumab and thus whether the drug has a differential impact in minority populations is not known." In other words, the under-representativeness of different racial groups in the clinical trials, means these differences are not taken into account.

2) The QALY averages value across populations, so underestimation of the true value of new medicines to certain population groups is inherent in resulting analyses

Our case study analysis highlights that different groups of patients, such as those from minority racial groups and underserved communities, have different experiences of disease states. Their experiences are exacerbated by the social determinants of health and disparities in access to care that are related to underlying structural racism. QALY-based cost-effectiveness approaches assess value based on average patient responses to a medicine, whereas health disparities and inequities can lead to certain racial groups having very different experiences and responses to the medicine. The implication of this is that the true value of new medicine to specific groups in society is not captured through QALY-based value assessment, which reinforces health inequities in coverage and access decisions.

Further, because HTA agencies that use the QALY measure estimate the average value of a treatment for a population, they consistently fail to consider the differential impact of a treatment on specific racial and ethnic groups' perceptions of symptom and life expectancy improvement. We consider this issue in particular because there remain significant differences in income level, labor market participation, access to health coverage and other social determinants of health that affect a patient's experience of disease. Determining the average value across a population may be accepted in a single-payer health system, but it is more problematic in the US's decentralized, pluralistic health system, where distinct payers establish formularies based on the specific needs of their patient populations.

3) Methods for calculating QALY are biased against racial groups (even if QALY is used only for specific groups)

Our findings indicate that even if the QALY approach were applied to specific racial groups, the existence of health disparities would mean that the true value of a new medicine would not be captured. Specifically:

- The QALY metric in current cost-effectiveness calculations is too restrictive in its measure of utility. For example, utility measures that feed into the QALY calculation enforce the measure of quality of life by consistent intervals or grades.[102] But quality of life is inherently personal and numerical grades cannot effectively reflect how patients from different backgrounds view these conditions. Distinguishing nuances in elements of value to patients and caregivers is difficult in relation to chronic conditions such as Alzheimer's disease. It is even more difficult to reconcile in population groups that have different experiences of the disease, which may be in part related to different socioeconomic conditions.[103]

[102] QALYs Are Not Valid for Health Decision-Making – Results from the European ECHOUTCOME Project. Data Mining International Blog (2013), http://www.datamining-international.com/qalys-are-not-valid-for-health-decision-making-results-from-the-european-echoutcome-project/.

[103] Pyenson, B. et al. (2021). Assessing the Value of Therapies in Alzheimer's Disease, *Millman*, https://www.agingresearch.org/app/uploads/2021/05/Assessing-the-Value-of-Therapies-in-Alzheimer percentE2 percent80 percent99s-Disease_FINAL.pdf.

- Life years and quality of life are linked. For example, the QALY -based approach assumes that the negative value of having CRC for two years is twice that of having CRC for one year. This difference in value can have significant implications among AD patients who are diagnosed earlier in life but at a later stage of disease progression, such as Black patients with Alzheimer's. The QALY also fails to incorporate changes in preference or perception as individuals adjust to life with a disease.

ICER itself has admitted that its QALY-based model "cannot capture the full psychosocial impact of systemic issues such as racism that may impact underserved populations" and that US decision-makers should consider providing a "special weighting to other benefits and to contextual considerations that would lead to coverage and funding decisions at higher prices and thus higher cost-effectiveness ratios." However, there is little evidence of this being applied in practice.

4) The use of the QALY in value assessment reinforces racism in the health system

Use of the QALY will inherently prioritize diseases with patients who can be treated at the lowest cost. First, the QALY is an imperfect measure of value, which suggests that access decisions do not reflect the true patient population and will thus be inconsistent with true need.[104] At a deeper level, our study highlights that the QALY reinforces racism in health systems since it fosters a systematic pattern of preference for certain population groups that are overrepresented in evidence collection and incorporates that bias the assessment of cost and benefits. In other words, given many of the reason for these differences is due to structural racism, it reinforces existing patterns of discrimination.

5) When QALY is used to grant access or set prices, it creates an incentive to study drugs on the populations which are advantaged by the CEA model

Evidence from our case studies highlight that clinical trial participants do not reflect the typical AD or CRC patient, who may have multiple underlying conditions and face other socioeconomic challenges. Multiple published studies have found that diverse groups are significantly underrepresented in clinical trial participants, so data commonly do not accurately reflect the diversity of the population that could benefit for the medicine. On average, trials enroll a significantly higher percentage of whites than is reflected in the population.[105] This inadvertently puts non-white patients at risk. When trials are not diverse, the result is a diminished *ability to identify effects that* may disproportionately affect minority communities and a limited understanding of the efficacy of treatments.[106] The number of people enrolled in clinical trials is established to show a clinically meaningful effect size; testing on more or fewer people than are needed to show the clinical effect would be unethical. If clinical trial data were used to determine prices in the US, there would be an incentive to design the trials to reflect the QALY approach. This may create an even stronger motive to exclude enrollees from racial

[104] Whitehead, S. J. & Ali, S. (2010). Health outcomes in economic evaluation: The QALY and utilities, *British Medical Bulletin,* 96: 5–21 DOI:10.1093/bmb/ldq033.

