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How to integrate evidence from patient preference studies into health technology assessment: a critical review and recommendations

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Commentary

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Abstract

Health technology assessment (HTA) agencies vary in their use of quantitative patient preference data (PP) and the extent to which they have formalized this use in their guidelines. Based on the authors' knowledge of the literature, we identified six different PP "use cases" that integrate PP into HTA in five different ways: through endpoint selection, clinical benefit rating, predicting uptake, input into economic evaluation, and a means to weight all HTA criteria. Five types of insight are distinguished across the use cases: understanding what matters to patients, predicting patient choices, estimating the utility generated by treatment benefits, estimating the willingness to pay for treatment benefits, and informing distributional considerations. Summarizing the literature on these use cases, we recommend circumstances in which PP can add value to HTA and the further research and guidance that is required to support the integration of PP in HTA. Where HTA places more emphasis on clinical outcomes, novel endpoints are available; or where there are already many treatment options, PP can add value by helping decision makers to understand what matters to patients. Where uptake is uncertain, PP can be used to estimate uptake probability. Where indication-specific utility functions are required or where existing utility measures fail to capture the value of treatments, PP can be used to generate or supplement existing utility estimates. Where patients are paying out of pocket, PP can be used to estimate willingness to pay.

Introduction

Interest in using patient preference (PP) data to support healthcare decision making is growing. This has been demonstrated through a number of recent research and collaborative initiatives calling for or developing guidelines for its use in the medical product life cycle, including to inform product design, clinical trial endpoint selection, regulatory approval, health technology assessment (HTA), and prescription decisions (1). The United States Food and Drug Administration (FDA) defines PP data as a "qualitative or quantitative assessment of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions" (2).

This manuscript focuses on the use of PP data in HTA. There are various reasons why PP should be integrated into HTA: patients have a right to participate in decisions impacting them, decision making will be more informed as patients hold experiential knowledge on their disease, and involving patients provides social legitimacy to decisions. HTA agencies have sought patient input during the technology review process, but often in the form of qualitative insights (3). Where agencies have sought quantitative preference data, they have tended to be from general population samples to inform the utility estimation required by economic evaluation (1).

Some HTA agencies have explicitly included quantitative PP in their guidelines (1;4), and recent reviews and research with agency staff suggest an appetite for a greater use of quantitative PP (1;5;6). The National Institute for Health and Care Excellence (NICE) in England and Wales has identified the use of PP as one of its research priorities and has disseminated the ways that quantitative PP can support its decision making (7). However, the integration of quantitative PP in HTA faces several challenges. Huls et al. (8) identified thirty-seven research issues associated with the use of quantitative PP in HTA, including methodological, procedural, normative, practical, and conceptual issues. This is supported

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by reviews and interviews with stakeholders, which attributed poor integration of PP into HTA to a lack of accepted methodology and guidelines (5;6).

Various roles for PP have been described or proposed in the literature, but no attempt has been made to review these and describe the types of evidence that PP can bring to HTA. This paper addresses this gap. Our objective is to identify the types of evidence that quantitative PP can provide in HTA, the circumstances in which these may be most relevant, and propose research required to further the use of PP in HTA. In doing so, we hope to start addressing two questions identified in Huls et al. (8): whether PP should be incorporated within the quality-adjusted life-year (QALY) or beyond the QALY and whether multiple-criteria decision analysis (MCDA) could be used to integrate PP into HTA.

Whichello et al. (9) identified six critical decision points within HTA at which PP could be integrated. This paper focuses on just one of those—assessment. We focus on the use of quantitative stated preference data that meet the FDA's definition and do not limit our consideration to any method for eliciting stated preferences. We do not concern ourselves with the methodological challenges associated with preference elicitation and assume that valid and reliable PP data are available. Finally, the points made in this paper are relevant for all medical products, including but not limited to, pharmaceuticals, medical devices, and diagnostics.

Based on the authors' collective knowledge of the relevant literature, the following sections describe PP use cases—alternate ways of integrating quantitative PP into HTA, present a framework for understanding how PP can contribute to HTA, and summarize HTA agency perspectives on and the challenges associated with using PP to generate these insights. We conclude with recommendations for how PP might support HTA.

