CALIFORNIA TECHNOLOGY ASSESSMENT FORUM℠

Insulin Degludec (Tresiba®, Novo Nordisk) for the Treatment of Diabetes

February 12, 2016

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CTAF Overview

- Core program of the Institute for Clinical and Economic Review (ICER)
- Goal: Help patients, clinicians, insurers, and policymakers understand and apply evidence to improve the quality and value of health care
- Deliberation and voting by CTAF Panel – independent clinicians, methodologists, and public representatives
- Supported by grants from the Blue Shield of California Foundation, the California HealthCare Foundation, and the Laura and John Arnold Foundation

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Agenda

- **Public Meeting Convened, Topic Overview** | 9:00 am
- **Presentation of the Evidence and Economic Modeling, Q&A** | 9:05 – 9:50 am (Dr. Jeff Tice and Dr. Rick Chapman)
- **Public Comments** | 9:50 – 10:20 am
- **CTAF Deliberation and Votes** | 10:20 – 11:00 am
- **Policy Roundtable Discussion** | 11:00 am – 12:00 pm
- **Reflections from CTAF Panel** | 12:00 – 12:15 pm
- **Lunch** | 12:15 pm
  - **Download meeting materials:** http://tinyurl.com/ctaf-degludec

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Evidence Review

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Disclosures:

I have no conflicts of interest.

Key review team members:

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Dan Ollendorf, PhD
Jed Weissberg, MD
Shanshan Liu, MS, MPH
Elizabeth Russo, MD
Patricia Synnott, MS
Karin Travers, DSc

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Topic in Context

- Diabetes Mellitus (DM): 29 million Americans
  - 95% type 2, 5% type 1
  - Insulin therapy: 6 million
- Intensive management
  - Pre-meal glucose 80-130 mg/dL; HbA1c ≤ 7.0%
  - Decreased retinopathy, nephropathy, neuropathy
  - Increase in hypoglycemic events and deaths from CVD
    - Severe hypoglycemia can lead to seizure, coma, and death

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Definitions of Hypoglycemia

- **Severe hypoglycemia**: requires assistance of another person to administer carbohydrate, glucagon, or other resuscitation
- **Confirmed hypoglycemia**: blood glucose level <70 mg/dL
- **Nocturnal hypoglycemia**: hypoglycemia at night
- **Clinically significant improvement**: 10-20% reduction in severe events or a 30% reduction in all events

From ADA Workgroup on Hypoglycemia

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Insulin Degludec (Tresiba)

- Long-acting insulin (U100 and U200 formulations)
  - Half-life approximately 25 hours: once daily to maintain a steady level
- FDA-approved in September 2015
  - To improve glucose control in Adults with type 1 or type 2 DM
- Other long acting insulins
  - Insulin detemir (Levemir)
  - Insulin glargine U100 (Lantus, Basaglar)
  - Insulin glargine U300 (Toujeo)

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Methods

- Systematic review following PRISMA guidelines
- Target population (FDA indication):
  - Adults with type 1 or 2 diabetes
- Intervention:
  - Insulin degludec
- Comparator:
  - Any long acting insulin
- Outcomes
  - Cardiovascular events, microvascular events, HbA1c, hypoglycemia, other adverse events

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Included Studies

- 8 industry-sponsored Phase III RCTs comparing insulin degludec to another long-acting insulin
  - 3 basal-bolus therapy type 1 DM
  - 4 basal-only therapy type 2 DM
  - 1 basal-bolus therapy type 2 DM
- All open-label "non-inferiority" trials
  - Treat to target AM fasting glucose 70-90 mg/dL
  - Long-acting insulin administration
    - Insulin degludec in the evening
    - Insulin glargine at any time, but always the same time
  - Primary outcome: HbA1c upper bound of 95% CI < 0.4%
  - Secondary outcomes: overall, severe, and nocturnal hypoglycemia

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Between-group Differences in HbA1c

