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A Health Opportunity Cost Threshold for Cost-Effectiveness Analysis in the United States

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Background: Cost-effectiveness analysis is an important tool for informing treatment coverage and pricing decisions, yet no consensus exists about what threshold for the incremental cost-effectiveness ratio (ICER) in dollars per quality-adjusted life-year (QALY) gained indicates whether treatments are likely to be cost-effective in the United States.

Objective: To estimate a U.S. cost-effectiveness threshold based on health opportunity costs.

Design: Simulation of short-term mortality and morbidity attributable to persons dropping health insurance due to increased health care expenditures passed though as premium increases. Model inputs came from demographic data and the literature; 95% uncertainty intervals (UIs) were constructed.

Setting: Population-based.

Participants: Simulated cohort of 100 000 individuals from the U.S. population with direct-purchase private health insurance.

Measurements: Number of persons dropping insurance coverage, number of additional deaths, and QALYs lost from increased mortality and morbidity, all per increase of $10 000 000 (2019 U.S. dollars) in population treatment cost.

Results: Per $10 000 000 increase in health care expenditures, 1860 persons (95% UI, 1080 to 2840 persons) were simulated to become uninsured, causing 5 deaths (UI, 3 to 11 deaths), 81 QALYs (UI, 40 to 170 QALYs) lost due to death, and 15 QALYs (UI, 6 to 32 QALYs) lost due to illness; this implies a cost-effectiveness threshold of $104 000 per QALY (UI, $51 000 to $209 000 per QALY) in 2019 U.S. dollars. Given available evidence, there is about 14% probability that the threshold exceeds $150 000 per QALY and about 48% probability that it lies below $100 000 per QALY.

Limitations: Estimates were sensitive to inputs, most notably the effects of losing insurance on mortality and of premium increases on becoming uninsured. Health opportunity costs may vary by population. Nonhealth opportunity costs were excluded.

Conclusion: Given current evidence, treatments with ICERs above the range $100 000 to $150 000 per QALY are unlikely to be cost-effective in the United States.

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For author, article, and disclosure information, see end of text.
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As health care spending in the United States continues to increase (1), life expectancy gains have failed to keep pace and are showing signs of reversal (2). Seeking partial explanations for both trends, economists point out that the U.S. health care system readily adopts and pays for costly new treatments without requiring improvements in health outcomes to justify those costs (3–8). Spending less on treatments that offer little or no improvement in outcomes would allow more spending on other treatments that may offer larger health gains without increasing the overall health care budget. Of course, we could simply spend more on health care overall, but that would leave us with less to spend on other important determinants of health and well-being, like education, housing, the environment, and poverty reduction (9). Either way, if we accept improving population health as a central goal of the health care system, we should seek to use health care resources more efficiently.

Cost-effectiveness analysis is a tool for assessing whether a new treatment is an efficient use of limited resources (10). The incremental cost-effectiveness ratio (ICER) measures the net resources needed to improve health outcomes by 1 unit when using a new treatment compared with the next best available treatment. The resources considered go beyond just treatment prices and include costs (or savings) resulting from treatment effects over time. Although any measurable health outcome (such as complete response, tobacco quits, or hemoglobin A_{1c} levels) can go in the denominator of an ICER, the most common measure is the quality-adjusted life-year (QALY), which integrates differences between treatments in both mortality and health-related quality of life (11). Using a broad measure like the QALY provides a common denominator for comparing the efficiency of treatments across the spectrum of health care, from cancer treatment to smoking cessation to diabetes management.

Many countries with centralized systems of health care provision or payment use cost-effectiveness to guide treatment coverage and pricing (12). In the United Kingdom, for example, the National Institute for Health and Care Excellence generally recommends that treatments with ICERs above a threshold of £20 000 to £30 000 per QALY not be covered by the National Health Service in England and Wales (13, 14). Thresholds used for recommending coverage or negotiating prices vary across countries; sometimes they are explicitly stated, whereas at other times they are inferred from past decisions (15).