Integrating PP in HTA

Table 1 summarizes PP use cases—the alternate ways that have been proposed to integrate PP into HTA. References are provided for illustrative purposes.

Typologizing PP Use Cases

Table 2 summarizes the application of a two-dimensional framework to describe the ways that the PP use cases support HTA. The first dimension in the framework is the type of evidence that PP can provide in HTA. The framework distinguishes five types of HTA evidence: endpoint selection, clinical benefit rating, predicting uptake, input into economic evaluation, and a means to weight all the criteria relevant to HTA. Within "input into economic evaluation," the framework distinguishes several roles for PP: the estimation of the within-therapy area efficiency of medical products and the estimation of the across-therapy area efficiency of medical products, through supporting either cost–benefit analysis or cost–utility analysis.

The second dimension of the framework is the insight provided by the PP use cases. Five types of insight are distinguished: understanding what matters to patients and how much this matters; predicting patient choices; estimating the utility generated by treatments benefits; estimating the willingness to pay for, or the opportunity cost associated with, treatment benefits; and informing distributional considerations, such as how the value of a QALY gained varies between patient groups.

Understanding What Matters to Patients and How Much

Trade-off assessment, including endpoint selection and clinical benefit rating, can help decision makers understand what matters

Table 1. Use cases describing the integration of patient preference (PP) into health technology assessment (HTA)

Use case	Description	Ref.
Trade-off assessment	PP data are used to understand how patients trade off between the differences in available technologies. Two applications of trade-off assessment include endpoint selection, in which PP data are used to understand the relative importance of endpoints, either clinician or patient-reported, and clinical benefit rating, in which the relative value of benefits can be assessed, such as minimum required benefit.	(7;10–12)
Preference share	PP are combined with the performance profiles of treatment to predict treatment uptake, which is used to parameterize economic models, such as cost-effectiveness and budget impact analyses.	(7;13)
Estimation of QALY gains	Two methods have been proposed to incorporate PP into the estimation of quality-adjusted life-years (QALYs). First, PP are used instead of general population preferences to estimate the utility associated with health states. These utility estimates are then used to estimate gains in QALYs generated by treatments. Second, PP are used to "translate" changes in treatment outcomes into a change in a dimension of the QALY that are of equivalent value, for instance, improvements in survival that generate the same value to patients as the treatment outcome of interest. These changes are then translated into QALYs. For instance, survival equivalents can be applied at the baseline quality of life and life expectancy implied in the elicitation method.	(14;15)
Construction of efficiency frontiers	PP are collected for indication-specific treatment attributes. These preferences are used to translate the performance of treatments on these attributes into an overall benefit score. Plotting treatment scores and costs allows the construction of an efficiency frontier. Treatments on or above this frontier are considered efficient.	(16)
Cost–benefit analysis	Including a monetary attribute in a PP study allows estimation of patients' willingness to pay (WTP) for improvements in benefits and/or reductions in risks. Combined with data on the changes in benefits and risks associated with treatments, this allows an estimation of patients' WTP for treatments. Comparing this with the cost of treatments allows an estimation of the net monetary benefit generated by treatments.	(4)
Multicriteria decision analysis (MCDA)	PP are used to weight criteria relevant to HTA, including, but not limited to, health gain (perhaps in the form of QALYs), cost, and disease severity. The MCDA generates an assessment of the overall value of a treatment.	(17)

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Table 2. Typology of roles and insights generated by PP for HTA

HTA Evidence Type			PP Use case	PP Insight				
				What matters/ how much	Predict patient choice	Utility	WTP/ opportunity cost	Distributional considerations
Endpoint selection			Trade-off assessment	✓				
Clinical benefit rating				✓				
Predicted uptake, adherence			Preference share		✓			
Valuation of benefits in economic evaluation	Within-therapy area efficiency		Overall benefit in efficiency frontier			✓		
	Across-therapy area efficiency	Cost–utility analysis (CUA)	Estimating QALY gains			✓		
		Cost–benefit analysis (CBA)	WTP			✓	✓	
MCDA			MCDA weights				✓	✓

Abbreviations: PP, patient preference; HTA, health technology assessment; MCDA, multicriteria decision analysis; QALY, quality-adjusted life-year; WTP, willingness to pay.

to patients and how much (7;10). This evidence is supportive, ensuring that clinical studies collect data on endpoints that matter to patients, or that data on the value proposition for patients are considered alongside other evidence.

