ICER Public Meeting: Evaluating Emerging Therapies for Psoriasis and Endometriosis

July 12, 2018

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INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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Targeted Immunomodulators for Plaque Psoriasis: Effectiveness and Value

Condition Update

Public Meeting – Morning Session
July 12, 2018

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Welcome and Introduction

Why are we here this morning?

The 2016 economic analyses resulted in incremental cost-effectiveness ratios across all agents that were well-aligned with commonly-accepted thresholds for cost-effectiveness. [ICER's Policy] Recommendations encouraged payers to abolish or limit the use of step therapy for these treatments… [Yet,] It is unfortunate that [since the last report] it appears the "access problem" may have gotten worse for individuals living with psoriasis.

- *National Psoriasis Foundation*

The psoriasis field has grown increasingly crowded over the last few years, thanks to a slew of biologic approvals. Novartis' Cosentyx kicked off the party back in early 2015, only to be followed by Eli Lilly's Taltz, Valeant's Siliq and Johnson & Johnson's Tremfya. And therapy areas that see waves of pricey new products tend to be the ones payers target to keep costs down.

- Fierce Pharma, Feb 21 2018

Welcome and Introduction

Why are we here this morning?

- Increasing health care costs affecting individuals, state and federal budgets
- New mechanisms of action often raise questions about appropriate use, cost
- Patients can have difficulty accessing drugs
  - Step therapy protocols
  - Requirements to switch drugs with new insurance
  - High out-of-pocket costs
- Need for objective evaluation and public discussion of the evidence on effectiveness and value
- ICER's first "condition update" – opportunity to evaluate new therapies, update evidence on established medicines, track policy/coverage changes