[105] Nazha B., Mishra M., Pentz R. & Owonikoko T. K., Enrollment of racial minorities in clinical trials: Old problem assumes new urgency in the age of immunotherapy. *Am Soc Clin Oncol Educ* Book. 2019 Jan; 39:3-10, doi: 10.1200/EDBK_100021. Epub 2019 May 17. PMID: 31099618.

[106] Clark et al. (2019). Increasing diversity in clinical trials: Overcoming critical barriers, *Current Problems in* Cardiology, Vol. 44, No. 5, pp. 148–172, https://www.sciencedirect.com/science/article/pii/S0146280618301889?via percent3Dihub.

groups for whom the QALY approach does not work.[107] This effect would run counter to the efforts of the US Food and Drug Administration (FDA), the National Institutes of Health (NIH) and the US Department of Health and Human Services (HHS), as well as state organizations, to diversify clinical trials, make them efficient and collect information about minority and lower-socioeconomic-status patients in drug development.[108]

Reliance on narrow measures of value in CEA approaches can exacerbate health access and outcomes disparities

Value assessment based on nonrepresentative clinical trials creates more bias in the results, leading to less-informed treatment choices and potentially worse outcomes. Furthermore, lack of diversity in clinical trials contributes to mistrust, which directly affects drug adherence, diagnosis and utilization, thus further exacerbating health disparities and outcomes.

Policy recommendations

Policy makers in the US have expressed a desire to address social and health inequities. This political support follows efforts in the healthcare space to raise awareness and address social determinants of health. Value assessment presents an opportunity to ensure that access and coverage decisions maximize value simultaneously with advancing health equity. However, as summarized above, our study finds that the use of QALY-based cost effectiveness analysis will fail to achieve the US's goals. Our conclusions suggest several policy solutions:

- To support the assessment of new medicines in diverse patient populations, the NIH should develop **nationally representative, integrated longitudinal datasets** that can be used to examine the value of medicine to different racial and ethnic groups.
- Any form of cost-effectiveness analysis should involve a **systematic consideration of the impact of new medicines by race and on health equity**. Congressional legislation could mandate the development of methods to better consider how new medicines could provide patient value and address health access and outcomes disparities. Organizations creating and implementing cost effectiveness approaches in the US, whether government backed or private, should commit to assessment approaches that balance the consideration of clinical value for diverse populations and the impact on reducing inequities. Organizations such as the Patient Centered Outcomes Research Institute (PCORI) and the Innovation and Value Initiative are already developing methodologies that move away from considering the average value of a medicine across diverse populations to factor in the impact of health disparities on specific population groups.
- An **alternative approach to traditional value assessment that incorporates health inequities** is needed. Approaches growing in popularity **include multi-criteria decision analysis and the distributional cost-effectiveness analysis method**. Further

[107] Cesana, B. M. & Antonelli, P. (2016). Sample size calculations in clinical research should also be based on ethical principles. *Trials* 17, 149, https://doi.org/10.1186/s13063-016-1277-5.

[108] US Food and Drug Administration Guidance, "Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry," November 2020, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial.

development of these metrics should focus on incorporating the range of outcomes important to distinct patient populations and include a focus on addressing health equity.

- To develop a more holistic and societal approach to value assessment, federal funding to develop diverse health economists in universities (e.g., through research grants) is needed. In addition, policy makers could establish standards and incentives to support the development and use of cross-functional research teams (social workers, economists, physicians) on state prescription drug affordability boards to conduct more nuanced assessments.

Appendix

Case study: Colorectal cancer treatment

Table 7: Summary of health disparities in CRC among racial and ethnic groups

Augustus, G. J., & Ellis, N. A. (2018). Colorectal Cancer Disparity in African Americans: Risk Factors and Carcinogenic Mechanisms. *The American journal of pathology*, *188*(2), 291–303. **https://doi.org/10.1016/j.ajpath.2017.07.023**

Zavala, V.A., Bracci, P.M., Carethers, J.M. *et al.* (2021) Cancer health disparities in racial/ethnic minorities in the United States. *Br J Cancer* **124,** 315–332 . **https://doi.org/10.1038/s41416-020-01038-6**

American Cancer Society (2020) Colorectal Cancer Rates Higher in African Americans, Rising in Younger People, **https://www.cancer.org/latest-news/colorectal-cancer-rates-higher-in-african-americans-rising-in-younger-people.html**