This is the more feasible of the PP use cases and easily acceptable to HTA agencies, as it does not attempt to analytically incorporate PP into an economic evaluation of an overall assessment of the value of a medical product (see below for more discussion). This is supported by a recent publication from staff at the NICE on how PP might support their decision making (7), by interviews with HTA agency staff from Germany, Canada, and Belgium (6), and by case studies of the use of PP by the Ontario HTA agency (11).

However, this acceptability is accompanied by concerns that the impact of this PP use case on reimbursement decisions will be limited without a more formal integration with evidence already considered by the agencies, such as economic analysis (6). This concern may, however, be mitigated by generating insights earlier in the product life cycle in order to inform the endpoints that will be included in the pivotal clinical trial (18). This way, the PP study can help the sponsor and HTA agency align on what constitutes patient value, ensuring that this is measured and considered during HTA.

There is also a lack of guidance on when and how quantitative data based on what matters to patients could support HTA. Bouvy et al. (7) illustrate how this PP use case could support NICE decision makers with an example of cancer treatments, where chemotherapy, radiation therapy, and immunotherapy differ in modes and ease of administration, effectiveness, and the risk of serious side effects. In such cases, a PP study could provide a committee with important insights into how patients with cancer would make trade-offs between treatment options and the probability that patients would prefer one treatment over another (7). However, no generalized guidance on this PP use case is available.

Predicting Patient Choice

The likelihood that patients will take and adhere to treatment is a critical component of HTA, not least as an input into cost-effectiveness and budget impact models (13). This is especially the case for technologies that require upfront costs, but from which only those patients who follow and adhere to the treatment would likely benefit, for example, screening, inpatient/physician-led procedures followed by prescription and monitoring, or chronic prophylactic medications such as statins.

At the point at which HTA is undertaken, uptake and adherence are usually uncertain. PP studies can be used to estimate the probability that patients will choose one treatment over others and their willingness to tolerate the inconvenience of taking medication or safety events. There is precedence for such studies being used in submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) to successfully support the argument that reduced injection frequency will result in improved adherence (19). It has also been argued that these insights can be used to parameterize economic analyses (13). However, we are not aware of any precedence of such an approach being used to support a reimbursement decision.

There are concerns about the external or theoretical validity of the choices predicted by PP studies. Thus, where possible, observations of patients' actual choices should still be preferred to their stated preferences. In the absence of such data, where PP data are used to help understand uptake or adherence, it is important to follow best practice to minimize hypothetical bias and ensure valid choice prediction (20).

Estimating Utility Generated by Technologies

Three of the PP use cases are concerned with valuing treatment outcomes and integrating these into economic evaluation. Three broad approaches are adopted: estimating utility in the form of patient willingness to pay (WTP) (4), estimating overall benefit within a therapy area-specific value framework (16), and supporting the estimation of QALY gains within a cost–utility analysis (14). The first of these is considered in the next subsection. This section deals with the latter two approaches.

By defining the evaluation problem as the assessment of within-therapy area efficiency of technologies for a given patient group, the use of PP to estimate overall benefit for efficiency frontiers avoids many of the challenges associated with comparing the preferences of different patient groups. Having conducted two pilot studies, the Institute for Quality and Efficiency in

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Healthcare (IQWiG) concluded that such methods for eliciting PP were "suitable and manageable" and delivered "useful results" (21). Although they identified some methodological questions raised by this use of PP, such as ensuring the use of representative samples of patients, they have adopted the efficiency frontier approach as the basis for their economic evaluation (1). However, it is unclear how many IQWiG assessments have been informed by such efficiency frontiers and to what extent PP evidence fed into these assessments. Furthermore, the IQWiG is unique in its adoption of the within-therapy area efficiency frontier assessments.