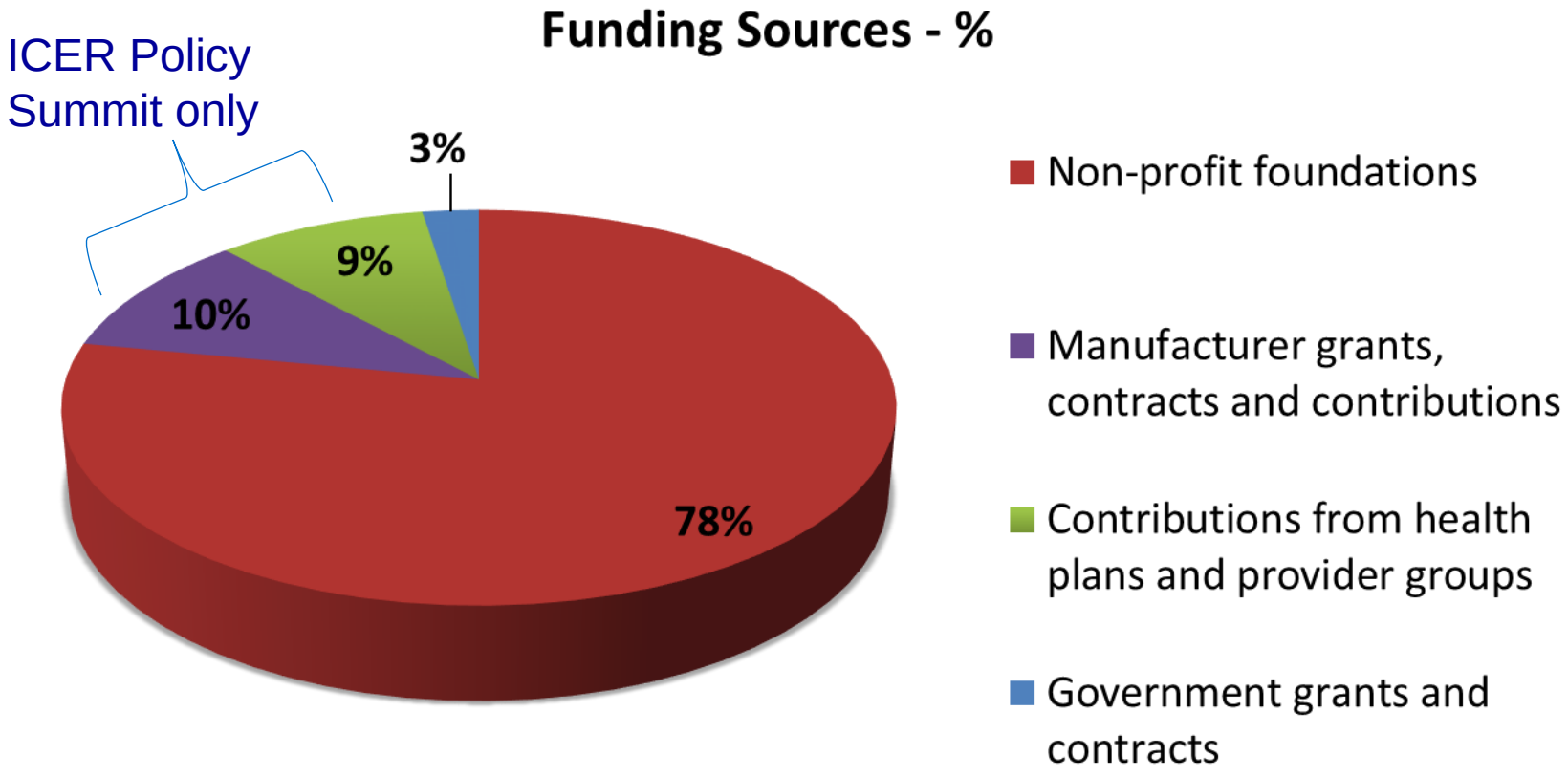
Welcome and Introduction

- New England Comparative Effectiveness Public Advisory Council (CEPAC)

- The Institute for Clinical and Economic Review (ICER)