Jackson, C. S., Oman, M., Patel, A. M., & Vega, K. J. (2016). Health disparities in colorectal cancer among racial and ethnic minorities in the United States. *Journal of gastrointestinal oncology*, *7*(Suppl 1), S32–S43. **https://doi.org/10.3978/j.issn.2078-6891.2015.039**

DeSantis, C.E., Miller, K.D., Goding Sauer, A., Jemal, A. and Siegel, R.L. (2019), Cancer statistics for African Americans, 2019. *CA A Cancer J Clin*, 69: 211-233. **https://doi.org/10.3322/caac.21555**

Augustus, G. J., & Ellis, N. A. (2018). Colorectal Cancer Disparity in African Americans: Risk Factors and Carcinogenic Mechanisms. *The American journal of pathology*, *188*(2), 291–303. **https://doi.org/10.1016/j.ajpath.2017.07.023**

Alexander D.D., Waterbor J., Hughes T., Funkhouser E., Grizzle W., Manne U., (2007) African-American and Caucasian disparities in colorectal cancer mortality and survival by data source: an epidemiologic review. *Cancer Biomark*.;3(6):301-13. doi: 10.3233/cbm-2007-3604

White, A., Vernon, S.W., Franzini, L. and Du, X.L. (2010), Racial disparities in colorectal cancer survival. *Cancer,* 116: 4622-4631. **https://doi.org/10.1002/cncr.25395**

Cuthbert, C.A, Hemmelgarn, B.R and Cheung, W.Y. (2018) Effect of comorbidities on outcomes in colorectal cancer (CRC) survivors. *Journal of Clinical Oncology* 36:15_suppl, 10055-10055, **https://pubmed.ncbi.nlm.nih.gov/15983985/**

Tramontano A.C, Chen Y, Watson T.R, Eckel A., Hur C., Kong C.Y (2020) Racial/ethnic disparities in colorectal cancer treatment utilization and phase-specific costs, 2000-2014. *PLoS ONE* 15(4): e0231599. **https://doi.org/10.1371/journal.pone.0231599**

White A., Liu CC, Xia R, Burau K, Cormier J, Chan W, Du XL. (2008) Racial disparities and treatment trends in a large cohort of elderly African Americans and Caucasians with colorectal cancer, 1991 to 2002. *Cancer*.113(12):3400-9. doi: 10.1002/cncr.23924

Kim Lynn Newcomer, Ronit Yarden, Danielle Peterson, and Never Too Young Advisory Board (2020) Gaps in caregiving for young-onset colorectal cancer patients. *Journal of Clinical Oncology* 38:4_suppl, 82-82

Martin, M. Y., Sanders, S., Griffin, J. M., Oster, R. A., Ritchie, C., Phelan, S. M., Atienza, A. A., Kahn, K., & van Ryn, M. (2012). Racial variation in the cancer caregiving experience: a multisite study of colorectal and lung cancer caregivers. *Cancer nursing*, 35(4), 249–256. **https://doi.org/10.1097/NCC.0b013e3182330850**

Table 8: Summary approach to CRC innovation cost-effectiveness assessment: Examples from Australia, Canada, and England

Whyte S, Pandor A, Stevenson M. (2012) Bevacizumab for metastatic colorectal cancer: a NICE single technology appraisal. *Pharmacoeconomics* 30(12):1119-32. doi: 10.2165/11597210-000000000-00000.

NICE (2007). Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer, Technology Appraisal guidance. **https://www.nice.org.uk/guidance/ta118/chapter/4-Evidence-and-interpretation#cost-effectiveness**

Center to Reduce Cancer Health Disparities (CRCHD) (2018) Economic Costs of Cancer Health Disparities: Summary of Meeting Proceedings. **https://chdi.wisc.edu/wp-content/uploads/sites/620/2018/07/NCIeconomiccosts.pdf**

NICE (2010) Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer, Final appraisal determination. **https://www.nice.org.uk/guidance/ta212/documents/colorectal-cancer-metastatic-bevacizumab-final-appraisal-determination3**

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Morrell, L., Wordsworth, S., Schuh, A., Middleton, M. R., Rees, S., & Barker, R. W. (2018). Will the reformed Cancer Drugs Fund address the most common types of uncertainty? An analysis of NICE cancer drug appraisals. *BMC health services research*, 18(1), 393. **https://doi.org/10.1186/s12913-018-3162-2**