See also:

Editorial comment 109

Web-Only
Supplement

Until recently, cost-effectiveness has played more of an informative and less of a formal role in the United States. Because of public and political concerns over rationing, Medicare has long avoided using cost-effectiveness in coverage decisions (16). In 2010, lawmakers even inserted language into the Patient Protection and Affordable Care Act (ACA) preventing Medicare from using a cost-per-QALY threshold to determine treatment coverage (17). So, what has changed? With rapid growth in health care costs (and in the amount of those costs paid by patients), clinicians are increasingly aware of "financial toxicity" and its effect on the health of their patients (18, 19). Calls for national action have included "value-based pricing" based on cost-effectiveness (20).

The Institute for Clinical and Economic Review, an independent, nongovernmental organization, has increased the visibility of cost-effectiveness as a tool for payers to negotiate prices (21, 22). In 2018, CVS Caremark announced a pharmacy benefits package where treatments with ICERs above $100 000 per QALY, as assessed by the Institute for Clinical and Economic Review, risk exclusion from its formulary (23). In 2018, the New York State Drug Utilization Review Board used an assessment from the Institute for Clinical and Economic Review to recommend that the state's Medicaid program pursue a manufacturer's rebate for the cystic fibrosis treatment lumacaftor–ivacaftor (Orkambi [Vertex]) to bring its ICER below $150 000 per QALY (24). The U.S. Department of Veterans Affairs is also collaborating with the Institute for Clinical and Economic Review to support drug coverage and price negotiation using value-based price benchmarks based on a range of cost-effectiveness thresholds from $100 000 to $150 000 per QALY (25).

The Elijah E. Cummings Lower Drug Costs Now Act (H.R. 3), passed in 2019 by the U.S. House of Representatives (26), would cap federally negotiated drug prices at 120% of an average international market price based on costs in 6 countries. Five of these countries either explicitly (Australia, Canada, and the United Kingdom) or optionally (France and Germany) use cost-effectiveness in coverage and pricing (27–30), and another (Japan) is considering formalizing its use (31). The Congressional Budget Office estimated that H.R. 3 would lower Medicare Part D spending by $456 billion between 2020 and 2029, assuming that the federal government will not agree to prices resulting in an ICER exceeding $520 000 per QALY (32, 33). A presidential executive order issued on 13 September 2020 would tie Medicare Part B and Part D payments for prescription drugs or biologic products to the "most-favored-nation price" among countries with "comparable per-capita gross domestic product," many of which base pricing and coverage on cost-effectiveness (34). These actions may pressure manufacturers to be more open to cost-effectiveness analysis in the United States. Companies may prefer using prices negotiated under a U.S. threshold to being tied to prices in other countries where thresholds are likely lower (35).

In this article, we assess potential cost-effectiveness thresholds for the United States using a health opportunity cost approach. This approach starts with the assumption that we wish to get the most population health for what we already spend on health care. The question of whether we spend too much or too little on health care overall is set aside temporarily. When health care spending is held fixed, covering a new, more costly treatment that may benefit one group of patients means spending less on care received by other patients. Health opportunity cost reflects the health lost among patients whose health care expenditures are reduced to pay for the new treatment. When a new treatment costs more per QALY gained than the health care it displaces, health opportunity costs exceed health benefits and overall population health (measured in QALYs) declines (36). The point where this occurs defines the threshold.

In countries with fixed health care budgets and centralized decision making, health opportunity cost makes a lot of sense. That is why, for example, researchers have based estimates of the U.K. cost-effectiveness threshold on how much health is lost when, to pay for a new treatment, less care is provided to the patient population served by the National Health Service (largely through decreased services, including longer wait times and more restrictive criteria for treatment eligibility) (37–40). These estimates suggest that services displaced when paying for new treatments in the United Kingdom cost about £5000 to £15 000 to produce 1 QALY (38), well below the threshold of £20 000 to £30 000 per QALY that the National Institute for Health and Care Excellence uses to judge cost-effectiveness.

The Second Panel on Cost-Effectiveness in Health and Medicine and the Institute for Clinical and Economic Review have both called for research on cost-effectiveness thresholds based on opportunity cost for the United States (41, 42). However, the United States has no single, defined budget for health care, and costs are spread across health insurance risk pools funded by taxes and premiums. Identifying where health opportunity costs fall is more challenging. To overcome this challenge, we relax the assumption that health care expenditures are fixed and instead consider what happens when private insurers spend more but increase premiums to cover costs (41, 43–45). We identify health opportunity costs for the U.S. population with direct-purchase health insurance on the basis of empirical estimates of the percentage of plan members who are likely to drop coverage when premiums increase and experience increased mortality and morbidity as a result.