Another PP use case involves PP in the estimation of QALYs. Two methods have been proposed to support this use case—using PP to re-estimate utility tariffs and to estimate QALY equivalents. Both involve estimating utility gains based on the amount of survival that patients would be willing to give up for a treatment benefit. Although both approaches could be used to estimate utility gains for a range of treatment benefits—improvements in health states, avoiding adverse events, or improvements in convenience—they differ in their emphasis. Estimating utility tariffs would conventionally focus on valuing health states, whereas estimating QALY equivalents may be more appropriate for estimating the utility associated with treatment benefits missed by conventional methods—acute events, such as pain or adverse events, or improvements in the mode of administration.

Both methods raise several methodological and normative questions. Consequently, the use of these methods in practice is relatively limited. We are not aware of any instances of HTA agencies using PP to estimate QALY gains in a cost–utility analysis (CUA). There is precedent for the supplementation of QALY estimation by using preference studies to estimate the QALY-equivalence of treatment benefits not captured by conventional QALY estimation methods, specifically process utilities (22). However, this was based on general population, rather than PP.

Most HTA agencies use public preferences to estimate utility gains (1) and are reluctant to estimate utility gains based on patients' preferences (6). The predominance of public preferences rests on two normative principles—the public is the recipient and often the funder of health care and patient's adaptation to their disease, for instance lowering their expectations of "full health," would disadvantage them if their preferences were the basis for utility estimation (23). However, various authors have raised challenges to this position, including that the public is unable to conceptualize what it is like to be in a certain health state and that the patient perspective, thus, provides important insight for decision makers, especially in the context of "laudable" adaptation where patients might be expected to put greater weight on their health gains than the public (24). Reflecting the idea that both the public and patients hold information that is relevant to estimating utility gains, various authors have put forward methods for integrating both sets of preferences into economic evaluation, including conducting CUA using both patient and public preferences, generating two efficiency estimates (23), or valuing health states using PP, and then addressing distributional concerns regarding health states using public preferences (25).

Estimating Willingness to Pay for Treatments

Using patients' WTP is accepted in specific circumstances by two HTA agencies. The PBAC recommend its use where nonhealth benefits are generated for the patient, such as a more convenient mode of administration (4). It is also recommended that WTP estimates be used in a cost–benefit analysis (CBA) where the health benefits of treatments are comparable. The Dental and Pharmaceutical Benefits Agency in Sweden recommend the use of patient WTP to capture either health gains that are not captured by the QALY, such as acute pain, or nonhealth gain (1). However, neither agency has provided data on the number of submissions supported by these data or how the PP data have impacted decisions.

There are several important objections to using PP to estimate WTP. First, it is argued that asking patients will result in unrealistic inflated WTP as they are self-interested in the outcome of a reimbursement decision while not having to cover the full cost of treatment themselves. Second, the efficiency of existing healthcare interventions should be the basis for opportunity cost rather than stakeholder's stated preferences (26). Third, WTP may be a function of income, potentially undermining agencies' objectives to ensure equality of access. Finally, questions about the external validity of preference studies mean that estimates of patients' WTP may not translate into WTP in practice (20). Although these objections apply to the use of PP to estimate WTP in a publicly funded healthcare system, they would also point to the potential use of PP in privately funded health care.

Distributional Considerations

One of the use cases—MCDA weights—involves patients weighing treatment outcomes, cost, and other factors, such as disease severity, to formally score these attributes in making a decision about the adoption of a technology (17). In this way, MCDA is an attempt to bring together many decision criteria, which may already include preference-based measures such as QALYs gained, into one composite criterion. If the MCDA includes a cost criterion, the approach also uses PP to determine WTP for treatment outcomes and how this should vary with, for instance, disease severity. Although there is precedent for the use of MCDA to support HTA, we are not aware of any instances where patients were exclusively the source of MCDA weights. Rather, patients tend to be one of a number of stakeholder groups who contribute weights (27).

The use of MCDA for HTA faces many challenges unrelated to the use of PP to generate weight inputs, which would nevertheless be a cause for concern, including the correct specification of value models and the selection of appropriate weighting methods (26). Furthermore, interviews with agency staff in Belgium, Canada, and Germany identified concerns about the practicality of such an approach, questioning the feasibility of eliciting PP for large numbers of criteria or in a manner timely with the HTA process (6). More fundamentally, using PP instead of public preferences as the basis for resolving distributional considerations is challenged by patients' vested interest in such decisions.