Cancer Drugs Fund requires further reform, BMJ 2016; 354 doi: **https://doi.org/10.1136/bmj.i5090**

pan-Canadian Oncology Drug Review (2014) Final Economic Guidance Report, Cetuximab (Erbitux) for Metastatic Colorectal Cancer. **https://www.cadth.ca/sites/default/files/pcodr/pcodr-erbitux-mcrc-fn-egr.pdf**

pan-Canadian Oncology Drug Review (2015) Initial Recommendation for Bevacizumab (Avastin) with Capecitabine for Metastatic Colorectal Cancer. **https://www.cadth.ca/sites/default/files/pcodr/pcodr_avastin_capecitabine_mcrc_in_rec.pdf**

NICE (2010) Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer, Final appraisal determination. **https://www.nice.org.uk/guidance/ta212/documents/colorectal-cancer-metastatic-bevacizumab-final-appraisal-determination3**

Case study: Alzheimer's disease treatment

Table 9: Summary of health disparities in AD among racial and ethnic groups

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Alzheimer's Association, Alzheimer's Impact Movement (2020) Race, Ethnicity, and Alzheimer's Fact Sheet **https://www.alz.org/aaic/downloads2020/2020_Race_and_Ethnicity_Fact_Sheet.pdf**

Alzheimer's Association (2021) Alzheimer's Disease Facts and Figures. *Alzheimers Dement*; 17(3) **https://www.alz.org/media/Documents/alzheimers-facts-and-figures-special-report.pdf**

Weiner M.F, Rosenberg R.N, Svetlik D., Hynan L.S, Womack K.B, White C 3rd, Good S., Fuller C., Wharton D., Richter R.. (2003) Comparison of Alzheimer's disease in Native Americans and Whites. *Int Psychogeriatr*. 15(4):367-75. doi: 10.1017/s104161020300961x.

Barnes, L. L., & Bennett, D. A. (2014). Alzheimer's disease in African Americans: risk factors and challenges for the future. *Health affairs (Project Hope)*, *33*(4), 580–586. **https://doi.org/10.1377/hlthaff.2013.1353**

Zuckerman, I. H., Ryder, P. T., Simoni-Wastila, L., Shaffer, T., Sato, M., Zhao, L., & Stuart, B. (2008). Racial and ethnic disparities in the treatment of dementia among Medicare beneficiaries. *The journals of gerontology. Series B, Psychological sciences and social sciences*, *63*(5), S328–S333. **https://doi.org/10.1093/geronb/63.5.s328**

Gaskin, D.J. et al. (2018) The Costs of Alzheimer's and Other Dementia for African Americans, *US Against Alzheimer's*. **https://www.usagainstalzheimers.org/sites/default/files/2018-02/USA2_AAN_Costs_Report.pdf**

Wu, S. et al. (2018) Latinos & Alzheimer's Disease: New Numbers Behind the Crisis. *US Against Alzheimer's*. **https://www.usagainstalzheimers.org/sites/default/files/2018-02/Latinos-and-AD_USC_UsA2-Impact-Report.pdf**

US Against Alzheimer's, Health Disparities, Race, and Alzheimer's **https://www.usagainstalzheimers.org/learn/disparities**

Kirby, J. B., & Lau, D. T. (2010). Community and individual race/ethnicity and home health care use among elderly persons in the United States. *Health services research*, *45*(5 Pt 1), 1251–1267. **https://doi.org/10.1111/j.1475-6773.2010.01135.x**

U.S. Department of Health and Human Services Assistant Secretary for Planning and Evaluation Office of Disability, Aging and Long-Term Care Policy. Racial And Ethnic Disparities In Alzheimer's Disease: A Literature Review
https://aspe.hhs.gov/system/files/pdf/178366/RacEthDis.pdf

K. M. Mehta, K. Yaffe, E. J. Pérez-Stable, A. Stewart, D. Barnes, B. F. Kurland, B. L. Miller (2008) *Neurology*, 70 (14) 1163-1170; DOI: 10.1212/01.wnl.0000285287.99923.3c
https://www.sciencedirect.com/science/article/pii/S1552526016331296

Table 10: Summary approach to AD innovation cost-effectiveness assessment: Examples from Australia, Canada, and England

PBS (2012) Report to the PBAC - Review of Pharmaceutical Benefits Scheme anti-dementia drugs to treat Alzheimers Disease. **https://www.pbs.gov.au/info/reviews/anti-dementia-report**

Bauer, A., Wittenberg, R., Ly, A., Gustavssond, A., Bexelius, C., Tochel, C., Knapp, M., Nelson, M., & Sudlow, C. L. M. (2020). Valuing Alzheimer's Disease drugs: A health technology assessment perspective on outcomes. International journal of technology assessment in health care, 1-7. **https://doi.org/10.1017/S0266462320000574**

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Paris, V. and A. Belloni (2013), "Value in Pharmaceutical Pricing", OECD Health Working Papers, No. 63, OECD Publishing, Paris, **https://doi.org/10.1787/5k43jc9v6knx-en**.