



COST-EFFECTIVENESS OF INSULIN ANALOGUES VERSUS HUMAN INSULIN IN TYPE 2 DIABETES

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1. INTRODUCTION

Insulin therapy is a long-term commitment for many people with type 2 diabetes. As beta-cell function declines and glucose targets are missed on oral agents, most patients are eventually offered a basal insulin, and a sizeable group goes on to mealtime or premixed regimens [1, 2]. Higher glycaemia goes with more microvascular complications, intensive glucose control reduces them, and benefits in the large United Kingdom trial persisted for years after the original treatment arms had converged [3, 4]. Insulin is therefore

Abstract

Insulin analogues cost considerably more than human insulin, and whether the extra spending buys value in type 2 diabetes is still debated. This review synthesises published clinical trials, meta-analyses, health economic evaluations and guidelines that compare analogue and human insulin regimens. It covers the clinical basis of the comparison, modelling methods and their assumptions, reported cost-effectiveness findings, the role of hypoglycaemia and adherence, and price and access issues across health systems. The review reports no new data or economic model. The literature shows similar glycaemic control but somewhat less hypoglycaemia with analogues, and cost-effectiveness depends heavily on assumptions, prices and the patient group considered.

both an old and an indispensable drug, and decisions about which type to choose are repeated across millions of patients. Most of

these patients are also managed in primary care, where prescribing habits, formulary rules and the cost of consumables, not trial evidence alone, decide which insulin is chosen. Practical guidance on starting and intensifying insulin therapy reflects this, and it stresses simple regimens that patients can follow [1, 5].

The choice is no longer simple. Human insulin, in its soluble and isophane (NPH) forms, was joined from the late 1990s by rapid-acting and long-acting analogues designed to shift the timing or the shape of insulin action [6, 7, 8]. Analogues cost more, often by a factor of two or three, and their clinical advantages in type 2 diabetes are smaller than in type 1 disease [9, 10]. Payers, guideline writers and prescribers have therefore asked a fair question: are the improvements worth the additional price, and for which patients? For health systems under budget pressure the issue is not abstract. Insulin and its delivery devices make up a large share of the spending on glucose-lowering drugs, and the proportion attributable to analogues has grown steadily in many countries, even as the evidence for superiority in type 2 diabetes remained modest [11, 12]. Pharmacists, who manage formularies and dispense these products, are often asked to justify substitutions.

This review addresses that question through published evidence. It reports no new trial, survey or model. It first outlines the clinical comparison, then the methods that economic evaluations use to translate small differences in hypoglycaemia and glycaemic control into costs and quality-adjusted life years, and then the findings of published studies. Later sections turn to hypoglycaemia, adherence, pricing and access. A recurring point is that cost-effectiveness is not a property of a molecule. It depends on the comparator, the price, the health system and the person being treated. The aim is not to rank products. It is to show how the published studies reach their conclusions, so that a reader can judge how far a result from one setting applies to another, and to identify the points at which the current evidence is weakest and where further work would be most useful.

2. CLINICAL BASIS OF THE COMPARISON

Human NPH insulin has a pronounced peak a few hours after injection and a duration that varies widely between injections, which produces a risk of hypoglycaemia overnight when given at bedtime [6, 8]. Long-acting analogues were built to flatten that profile. Glargine forms microprecipitates at the injection site, and detemir binds albumin through a fatty acid chain, giving a longer, smoother and more reproducible effect, with day-to-day variation lower than NPH in clamp studies [8]. Rapid-acting analogues such as lispro, aspart and glulisine are absorbed faster than soluble human insulin, so they can be injected close to meals and act for a shorter time [7]. The practical consequence is that analogues behave more predictably, which helps most when doses are tight to the glucose target. Clamp data, however, describe pharmacology and not outcomes, and the step from a smoother profile to fewer clinical events has to be shown in trials, not assumed [7, 8]. Regulators approved most analogues on non-inferiority of HbA1c, not on superiority.