METHODS

Statistical Analysis

The first step in our simulation was to estimate how many individuals would become uninsured because of a premium increase. We simulated a cohort with the same age distribution as the U.S. population covered

by direct-purchase insurance (46). Using 2019 average premiums from the ACA Marketplace (47) as a baseline, we then estimated the percentage premium increase necessary for an insurance plan to fully pass along a hypothetical increase in health care cost to plan members. Using estimates of the percentage of plan members becoming uninsured per percentage increase in premiums (known as the premium elasticity of coverage) by age group from a study of ACA Marketplace premium increases (48), we simulated the number who would become uninsured by year of age.

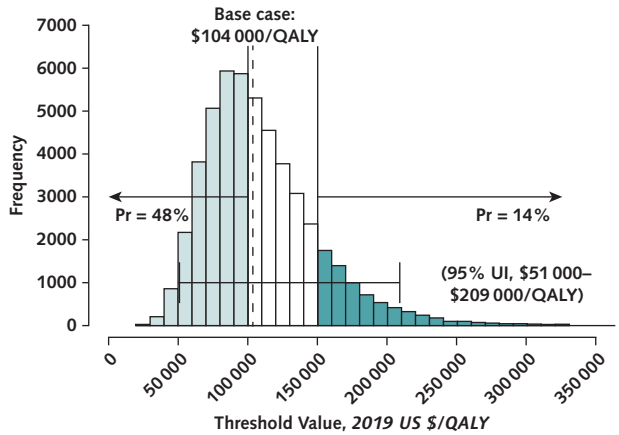
The second step was to estimate how much mortality and morbidity would likely result among persons losing insurance coverage in step 1. Using an estimate of the number needed to gain health insurance to avert 1 death over a short time horizon from a study of mortality reductions associated with ACA Medicaid expansion (49), we solved for the implied relative risk for death from becoming uninsured. This implied relative risk, when applied to mortality rates by age from U.S. life tables (50) in proportion to the age distribution of those simulated to drop coverage in step 1, would yield the expected number of deaths in 1 year. This allowed us to apportion deaths attributable to becoming uninsured to each year of age, reflecting varying baseline mortality rates. Accounting for remaining life expectancy, we estimated QALYs lost due to death using U.S. life tables, to which we applied health-related quality of life (SF-6D-12V2) by year of age estimated from the National Health Measurement Study (51). Lost quality-adjusted life expectancy was discounted at 3% per year, following recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine (41). Finally, we estimated QALYs lost due to morbidity attributable to becoming uninsured among survivors for 1 year. On the basis of a recent evidence synthesis (52), we assumed that 10% of morbidity is amenable to health care. We further assumed that losing insurance had the same proportional effect on amenable morbidity as it had on mortality.

Using these estimates, we then calculated health opportunity costs as QALYs lost per additional dollar spent (2019 U.S. dollars). We note that multiplying additional expenditures by a factor results in a directly proportional effect on QALYs lost. Therefore, the health opportunity cost ratio stays constant for any hypothetical cost increase. For similar reasons, the health opportunity cost ratio does not vary with cohort size. For interpretability, we report QALYs lost attributable to a hypothetical expenditure increase of $10 000 000 in a cohort of 100 000 plan members, causing a $100 (1.6%) premium increase per member per year. The implied cost-effectiveness threshold is the reciprocal of the health opportunity cost ratio.

Because our model inputs come from uncertain estimates, we used a Bayesian approach to see how uncertainty affects the threshold. We repeated the simulation 50 000 times using different sets of model inputs randomly chosen from probability distributions with means and spreads reflecting available evidence about each input's likely value. We estimated the probability that the threshold exceeds a specified value by counting the number of times the simulated threshold exceeded that value and dividing by 50 000. For policy relevance, we assessed the probabilities that the threshold lies above and below the range of $100 000 to $150 000 per QALY that the Institute for Clinical and Economic Review uses for value-based pricing (42). For a detailed description of our simulation, see the **Supplement** (available at Annals.org).