Trial	Comparator	Change in HbA1c* (Degludec – Comparator)
Type 1 DM		
Heller 2012	Glargine U100	-0.01% (-0.14 to 0.12)
Davies 2014	Detemir	-0.09% (-0.23 to 0.05)
Mathieu 2013	Glargine U100	**0.17% (0.04 to 0.30)**
Type 2 DM Basal-only		
Zinman 2012	Glargine U100	0.09% (-0.04 to 0.22)
Gough 2013	Glargine U100	0.04% (-0.11 to 0.19)
Onishi 2013	Glargine U100	0.11% (-0.03 to 0.24)
Meneghini 2013	Glargine U100	**0.2 (NR)**
Type 2 DM Basal-bolus		
Garber 2012	Glargine U100	0.08% (-0.05 to 0.21)

* A negative number indicates a greater reduction in HbA1c with insulin degludec

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Meta-analysis for Hypoglycemia

Patient Population	Total Hypoglycemia Rate Ratio (95% CI)	Nocturnal Hypoglycemia Rate Ratio (95% CI)	Severe Hypoglycemia Rate Ratio (95% CI)
Type 1 DM	1.10 (0.96, 1.26)	0.83 (0.69, 1.00)	1.12 (0.68, 1.86)
Type 2 DM Basal-only	0.83 (0.70, 0.98)*	0.64 (0.48-0.86)*	0.14 (0.03, 0.70) †
Type 2 DM Basal-bolus	0.82 (0.69, 0.99)*	0.75 (0.58, 0.99)*	>1.0

* p<0.05
† Likely an error. It is identical to an outlier from one trial only.
The meta-analysis does not report that the other trials were excluded.

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Major Adverse Cardiovascular Events (MACE)

- Higher MACE rates for patients treated with insulin degludec were a concern of the FDA when it initially declined to approve the drug in 2012
  - 70/5794 versus 21/3461
  - RR 1.67, 95% CI 1.01 to 2.75
- Interim data from an ongoing trial were submitted to FDA prior to its decision to approve degludec in 2015
  - These data have not been made public

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Effectiveness: Controversies and Uncertainties

- Primary uncertainty: lack of peer-reviewed data on MACE
- Major benefit of insulin degludec is lower rates of nocturnal hypoglycemia, but the clinical impact of these events is controversial
- Non-inferiority goal was met, but the change in HbA1c consistently greater with glargine U100
- Variation in timing of glargine U100 administration may impact nocturnal hypoglycemia

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Effectiveness: Summary

- Moderate certainty of small comparative net health benefit in comparison to insulin glargine/detemir in patients with type 2 DM on basal-only or basal-bolus insulin regimens
  - Based on “non-inferior” glycemic control and consistent findings of reduced nocturnal hypoglycemia
- Greater uncertainty in patients with type 1 DM, as no consistent and statistically significant reductions in hypoglycemia observed
- Residual concerns about potentially higher rates of MACE in all subpopulations
- Comparative clinical effectiveness of insulin degludec judged “**promising but inconclusive**” using the ICER Evidence Rating Matrix

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Public Comments Received

- HbA1c reduction nominally greater with comparator insulin than with insulin degludec
- The definition of confirmed hypoglycemia (<56 mg/dL) is not standard
- The timing of insulin administration was always in the evening for insulin degludec, but was variable for insulin glargine
- The target AM glucose level was unusually tight
- Differentiate between glargine U100 (Lantus), which was the comparator and glargine U300 (Toujeo)

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Incremental Costs Per Outcomes Achieved

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Director of Health Economics
Institute for Clinical and Economic Review

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Disclosures:

I have no conflicts of interest.