The key randomised evidence for basal insulin comes from head-to-head trials in patients who had not reached target on oral drugs. In the Treat-to-Target trial, glargine and NPH produced similar HbA1c reductions when titrated to the same fasting glucose goal, but fewer participants on glargine experienced nocturnal hypoglycaemia [13]. A Cochrane review of long-acting analogues against NPH found no clinically important difference in glycaemic control and, at most, a small reduction in symptomatic and nocturnal hypoglycaemia, with limited long-term data on complications or mortality [9]. Other pooled analyses reached a similar conclusion [14, 15]. Trials in which participants titrated insulin by algorithm to a fixed fasting target tend to equalise HbA1c, which means that any benefit appears as less hypoglycaemia at a given control and not as lower glucose. The 4-T study took a different approach, comparing biphasic, prandial and basal analogue strategies in a pragmatic design over three years, and found that all three achieved similar control while differing

in hypoglycaemia and weight gain [16].

Newer basal insulins have extended the argument. Degludec has a half-life of about a day, and in randomised comparison with glargine 100 units/ml it lowered the rate of hypoglycaemia in patients at high cardiovascular risk and in those switched from other basal insulins, without any rise in cardiovascular events [17, 18]. Glargine 300 units/ml produced less nocturnal hypoglycaemia than glargine 100 units/ml at similar HbA1c in a pooled analysis of type 2 diabetes studies [19]. These second-generation products are priced above first-generation analogues, so a further question arises about the incremental value of each step. It is notable that the cardiovascular outcome data for degludec involved a comparator that was itself an analogue, so the trial says nothing directly about the value of analogues over human insulin. For the economic question, the relevant contrast is usually NPH or soluble human insulin, a comparison that has attracted fewer large modern trials than comparisons among the analogues [9, 17, 20].

3. METHODS OF ECONOMIC EVALUATION

Cost-effectiveness analysis compares the extra cost of one strategy with the extra health it produces, usually expressed as cost per quality-adjusted life year (QALY) gained. This ratio is then compared with a threshold that reflects what the health system is willing, or able, to pay [21, 22]. For insulin in type 2 diabetes the health gains are small and the time horizon is long, so analysts nearly always use simulation models, not trial-based analyses, to extrapolate from a difference in HbA1c or hypoglycaemia to lifetime complications and costs [23, 24]. The choice of comparator matters as much as the choice of method. An evaluation in which analogue is compared with NPH answers a different question from one comparing it with soluble human insulin taken at mealtimes, and a model of switching existing patients differs again from one of starting treatment in people new to insulin. Careful authors specify the decision problem first and describe the population, the starting HbA1c and the dose assumed for each regimen [21, 25].

The two best-known diabetes models are the CORE Diabetes Model and the UKPDS Outcomes Model. Both use equations derived from long-term cohorts to predict events such as myocardial infarction, renal failure, retinopathy and amputation from risk factors, and both let the user add the costs and utility effects of events [23, 24]. Models of this kind are only as good as their inputs. A small difference in HbA1c carried over thirty years can generate sizeable benefits that are not backed by direct trial evidence, and the choice of risk equations can alter results considerably. Another recurring problem is that risk equations were developed in older cohorts who received treatments that differ from those of today. Cardiovascular risk in people with type 2 diabetes has fallen with statins and blood pressure control, so models calibrated on old data can overstate both the baseline risk and the benefit of any modest improvement in glycaemic control.

Perspective, time horizon and discounting also shape the numbers. A health system perspective counts only direct medical costs, while a societal perspective adds productivity and care costs. Discount rates differ between countries, and the weight put on future benefits matters when most gains arrive decades after treatment starts [21, 25]. Reporting standards such as CHEERS were developed to make these choices visible, so that readers can see what was assumed and what was tested in sensitivity analysis [25]. Studies that skip such detail are difficult to compare, and they are not rare. Sensitivity analysis is the part of the paper that deserves most attention. One-way analyses show which inputs matter, and probabilistic analyses show the chance that a strategy is cost-effective at a given willingness to pay. In analogue studies the hypoglycaemia rate ratio, the cost per severe event and the utility penalty usually emerge as the leading drivers, ahead of drug price differences in some analyses and behind them in others [10, 26].