Our study was not human subjects research as covered under 45 C.F.R. part 46.

Figure. Frequency of calculated threshold values in 50 000 simulations with varying input values.



The light green shaded area contains 23 902/50 000 (48%) threshold values <$100 000/QALY, and the dark green shaded area contains 7006/50 000 (14%) threshold values >$150 000/QALY. The horizontal error bar shows the 95% UI. The vertical dashed line depicts the base-case estimate of $104 000/QALY. Pr = probability; QALY = quality-adjusted life-year; UI = uncertainty interval.

Role of the Funding Source

This study received no external funding.

RESULTS

For each additional $10 000 000 (2019 U.S. dollars) in health care expenditures, about 1860 persons (95% uncertainty interval [UI], 1080 to 2840 persons) with direct-purchase private insurance were simulated to become uninsured because of passed-through premium increases, causing 5 additional deaths (UI, 3 to 11 deaths), 81 QALYs (UI, 40 to 170 QALYs) lost due to death, and 15 QALYs (UI, 6 to 32 QALYs) lost due to illness. A new treatment with an incremental cost of $10 000 000 would therefore need to increase QALYs by at least 96 (UI, 48 to 195 QALYs) to avoid reducing total population health, implying a threshold of $10 000 000 per 96 QALYs, equal to $104 000 per QALY (UI, $51 000 to $209 000 per QALY) in 2019 U.S. dollars.

The threshold exceeded $150 000 per QALY in 7006 of 50 000 simulations, suggesting 14% probability that the threshold exceeds $150 000 per QALY (**Figure**). The threshold was less than $100 000 per QALY in

Table. Key Input Values and 1-Way Sensitivity Analysis Results

Model Input*	Input Base-Case Value	Input 95% UI	Threshold 95% UI, *2019 US $/QALY*†	Input Values		Study, Year (Reference)
				Threshold <$100 000/QALY	Threshold >$150 000/QALY	
Persons needed to lose insurance to result in 1 expected death in 1 y, *n*	277.5	155.9 to 435.1	61 000 to 157 000	<267	>414	Sommers, 2017 (49)
Premium elasticity of coverage: age 18–34 y, %/%	−1.5	−2.38 to −0.62	78 000 to 152 000	<−1.6	>−0.65	Saltzman, 2019 (48)
Premium elasticity of coverage: age 35–54 y, %/%	−1.05	1.78 to −0.43	81 000 to 136 000	<−1.15	>−0.24	Saltzman, 2019 (48)
Additional costs passed through as premium increases, %	100	83 to 117	125 000 to 89 000	>104	<69	Assumption
Baseline annual premium for direct-purchase private insurance, *2019 US $*	6214	5147 to 7369	86 000 to 123 000	<5993	>8990	CMS 2019 (47)
Morbidity amenable to health care, %	10	5.7 to 15.5	111 000 to 95 000	>12.2	‡	Kaplan and Milstein, 2019 (52)
Premium elasticity of coverage: age 55–64 y, %/%	−0.7	−1.23 to −0.28	99 000 to 105 000	<−1.16	‡	Saltzman, 2019 (48)

CMS = Centers for Medicare & Medicaid Services; QALY = quality-adjusted life-year; UI = uncertainty interval.
* Ordered from most to least influential on the width of the 95% UI for the resulting threshold value.
† The ordering of values in the threshold 95% UIs corresponds with the ordering of inputs in the input 95% UIs.
‡ No value for this input can cause the threshold to exceed $150 000/QALY when all other inputs are fixed at their base-case value.

23 902 of 50 000 simulations, suggesting 48% probability that the threshold lies below $100 000 per QALY. The **Table** presents input base-case values and 1-way sensitivity analysis results (for additional details, see **Supplement Tables 1** and **2** and the **Supplement Figure**, available at Annals.org). Estimated thresholds were most sensitive to the effect of losing insurance on mortality, followed by premium elasticity of coverage among persons aged 18 to 34 years and 35 to 54 years. Input values indicating a larger effect of becoming uninsured on mortality and morbidity, more persons dropping coverage because of premium increases, or a larger proportion of costs passed through to plan members increased the opportunity cost and therefore lowered the threshold.