Key modeling team members:

Dan Ollendorf, PhD

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Research Question

- What is the cost-effectiveness of insulin degludec vs. insulin glargine U100 in:
  - Patients with type 1 DM
  - Patients with type 2 DM on basal-only regimens
  - Patients with type 2 DM on basal-bolus regimens

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Methods

- Used UKPDS Outcomes Model v.2
  - Added hypoglycemia sub-model
- Population: Adults ages 18 years and older with type 1 DM or type 2 DM, considered as separate populations
  - UKPDS evaluated patients with type 2 DM only
  - Type 1 DM cohort modeled by setting age & other patient characteristics consistent with those reported in type 1 DM insulin degludec trials
- Payer perspective: direct health care costs only
- Lifetime horizon

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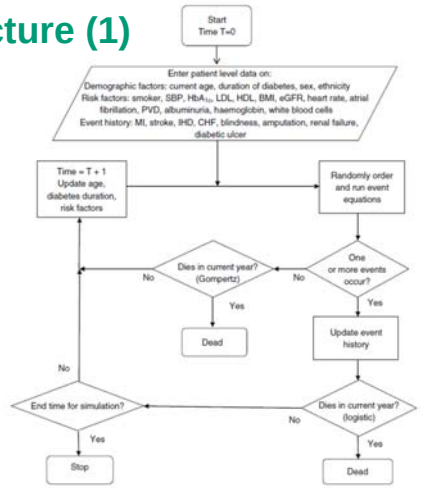
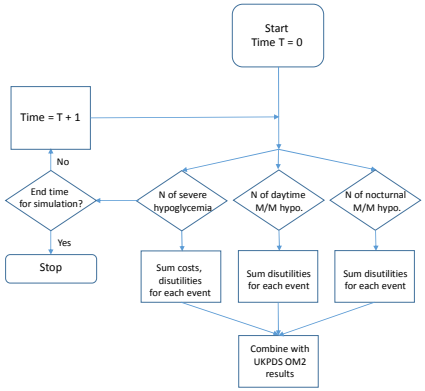
Model Structure (1)

UKPDS OM2



Model Structure (2)

Hypoglycemia Submodule



Key Assumptions

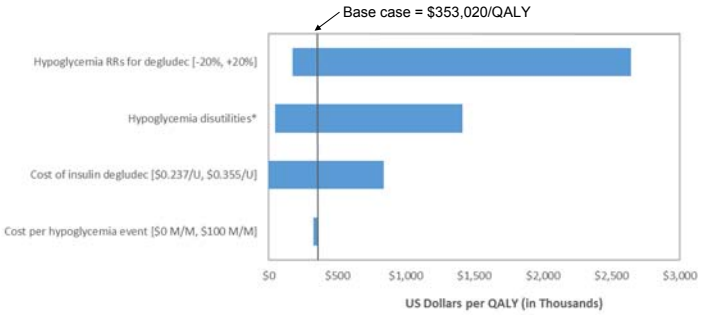
- Non-inferiority trials, so no comparisons of glycemic control & extrapolation to downstream micro-/macro-vascular complications
- Primary effect: avoided mild/moderate hypoglycemic events in type 2 DM
  - Short-term reduction in health-related quality of life for each event (different for daytime, nocturnal, severe)
  - Cost for each severe event (no cost assumed for mild/moderate events)
  - Note: No significant differences in hypoglycemia for type 1 DM patients

Results: Base Case

	Type 2 DM Basal-only		Type 2 DM Basal-bolus	
	QALY	Total Costs	QALY	Total Costs
Insulin glargine U100	11.779	$109,609	10.312	$217,405
Insulin degludec	11.813	$121,631	10.549	$256,903
Increment (insulin degludec – insulin glargine U100)	0.034	$12,022	0.237	$39,498
Cost/QALY		$353,020		$166,644

Note: Cost/QALY could not be calculated for type 1 DM because there were no QALY differences under our base case assumption of no difference in hypoglycemia between insulin degludec and insulin glargine U100.

Results: One-way Sensitivity Analyses (Type 2 DM Basal-Only)



*Hypoglycemia disutilities varied from -0.02357 to -0.00076 for daytime mild/moderate hypoglycemia, -0.038426 to -0.00124 for nocturnal mild/moderate hypoglycemia, and -0.020 to -0.005 for severe hypoglycemia.