Thresholds deserve their own comment. The familiar benchmark of fifty thousand US dollars per QALY has a history rather than a firm empirical basis, and it has been criticised for decades [22]. Reviews of how thresholds have been derived show that estimates based

on what health systems actually displace tend to sit well below the figures used in many appraisals, and cross-country estimates suggest that thresholds in low-income countries are far lower still [27, 28]. A result of cost-effective in one analysis can therefore be unaffordable in another country even when the model inputs are identical, which limits what can be transferred between settings. Transferability between countries is a related point. Unit costs, patterns of care, risk profiles and thresholds all differ, so a model built on one health system needs adaptation before use in another, and a few good studies explicitly rerun their model with local data [27, 28].

4. PUBLISHED COST-EFFECTIVENESS FINDINGS

Systematic reviews of economic evaluations give a cautious picture. A review of studies of insulin analogues found that the evidence for cost-effectiveness was stronger in type 1 diabetes than in type 2, where results were mixed and highly dependent on the hypoglycaemia assumptions [10]. A health technology assessment that combined a systematic review with modelling found limited grounds for routine use of long-acting analogues in all patients with type 2 diabetes, because the clinical advantage was small relative to the price premium [26]. These conclusions rest on prices of the time, which have since moved in both directions. It is helpful to recall that the evaluations on file were assembled over a period in which analogue patents expired, biosimilars appeared and discounts were negotiated. Results from 2005 to 2010 therefore describe a market with large price gaps, and more recent work, where available, may paint a different picture. The direction of results is often stable even when the size of the ratios is not [10, 26].

Individual model-based studies produce a wider range. Where analogue prices are modest and hypoglycaemia is given a high cost and quality-of-life penalty, analysts have reported analogues as cost-effective or even dominant, since fewer events offset the drug cost [10, 29, 30]. Where analogues cost much more and the difference in hypoglycaemia is small, incremental ratios exceed usual

thresholds [26]. Sponsorship patterns also matter, because many published models were funded by manufacturers and tend to report favourable ratios for the sponsor's product, even though the methods are usually sound [10, 26]. Claims of dominance, meaning lower cost and better outcomes, deserve special care. They arise when the avoided events outweigh the drug acquisition cost across the model horizon, and they depend on assumptions about hypoglycaemia that few trials were designed to test. Reviewers have asked that the key assumptions be listed beside the headline result, which seems a reasonable standard to apply to any claim of this kind [10, 25, 26].

Findings are clearer for specific subgroups than for type 2 diabetes as a whole. Analogues look most defensible in patients with recurrent or severe hypoglycaemia on human insulin, with a history of nocturnal events, with impaired awareness, in older or frail people living alone, and in those who depend on a carer to inject [1, 31, 32]. For these groups the avoided events are costlier and carry a larger loss of quality of life. For a younger person newly starting basal insulin with no hypoglycaemia history, the gain is smaller. The main findings are collected in table 1 and their distribution by type of evidence is shown in fig. 1. Patients on multiple daily injections or premixed insulin are a separate case. Rapid-acting analogues act faster and last for a shorter time than soluble human insulin, and they allow injection at the start of a meal, but their effect on postprandial glucose and late hypoglycaemia is modest in type 2 disease [7, 16].

Second-generation basal analogues have not yet settled the matter. Modelling work on degludec and on glargine 300 units/ml generally reflects the trial reductions in hypoglycaemia, but the strength of the economic case varies with the comparator and with how a model treats the benefit beyond the first year [17, 18, 19, 26]. Since the clinical differences are modest, long-term modelled gains are fragile. A fair reading is that these insulins may be good value for people at particular risk of nocturnal events and doubtful value as a default for everyone.

For most health systems, the net result is a conditional recommendation. If prices are close, analogues are reasonable. If prices differ widely, the case needs hypoglycaemia risk to justify it. Both statements follow from the same models, run with different inputs, which explains why national bodies can reach different decisions from the same published literature [1, 26, 32].

Table 1: Published evidence comparing insulin analogues with human insulin in type 2 diabetes