DISCUSSION

Historically, U.S. cost-effectiveness studies have compared ICERs against various thresholds ranging from roughly $50 000 to $300 000 per QALY (53–56). The lower end of that range has been justified on an apocryphal argument that Medicare revealed its willingness to pay per QALY by creating a special program covering dialysis for end-stage renal disease, a treatment supposedly having an ICER of about $50 000 per QALY (53). The upper end of that range is supported by Braithwaite and colleagues (56), who estimated individual willingness to pay to reduce morbidity and mortality through purchases of private insurance that increase health care use. Our uncertainty analysis suggests that these bounds are likely inconsistent with a threshold based on health opportunity costs, given available evidence (**Figure**).

Phelps (57) recently derived a threshold directly from principles of individual economic choice. Assuming that persons with typical aversion to financial risk balance their expenditures on health and other consumption over time to maximize their expected well-being, Phelps found that those with an income of $50 000 (approximately the U.S. disposable personal income per capita of $50,731 in December 2019) (58) should be willing to pay twice that amount ($100 000) to increase quality-adjusted life expectancy by 1 QALY. This result is close to our own base-case estimate of $104 000 per QALY despite being based on a very different approach.

All 3 of the thresholds referenced in the previous paragraphs are grounded in "welfarist economics," where individuals make choices to maximize their overall well-being, not just their health (59, 60). If consumers are rational and are well informed about the true benefits and costs of health care relative to other things that they could do with their money, and if health care is bought and sold in a perfectly competitive market, then willingness to pay per QALY should coincide with the full opportunity cost of health care expenditures (61).

Our analysis cannot make such a claim. First, although we rely on empirical estimates of individuals choosing whether to continue purchasing health insurance when premiums increase, we do not assume that their choices are fully informed or made in perfectly competitive markets. Health economists have long recognized that health care is unlike other goods and services because full information about its benefits is never known by all parties in advance (62), and many factors about the U.S. market for health care cause prices to differ from actual costs (63, 64). A reviewer noted that if consumers underestimate the health risks of becoming uninsured, then observed premium elasticity of coverage may be higher than optimal, and our estimate could serve as a lower bound for the willingness-to-pay threshold.

Second, our analysis considered just one possible mechanism of action, or, as economists like to say, one margin: the effect of treatment cost increases on premiums and insurance coverage for direct-purchase private insurance. We did not consider other relevant margins, such as the possible effects of increasing health care costs on patient copayments or wait times; on the offering and generosity of employer-sponsored insurance coverage; or on public insurance programs, such as Medicare and Medicaid. In such cases, the opportunity costs of increasing health care expenditures will be borne by someone (for example, by insured patients through their health and finances, by employees through their take-home income, by taxpayers, or by beneficiaries of other government expenditures). The existence of multiple margins emphasizes that many opportunity costs are possible in the heterogeneous U.S. health economy and that a range of thresholds may therefore be valid.

Third, we do not estimate the full opportunity cost of increased health care expenditures (including reduced overall well-being from consuming less of goods and services like housing, food, or education; from reduced savings; or from the lost value of financial risk protection that having health insurance is meant to confer). Rather, we frame our argument on health opportunity costs alone. Although our approach is incomplete from the standpoint of welfarist economics, it is consistent with "extra-welfarism" (59, 65). Under that framework, the goal of health policymakers is to maximize total population health given available health care resources—a goal that requires an understanding of health opportunity costs. We believe that this perspective is valid and compelling. By focusing on health opportunity costs, we bring the tradeoff between the health of identified patients and that of the overall population to the surface (66).

Other studies have estimated U.S. thresholds based on health opportunity costs by extrapolating from other countries. Using estimates for the United Kingdom by Claxton and colleagues (37), Woods and colleagues (67) estimated a range for the U.S. threshold of $24 283 to $40 112 per QALY. Their analysis assumes a consistent relationship between gross domestic product per capita and health opportunity costs across several countries, which, given fundamental differences between the U.S. health care system and others, may be strained. Ochalek and Lomas (68) estimated that the U.S. threshold is $60 475 to $97 851 per disability-adjusted life-year averted based on cross-sectional, country-level estimates of disability and life expectancy as a function of national expenditures on health care and other determinants of health, including income, education, and sanitation. Beyond potential difficulties in comparison due to the use of disability-adjusted life-years (69), their range may be lower than ours because of the ecological assumption that the relationship between health care expenditures and health outcomes across countries applies within the United States.