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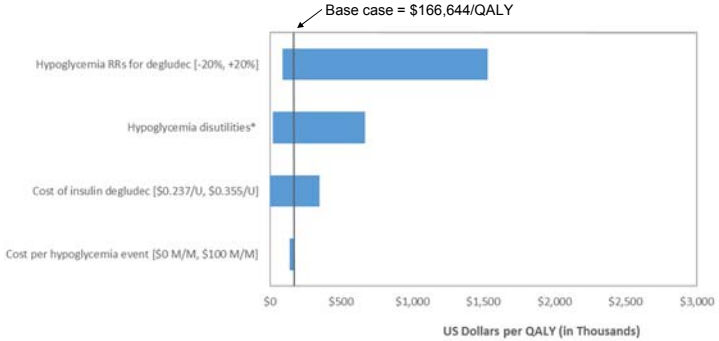
Results: One-way Sensitivity Analyses (Type 2 DM Basal-Bolus)



*Hypoglycemia disutilities varied from -0.02357 to -0.00076 for daytime mild/moderate hypoglycemia, -0.038426 to -0.00124 for nocturnal mild/moderate hypoglycemia, and -0.020 to -0.005 for severe hypoglycemia.

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Results: Threshold Analysis for Annual Cost of Insulin Degludec

ICER	Type 1 DM	Type 2 DM Basal-only	Type 2 DM Basal-bolus	Total (Weighted Average)
$50,000/QALY	$2,688*	$4,801	$12,878	$6,850
$100,000/QALY	$2,688*	$4,914	$13,683	$7,006
$150,000/QALY	$2,688*	$5,025	$14,498	$7,154
List Price Annual Cost	$2,873	$5,486	$14,765	$7,800

*Insulin glargine U100 cost as reference price; thresholds could not be calculated, as no clinical differences were assumed for the base-case.

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Results: Scenario Analysis

Using point estimates for hypoglycemia events, HbA1c, and weight change regardless of statistical significance

	Type 1 DM		Type 2 DM Basal-only		Type 2 DM Basal-bolus	
	QALY	Total Costs	QALY	Total Costs	QALY	Total Costs
Insulin glargine U100	12.769	$104,785	11.779	$109,765	10.327	$216,814
Insulin degludec	12.632	$111,248	11.793	$121,401	10.546	$256,859
Increment (insulin degludec – insulin glargine U100)	-0.136	$6,463	0.014	$11,636	0.220	$40,045
Cost/QALY		Dominated*		$807,942		$182,298

*Insulin degludec provides fewer QALYs at higher cost than insulin glargine U100

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Key Model Limitations

- Given non-inferiority nature of the trials, results were sensitive to relative rates of hypoglycemia events, as well as disutility associated with these events
- Limited long-term data on effects of insulin degludec
  - Assumed that effects observed in short-term efficacy trials will continue over lifetime and will remain constant over time
- Need for research examining:
  - Micro- and macro-vascular complications
  - Long-term impact of severe and non-severe hypoglycemic episodes

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Public Comments Received

- Primary analysis does not consider numeric differences in clinical results
- U.S.-specific cost and disutility measures should be used instead of international pooled estimates
- Analysis uses wholesale acquisition cost, which does not factor in negotiated discounts
- UKPDS OM2 model is not appropriate for patients with type 1 DM
- Model considers costs for severe hypoglycemia only
- Hypoglycemia costs and utilities appeared “front-loaded,” and did not seem to be discounted appropriately

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Conclusions

- Use of insulin degludec appears to confer small net health benefits in comparison to insulin glargine in patients with type 1 or type 2 DM, limited to episodes of nocturnal hypoglycemia
- Estimated cost-effectiveness of insulin degludec exceeds commonly-cited thresholds
  - However, achieving levels of value more closely aligned with patient benefit would require relatively modest discounts (8-10%) from current list price

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Potential Budgetary Impact

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Budget Impact: Methods

- Estimated entire candidate populations for treatment:
  - Patients with type 1 DM on basal-bolus regimens = 0.55 million
  - Patients with type 2 DM on basal-only regimens = 3.5 million
  - Patients with type 2 DM on basal-bolus regimens = 1.55 million
  - TOTAL = 5.6 million
- Assumed uptake: 10% by year 5
- Year 5 treated estimates:
  - Patients with type 1 DM on basal-bolus regimens = 55,000
  - Patients with type 2 DM on basal-only regimens = 350,000
  - Patients with type 2 DM on basal-bolus regimens = 155,000
  - TOTAL = 560,000