Discussion

Although eliciting public preferences remains the primary focus of stated preference studies to inform HTA, agencies are showing an appetite for a greater use of PP in decision making. However, the exact role that PP should take is unclear. The objective of this paper was to identify possible roles that quantitative PP can play in HTA, identify circumstances in which these roles may be most relevant, and identify areas for further research. Six PP use cases are identified, generating different combinations of insights: what matter to patients and how much, predictions of patient choice,

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Table 3. Recommendations for using PP for HTA

Insight	When can PP add value?	Research/guidance required
What matters/how much	• If HTA places more emphasis on clinical benefit rating than economic evaluation. • If novel endpoints are available and/or a choice must be made about which endpoints to include in a trial. • If the meaningfulness to patients of changes in endpoints has not been established. • Many treatment options with different characteristics, such as different benefit, risk, and convenience profiles.	Guidance: When can this insight add most value?
Predicting patient choice	• If uptake probability is uncertain.	Guidance: In which circumstances can PP generate meaningful insights into uptake probability?
		Guidance: What good practice should be followed to ensure that estimates are externally valid?
Utility estimation	• If indication-specific utility functions are required. • If treatment includes dimensions that existing value methods fail to capture. • If the public's lack of familiarity with a disease means they may undervalue treatment benefits.	Research: When do the public undervalue treatment benefits?
		Research: How do preferences vary between patients and does this align with agencies' normative goals?
WTP/Opportunity cost	• If patients are paying out of pocket	Guidance: What good practice should be followed to ensure that estimates are externally valid?
Distributional considerations	It is not recommended that PP inform distributional considerations.	

PP, patient preference; HTA, health technology assessment; WTP, willingness to pay.

utility estimation, estimation of WTP or opportunity cost, and distributional considerations. Based on a review of these use cases, Table 3 summarizes our recommendations for when PP can support HTA and the research required before PP can fulfill this role.

With an increased focus on value-based health care, PP can support HTA to ensure that decisions are made considering the value that a technology generates for patients. Furthermore, the use of PP to estimate utility gains may not always require significant research expense. PP studies are increasingly already performed for other purposes, such as informing regulatory approval. Using these data to also support HTA may require only minor updates to the design of the study. Further application of PP to HTA will help identify the design requirements of such studies undertaken for these purposes.

Most obviously, PP can ensure that the patients' perspective is brought to the selection and interpretation of clinical endpoints. Such insight is generally important for HTA but is particularly important where an HTA agency places greater emphasis on clinical benefit rating and less emphasis on economic evaluation, such as in Germany. For PP to be impactful, it is important that such insights are generated in time to allow sponsors and HTA agencies to consider the patient voice when aligning on the endpoints included in pivotal studies. This use of PP will be particularly important where novel endpoints are available, where many endpoints are available and a choice must be made about which to include in a trial, or where there is limited evidence on the meaningfulness to patients of changes in endpoints. However, further guidance would help determine precisely how and when PP might support HTA in this way, including how endpoints can be selected to both reflect PP and provide the evidence HTA agencies need to input into economic analyses.

PP can also support determining the value that should be attached to endpoints and other treatment characteristics. Public preferences still dominate HTA agencies' valuation of treatment benefits, but we recommend that PP support value estimation in certain circumstances. Where economic evaluation is based on indication-specific utility function, as is the case with the IQWiG's efficiency frontiers, PP has an obvious role in the generation of the overall value estimated. Where economic evaluation is based on cross-indication utility measures, such as when QALYs are used, further debate about the normative foundations of economic evaluation is required before HTA agencies will accept a role for PP in QALY estimation. The predominance of public preferences in the estimation of QALYs rests on a number of normative positions: the public being the funder and beneficiary of health care; that patients may adapt to their diseases; and concern that variation in the marginal utility of numeraires between patients may introduce inequalities into HTA. However, other normative arguments have been put forward which give the patient a greater role in utility estimation, including that the public is less aware of what it is like to live with a disease and patients would place greater value on benefits than the public. Further discussion of these competing normative arguments is required to help identify when and how PP should play a role in QALY estimation. We recommend the use of PP where the public's unfamiliarity with a disease means they may undervalue treatment benefits—the public would value a benefit more if they were to find themselves in the position of the patient. That is, if patients trade more survival for a treatment benefit than the public, then PP has an important role ensuring that utility estimation reflects how difficult it is to live with a disease. Where patients trade less survival for a treatment benefit than the public, it may reflect patients' adaptation to their disease, and we may want to use public preferences in utility estimation. However, two types of further research are required to support this discussion: a further comparison of patient and public preferences to understand how and why they vary and further work with the public to understand when they would want to defer to PP.