Source / comparison	Reported finding	Ref.
Treat-to-Target trial glargine versus NPH	Similar HbA1c at target titration; less nocturnal hypoglycaemia with glargine.	[13]
Cochrane review long-acting analogues versus NPH	No clinically important HbA1c difference; small reduction in hypoglycaemia; long-term data scarce.	[9]
Meta-analyses glargine and detemir versus NPH	Lower hypoglycaemia, mainly nocturnal, with similar glycaemic control.	[14, 15]
Degludec versus glargine U100 high-risk and switch trials	Lower hypoglycaemia without excess cardiovascular events.	[17, 18]
Glargine 300 versus 100 units/ml pooled analysis	Modest reduction in nocturnal hypoglycaemia at similar HbA1c.	[19]
Review of economic evaluations insulin analogues	Stronger case in type 1; mixed results in type 2, sensitive to hypoglycaemia values.	[10]
Health technology assessment systematic review and model	Limited support for routine analogue use at prevailing price premiums.	[26]
Cost of hypoglycaemia US economic analysis	Severe events cost several times more than non-severe ones.	[29]
English national guideline type 2 diabetes	NPH first choice; analogues in defined circumstances such as recurrent hypoglycaemia.	[32]
Consensus guidance AACE and IDF	Analogues may reduce hypoglycaemia; cost and availability to be weighed in choice.	[1, 2]
Access surveys low- and middle-income countries	Human insulin more available and affordable than analogues.	[33, 34]

A different line of evidence considers delivery. Prefilled pens and fine needles are associated with convenience and fewer dosing errors, and the shift from vials to pens accompanied the spread of analogues, which makes it difficult to separate the effect of the molecule from that of the device [35, 36]. Where human insulin is also supplied in pens, as in several European systems, the gap in cost is narrower and the device argument weaker. Authors of economic models rarely separate the two, and they should. Pens may also improve accuracy in the elderly and those with poor vision or dexterity, which is not captured in costs.

5. HYPOGLYCAEMIA, ADHERENCE AND DOWNSTREAM COSTS

Hypoglycaemia drives much of the economic argument, so its measured costs deserve scrutiny. Severe events require help from another person or emergency care, and they produce ambulance calls, admissions and, in some cases, falls and injuries or cardiovascular events [29, 37]. Cost analyses from the United States show that a severe episode is several times more expensive than a mild one, and that the absolute cost per patient depends on the frequency of severe events, which is low in most trial populations [29]. Mild and nocturnal episodes cost little directly but disturb sleep, work and confidence. Cost estimates differ between countries, and most come from the United States. Even there, the proportion of patients with a severe episode in a year is small, so the budget impact of hypoglycaemia is concentrated in a minority of high-risk individuals. This is the strongest argument for targeting, and it explains why guideline writers tend to focus on patients with a history of events [29, 32, 37].

Fear of hypoglycaemia changes behaviour. Patients who have had a frightening episode may reduce doses, skip injections, or run their glucose higher than advised, so the avoided harm is not only the event itself but the undertreatment that follows [30, 37]. Models that include a disutility for the fear of hypoglycaemia raise the apparent value of analogues, while those limited to events do not. Evidence that analogues improve persistence and adherence is mixed, with

cohort studies suggesting some benefit and randomised trials usually showing none [9, 36, 37]. Utility estimates for hypoglycaemia come mostly from time trade-off and standard gamble exercises in population samples, and from regression of patient-reported outcomes on event counts [30, 31]. They are plausible but not precise. Since analogues act on the most frequent and least severe events, models must multiply a small utility loss by a large number of events, and the result is sensitive to both figures.

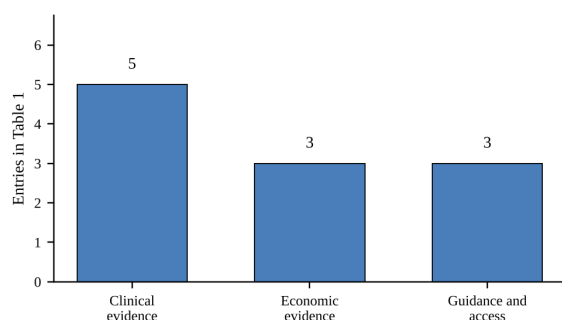


Fig. 1: Number of entries in table 1 by type of evidence

Weight is a smaller part of the story in type 2 diabetes. Some long-acting analogues, especially detemir, were associated with a little less weight gain than NPH in trials, but differences were generally small and did not translate into large modelled benefits [9, 14]. Complication costs, in contrast, dominate any lifetime model: dialysis, amputation, blindness and cardiovascular events are far more expensive than insulin itself, which is why even a very small shift in glycaemic control can produce a large modelled difference [3, 4, 23, 24]. The argument for analogues rests, in practice, on safety and tolerability and not on better control. Practical differences between regimens can also affect adherence indirectly. Twice-daily NPH needs a second injection and a stricter meal pattern, whereas a once-daily analogue may fit more easily around work and family life [6, 35]. Evidence that this converts into measurable cost savings through better control is thin, though patient preference studies often favour simpler schedules.