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Annual Budget Impact Threshold: Methods

- Based on calculations involving:
  - Target for overall health care cost growth (GDP+1%)
  - Number of new drug approvals annually
  - Contribution of drug spending to overall health care spending
- Serves as "policy trigger" for discussion of managing cost of new interventions
- 2015-2016 threshold is $904 million for each new drug

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Budget Impact: Results at 5 Years

Insulin Degludec	Eligible Population (millions)	Number Treated (thousands)	Weighted BI per Patient ($)	Average BI per year (millions)
Type 1 DM	0.55	54.9	$538	$5.9
Type 2 DM Basal-only	3.50	350.1	$2,365	$165.6
Type 2 DM Basal-bolus	1.55	155.2	$7,950	$246.8
Total	5.60	560.3	$3,733	$418.3

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Public Comments Received

- Budget impact analysis uses "arbitrary" thresholds, does not consider value to patients
- Economic analysis of an intervention deemed "inconclusive" is inappropriate.

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Public Comments

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Insulin Degludec (Tresiba®, Novo Nordisk) for the Treatment of Diabetes

Questions for Deliberation

February 12, 2016

Comparative *Clinical Effectiveness* Example Question

For patients with "**condition X,**" is the evidence "**adequate**" to demonstrate that the net health benefits of "**intervention A**" is greater than that of "**comparator B**"?

Yes

No

Care Value Example Question

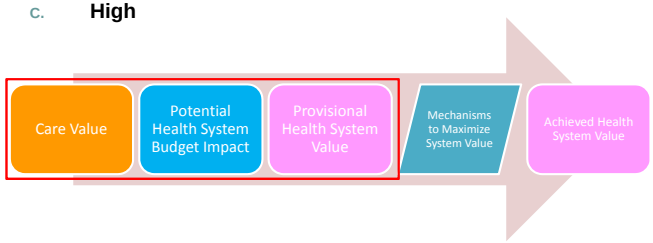
Given the available evidence, what is the care value of "**intervention A**" vs. "**comparator B**"?

A. **Low**
B. **Intermediate**
C. **High**

Health System Value Example Question

Given the available evidence, what is the **provisional health system value** of "**intervention A**" vs. "**comparator B**"?

A. **Low**
B. **Intermediate**
C. **High**



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Practice Question

What is the best Valentine's Day gift?

A. Diamonds
B. Flowers
C. Chocolates
D. Dinner
E. Tickets to a play
F. All of the above

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Type 1 DM: Clinical Effectiveness

Q1. For patients with type 1 diabetes mellitus (DM), is the evidence adequate to demonstrate that the net health benefit of treatment with ***insulin degludec*** is greater than that of treatment with ***insulin glargine U100***?

Yes

No

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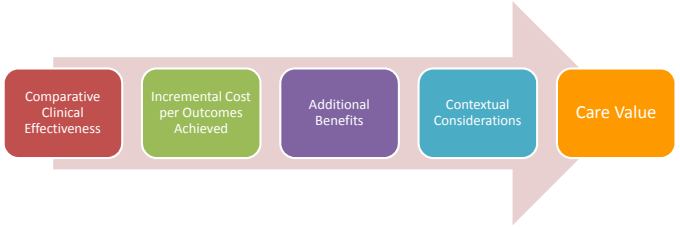
Type 1 DM: Care Value

Q2. Given the available evidence for patients with type 1 DM, what is the care value of treatment with ***insulin degludec*** vs. treatment with ***insulin glargine U100***?

A. Low
B. Intermediate
C. High



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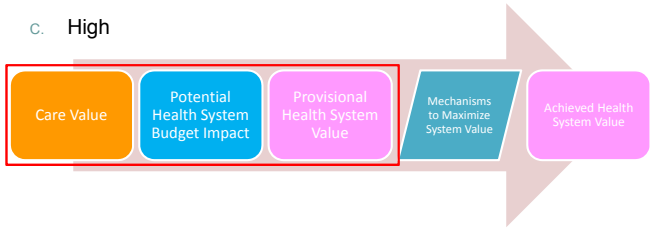
Type 1 DM: Provisional Health System Value

Q3. Given the available evidence for patients with type 1 DM, what is the provisional health system value of treatment with ***insulin degludec*** vs. treatment with ***insulin glargine U100***?