Our approach has other limitations. Although informed by theory and empirical estimates, our model inputs are uncertain. For example, estimates of the premium elasticity of coverage vary substantially (70–72). We used an estimate by Saltzman (48) because of its recency; its focus on the ACA Marketplace; and its estimation of elasticity by age group, which we believed was important given age-related differences in morbidity and mortality. Although the weight of evidence demonstrates that extending health insurance coverage reduces morbidity and mortality, estimates of that effect vary widely (73–76). We chose the midpoint of a range of 239 to 316 persons needed to gain insurance to avert 1 death for those newly covered by Medicaid expansions in California and Washington estimated by Sommers (49). Persons who gained Medicaid coverage may differ from those covered by direct-purchase private insurance; however, we note that many persons cycle among Medicaid, direct-purchase insurance, and being uninsured (77). Sommers noted that up to 20% of the estimated mortality reduction may have come from increased use of antiretroviral drugs for HIV in the late 1990s and early 2000s. A recent study by Borgschulte and Vogler (75) of post-ACA Medicaid expansions from 2014 to 2017 estimated that 310 persons would need to gain insurance to avert 1 death, which is within the range of 239 to 316 persons estimated by Sommers (49). Our sensitivity analysis range is wider still (range, 65 to 701 persons; UI, 155.9 to 435.1 persons), reflecting substantial uncertainty. Using the Borgschulte and Vogler estimate (75) would increase our estimated threshold to $115 000 per QALY.

We also note that our analysis assumes that health opportunity cost in QALYs lost per dollar spent is a constant ratio, regardless of the magnitude of additional health expenditures considered. Blockbuster treatments for common chronic diseases, or those that offer potential cures for uncommon but life-threatening diseases, may be cost-effective when assessed against a fixed threshold but may not be affordable (78). As such treatments claim a larger share of a health care budget, opportunity costs may increase disproportionately—effectively lowering the threshold (79). Price negotiations for treatments with large budget impacts could target the lower end of a range of threshold values to account for affordability (80).

Given overall uncertainty about cost-effectiveness thresholds, it would be prudent to avoid the temptation to set in stone any single threshold as the sole test for determining whether treatments are of individual or social value (81). Although attempts have been made to broaden economic evaluation of new treatments beyond costs per QALY gained (82), we must recognize that cost-effectiveness analysis, as currently practiced, largely ignores important ethical considerations, including concerns for equity and the intrinsic value of human life regardless of age or underlying health (83).

New treatments are often rightly met with enthusiasm from patient groups and clinicians, but the health consequences that increased treatment costs have on others in the health care system more broadly also tend

to be ignored. Individuals bearing health opportunity costs through the mechanism we describe are likely to come from poorer population groups lacking political representation. In a review of health economist Uwe Reinhardt's final work, *Priced Out*, Jeff Goldsmith notes that "those who remain out in the cold [the uninsured] are a diverse bunch, united only by their marginality or invisibility and lacking organized advocacy in Congress" (84).

Although we cannot expect individual clinicians to consider the health of any patients other than their own while at the bedside, the health opportunity costs borne by anonymous members of society remain an ethical and policy imperative (66). Collectively, clinicians have substantial power to shape the debate over the affordability of care they provide. Clinicians can and do play a role in making health care costs visible to the public and to policymakers. The question of whether and where to draw the line on what makes a treatment cost-effective is becoming a matter of urgent economic and clinical significance. Clinicians who are concerned about the effects of increasing costs on patient and population health, or who are wary of the ethical, economic, or health consequences of using cost-effectiveness thresholds, should engage in this debate.

Despite the limitations of our analysis—and of cost-effectiveness more broadly—we believe that it is reasonable to expect that when an authority, be it a government agency or a private insurance plan, agrees on whether or how much to pay for a treatment, that decision will "first, do no harm" to population health. Setting cost-effectiveness thresholds too high (or ignoring them altogether) sustains current conditions for a self-reinforcing cycle of escalating health care costs and continued disappointing progress on improving population health.

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