Real-world data complement trials but carry their own biases. Patients given analogues in routine practice tend to be those with more difficult diabetes, more hypoglycaemia, or better-off health insurance, so naive

comparisons make analogues look worse or better depending on which factor dominates [1, 37]. Studies using routinely collected claims or records need strong adjustment, and even then the answer may reflect prescriber choice. Randomised pragmatic trials of analogue against human insulin, with costs collected alongside, would be the most direct way to resolve the issue, yet they are rarely funded. Some of the apparent benefit in observational work reflects the type of patient who receives a new product.

6. PRICES, ACCESS AND POLICY

Price is the variable most likely to change a conclusion, and prices change often. Expenditure on insulin in the United States rose steeply over the last decade, and out-of-pocket costs for patients increased as well, driven largely by newer, more expensive formulations [11, 12]. In many European systems, prices are negotiated and lower, and analogue use is high. Elsewhere, an analogue that is cost-effective at one price is not at another, so a published ratio can become obsolete within a few years of publication [11, 26]. Rebates and confidential discounts complicate matters further. The price paid by a hospital or insurer is often below the list price, and these negotiated prices are rarely public, so researchers use list prices that overstate actual spending, and payers know that published ratios are only an approximation of their own position [11, 12].

Guidelines reflect these trade-offs. The English national guideline recommends human NPH insulin as the first choice for starting basal therapy and reserves analogues for defined situations, such as when a carer injects, when hypoglycaemia is recurrent or problematic, or when a patient would otherwise need twice-daily injections [32]. International guidance takes a broader view, acknowledging that analogues may reduce hypoglycaemia while saying that cost and availability should shape the choice [1, 2]. The guidance is consistent in direction even if it differs in emphasis. These recommendations are not identical across guidelines, but they converge on a principle of individualisation. Cost is stated openly as a factor, and the choice is tied to hypoglycaemia history, to injection support

and to the patient's own priorities [1, 2, 32]. Local formularies often turn this into a short list of conditions that must be met before an analogue is prescribed.

In low- and middle-income countries the question is different, because basic access is the problem. Surveys of insulin and wider medicine availability and affordability describe frequent stock-outs, high patient payments, and a much wider availability of human insulin than of analogues in public facilities [33, 34, 38]. When money is limited, a policy that diverts funds to analogues may reduce the number of people who can obtain any insulin at all. In that setting the efficient choice is almost always to secure reliable supply of human insulin and syringes first, and to reserve analogues for the highest-risk patients. The global burden gives the argument weight. Diabetes prevalence is rising fastest in low- and middle-income countries, where most people with diabetes live, and insulin is on the essential medicines list in its human forms [33, 38]. Out-of-pocket payment is common, and monthly insulin costs can consume a large share of household income, which leads to rationing and dangerous underdosing [33, 34].

Biosimilar insulins add further complexity. Follow-on glargine and other products are now licensed in several markets at lower prices, and they may narrow the cost gap and change economic conclusions [36]. Their regulatory pathway differs from that of generic small molecules because insulin is a complex protein, and clinicians have asked for post-marketing surveillance. Procurement strategies such as tendering and reference pricing can change cost-effectiveness more than any clinical refinement, which is a reminder that the policy environment is as important as the evidence. Some countries have responded with local manufacture, pooled procurement or price caps, measures that are likely to change the economics more than any new clinical trial. Evaluations of these policies are only beginning to appear, and generalisable evidence is limited [34, 36].

Equity considerations run in both directions. Restricting analogues to selected groups could deny some patients a safer regimen,

while liberal use could crowd out spending on other proven interventions such as retinal screening, foot care and blood pressure control, which are often highly cost-effective themselves [21, 27]. Choices should therefore be made in the context of the whole diabetes budget, not insulin alone. Stakeholder involvement, including patient groups, can help make such trade-offs more transparent. Transparent processes, including published criteria and appeal routes, make restrictions on analogue prescribing easier for clinicians and patients to accept, and they allow the policy to be revised as prices fall.