A. Low
B. Intermediate
C. High



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Type 2 DM Basal-only: Clinical Effectiveness

Q4. For patients with type 2 DM on basal-only insulin regimens, is the evidence adequate to demonstrate that the net health benefit of treatment with ***insulin degludec*** is greater than that of treatment with ***insulin glargine U100***?

Yes

No

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Type 2 DM Basal-only: Care Value

Q5. Given the available evidence for patients with type 2 DM who are on basal-only insulin regimens, what is the care value of treatment with ***insulin degludec*** vs. treatment with ***insulin glargine U100***?

A. Low
B. Intermediate
C. High

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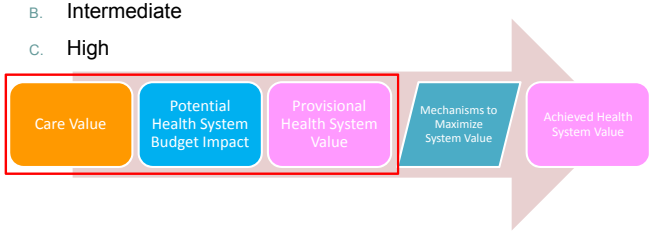
Type 2 DM Basal-only: Provisional Health System Value

Q6. Given the available evidence for patients with type 2 DM who are on basal-only insulin regimens, what is the provisional health system value of treatment with ***insulin degludec*** vs. treatment with ***insulin glargine U100***?

A. Low
B. Intermediate
C. High



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Type 2 DM Basal-bolus: Clinical Effectiveness

Q7. For patients with type 2 DM who are on basal-bolus insulin regimens, is the evidence adequate to demonstrate that the net health benefit of treatment with ***insulin degludec*** is greater than that of treatment with ***insulin glargine U100***?

Yes

No

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Type 2 DM Basal-bolus: Care Value

Q8. Given the available evidence for patients with type 2 DM who are on basal-bolus insulin regimens, what is the care value of treatment with ***insulin degludec*** vs. treatment with ***insulin glargine U100***?

A. Low

B. Intermediate

C. High

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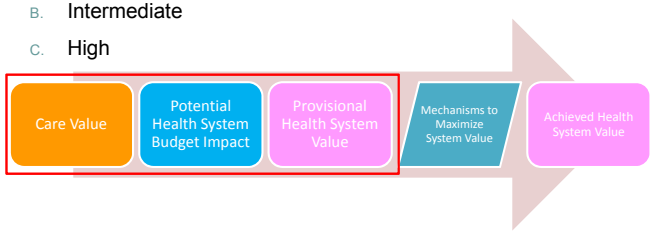
Type 2 DM Basal-bolus: Provisional Health System Value

Q6. Given the available evidence for patients with type 2 DM who are on basal-bolus insulin regimens, what is the provisional health system value of treatment with ***insulin degludec*** vs. treatment with ***insulin glargine U100***?

A. Low

B. Intermediate

C. High



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Policy Roundtable Participants

- **Neal Kohatsu, MD, MPH**, Medical Director, California Department of Health Care Services
- **Elizabeth Murphy, MD, DPhil**, Chief, Endocrinology and Metabolism Division and Director of Diabetes Center for High Risk Populations, San Francisco General Hospital; Professor of Clinical Medicine, UCSF
- **Manuel Quinones, MD**, Internal Medicine and Diabetology, Healthcare Partners - Anaheim
- **Tony Van Goor, MD, MMM, CPE, FACP,** Senior Director, Medical Affairs, Medical Director for Policy and Technology Assessment, Blue Shield of California

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Reflections from CTAF Panel

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Summary and Closing Remarks

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Lunch (12:15 – 12:40)

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