Further consideration should also be given to how PP use cases can support HTA where it is more challenging to apply

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conventional methods. For instance, for rare diseases, it is generally the case that the disease is less well researched, there are gaps in the clinical (and economic) evidence package, and a lack of familiarity with the disease among the public may undermine attempts to derive utility estimates. In these circumstances, PP may be of value, providing insights into the willingness of patients to make the trade-offs involved in taking treatments even in the presence of uncertain outcomes or providing alternate sources of utility estimates (28).

Research should also be undertaken on how valuations vary between patients and how this compares with agencies' normative positions. For instance, the value that patients attached to unit increases in survival is inversely related to their baseline life expectancy (29). Such variation conflicts with multiple agencies' goal of maximizing health-related utility. However, agencies have objectives other than maximizing utility, and it is possible that patients' preferences may align with these objectives. For instance, agencies often place a greater weight on health gains in the context of severe diseases or end-of-life care, which may mirror the variation in patients' valuation of survival. If so, incorporating PP into QALY estimation may present a mechanism for agencies to operationalize their normative positions. Further research on the variation in PP and how this compares with agency goals should test this possibility.

In the meantime, and regardless of the PP use case, scientific advice between the sponsor and the HTA agency provides an opportunity to align on the appropriate use of PP, as well as the appropriate study design to generate PP for this purpose (18).

Other uses of PP face greater challenges. Normative obstacles face the use of PP to determine the weight that should be given to benefits experienced by different patient groups, one of the roles given to PP as part of MCDA. Normative challenges are also raised to basing opportunity cost on patients' WTP. The exception would be instances where the patient pays for treatments out of their own pocket, though concerns remain about the external validity of such estimates of WTP.

As PP use cases are developed, it will also be important to consider how heterogeneity in patients' preferences will influence reimbursement decisions. This will depend on the use case and the extent of the heterogeneity. Understanding the implications of preference heterogeneity is integral to some use cases, such as "predicting choices," in which a consideration of preference heterogeneity is necessary to generate accurate estimates of the uptake of interventions. In other use cases, such as "endpoint selection," the implications will depend on the extent of heterogeneity—for instance, if some cancer patients prioritize overall survival, whereas others prioritize quality of life, this may point to different endpoints being needed to capture what matters to patients. Finally, in other use cases, such as "utility estimation," preference heterogeneity may have implications for which patient groups have access to an intervention, if this implies that the intervention is cost-effective for some patients but not others. In the extreme, this could be the basis for personalized cost-effectiveness. In this instance, it will be important for HTA agencies to guide the conduct of preference studies to ensure that they generate the appropriate insights into preference heterogeneity. This should include a consideration of how such insight can be operationalized—requiring heterogeneity to be attributable to patient characteristics by which it would be appropriate to determine access.

This review assumed that robust PP data are available for use in HTA decision making and did not concern itself with the methodological or practical challenges posed by the elicitation of PP. Multiple such challenges exist, not least the selection of an appropriate preference elicitation method, and the extent to which values can be transferred across patients and/or geographies. We would refer the reader to other recent reviews for more details on these challenges (8).

In summary, PP can add value to HTA by supporting the selection, interpretation, and valuation of endpoints and other treatment benefits. Efforts to integrate PP into HTA would be facilitated by greater guidance from agencies on when and how data on what matters to patients might support HTA and through further research on how integrating PP into economic evaluation would help HTA agencies to meet their goals.

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