7. UNCERTAINTY AND LIMITATIONS

The evidence base has several weaknesses. Few trials compared analogues with human insulin in type 2 diabetes for longer than a year, and none were powered for complications, so economic models borrow their long-term links from observational cohorts and from trials of glucose control that did not randomise insulin type [3, 4, 9, 23]. Differences in hypoglycaemia definition across trials complicate pooling, and the extent of blinding varies. Probabilistic sensitivity analysis, where reported, often shows uncertainty bands wide enough that a result on either side of the threshold is plausible [10, 25]. Heterogeneity of treatment effect is a further gap. The average reduction in hypoglycaemia hides large differences between patients, but few trials report subgroup results by age, kidney function, duration of insulin use or baseline risk, so economic models apply a single relative effect to everyone [9, 18]. Targeting would be easier if predictors of benefit were known.

The literature also has a context problem. Most economic evaluations come from a handful of high-income countries and use local costs, so results do not transfer neatly [27, 28, 33]. Changing prices, new biosimilars and new classes of glucose-lowering drug, including agents that lower weight and cardiovascular risk, shift the position of insulin in treatment pathways and alter the relevant comparator [1]. A study that compares analogues with human insulin may already ask a narrower question than the one that clinicians face when deciding whether insulin is the next step at all. Another

consideration is time. Insulin analogues were introduced before the era of continuous glucose monitoring and newer glucose-lowering drugs, and the treatment of type 2 diabetes has changed since. When agents with weight and cardiorenal benefit are used earlier, fewer patients may need insulin, or may need it later and at lower doses, which affects both the likely benefit and the budget impact of analogue choice [1].

Future work could usefully focus on a few things. Trials that record cost, hypoglycaemia including mild nocturnal events, adherence and quality of life together, in realistic populations, would supply the inputs that models now guess [9, 18, 31]. Modelling studies should state prices, thresholds and utility sources clearly, test them in scenario analyses, and be open about funding [21, 25]. Decision tools that identify which patients are likely to benefit from an analogue would help to turn an average result into a targeted policy. Reporting should follow accepted standards and include enough detail for others to replicate results. Data sharing of trial-level hypoglycaemia events and costs would help modellers who currently rely on published summary figures. Independent funding of at least some comparative economic studies would reduce concern about sponsor bias [21, 25, 26].

A final limitation concerns this review itself. It is a narrative synthesis, not a systematic search, and it cannot guarantee that every relevant economic evaluation is covered. Readers who need a specific cost-effectiveness estimate for their own setting should examine the original models and update them with local prices, and they should note that costs quoted in older studies reflect market conditions that no longer apply [10, 11, 26]. Readers should treat the numbers reported here as illustrations of direction and not as inputs. Some of the sources cited were available only as summaries, and several of the economic evaluations are now more than a decade old.

8. CONCLUSION

Published evidence indicates that insulin analogues and human insulin give broadly similar glycaemic control in type 2 diabetes,

with analogues producing somewhat less hypoglycaemia, especially at night [9, 13, 14, 15]. Economic evaluations convert that modest advantage into widely varying cost-effectiveness estimates, depending on the price premium, the cost and disutility attached to hypoglycaemia, the model, and the population considered [10, 26, 29]. Because most of the variation in published ratios comes from assumptions and not from clinical differences, readers should look first at the inputs that drive each result.

A sensible reading is selective use. Human insulin remains a reasonable and affordable starting point for many patients, while analogues are best directed to people with recurrent or severe hypoglycaemia, dependence on a carer, or other particular risk [1, 2, 32]. In settings where access to any insulin is uncertain, securing basic supply comes first [33, 34]. Better long-term trials with costs recorded, transparent models and updated price data would sharpen these judgements considerably.

9. ABBREVIATIONS

ADA-American Diabetes Association, CHEERS-Consolidated Health Economic Evaluation Reporting Standards, EASD-European Association for the Study of Diabetes, HbA1c-Glycated haemoglobin, NPH-Neutral protamine Hagedorn (isophane insulin), QALY-Quality-adjusted life year, CORE-Center for Outcomes Research (diabetes model), UKPDS-United Kingdom Prospective Diabetes Study

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Nil

11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

13. REFERENCES

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