Sources of Funding, 2018

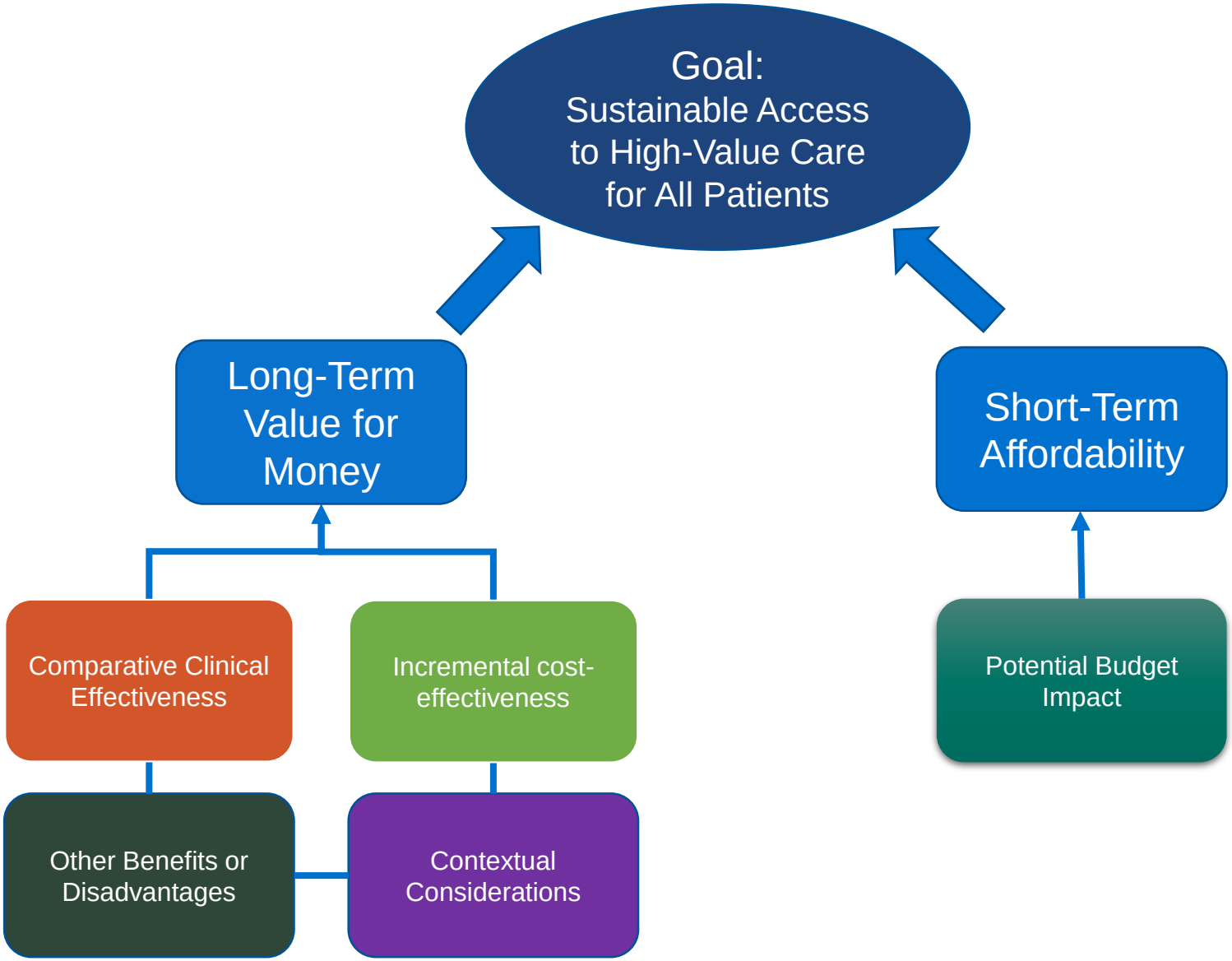
ICER Policy Summit only



Welcome and Introduction

How was the ICER report on therapies for plaque psoriasis developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Washington cost-effectiveness modeling
- Public comment and revision
- Expert report reviewers
  - Dr. Alexa Kimball
  - Dr. Joseph Merola
  - Leah McCormick Howard, J.D. (National Psoriasis Foundation)
  - Bram Ramaekers, PhD (health economist)
- How is the evidence report structured to support CEPAC voting and policy discussion?


Goal:
Sustainable Access to High-Value Care for All Patients
Long-Term Value for Money
Short-Term Affordability
Comparative Clinical Effectiveness
Incremental cost-effectiveness
Potential Budget Impact
Other Benefits or Disadvantages
Contextual Considerations

Morning Agenda

9:00am: Welcome and Opening Remarks

9:15 am: Presentation of the Evidence and Economic Modeling

- Reiner Banken, MD, MSc, Senior Fellow, ICER
- David Veenstra, PharmD, PhD, University of Washington

10:15 am: Public Comments

10:30 am: Manufacturer Panel and Discussion

10:45 am: NE CEPAC Vote on Clinical Effectiveness and Value

11:45 am: Reflections from Experts and NE CEPAC Panel

12:00 pm: Break for Lunch

Evidence Review

Reiner Banken, MD MSc

Senior Fellow

Institute for Clinical and Economic Review

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AND ECONOMIC REVIEW

Key review team members:

Foluso Agboola, MBBS, MPH

Alexandra Ellis, PhD

Katherine Fazioli, BS

Disclosures:

We have no conflicts of interest relevant to this report.

Condition Update

- Update from New England CEPAC Meeting on November 18, 2016
- **New therapies**: new class of drugs IL23 (guselkumab, tildrakizumab, risankizumab) and new indication for certolizumab pegol
- Update on clinical data and costs for therapies reviewed in 2016

Topic in Context

- Autoimmune skin disease that causes itchy, red, scaly raised plaques
- Affects 3% of the population
- Associated with
  - Other autoimmune diseases
  - Metabolic syndrome and cardiovascular disease
  - Psoriatic arthritis: in up to 30%
- Moderate-to-severe when affecting 5% to 10% of a patient's body surface; lesions significantly reducing quality of life

Effect on Lives Can Be Profound

- Life long disease
- Higher likelihood of having depression, anxiety, and suicidal ideation
- Impact of lesions in particular areas: nails, scalp, face, flexural areas, palms, soles of feet, and genitals

Management

- Topical Therapies: emollients, topical steroids and others (effective for 70-80% of patients)
- Older systemic therapies: cyclosporine, methotrexate
- Phototherapy
- Targeted immunomodulators: TNFα, interleukins 17-A, 12 and 23, PDE-4

Insights from Patients and Patient Groups

- Research is not patient-centered
- Patient dissatisfaction
- Challenges of Black and Hispanic patients
- Using treatments can be challenging
- Affects social functioning
- Psychological and emotional effects
- Concern about lack of access

Issues of Focus

Review Scope (PICOTS)

- **Population*:*** Adults with moderate-to-severe plaque psoriasis
- **Interventions:** Targeted immunomodulators
- **Comparators:** Placebo and head-to-head
- **Main Outcomes:**
  - Psoriasis Area and Severity Index (PASI)
  - Physician Global Assessment (PGA)/ Investigator Global Assessment (IGA)
  - Patient-reported outcomes (DLQI, Symptom measure scales)
  - Treatment-related adverse events

Updated Evidence Base

- 48 key trials included in the update
  - 34 were included in the 2016 review
- 10 of the newly identified trials relates to the four new drugs of interest
- 4 additional trials were identified on the old drugs
  - Placebo controlled adalimumab trial
  - Placebo controlled infliximab trial
  - Head-to-head between infliximab and etanercept (PIECE)
  - Head-to-head between secukinumab and ustekinumab (CLARITY)

Phase III Trials on New drugs

Drug	Trial names	N	Primary endpoints (weeks)	Mean baseline PASI	Age (years)
Guselkumab	VOYAGE 1* VOYAGE 2*	1,829	16	22	44
Tildrakizumab	RESURFACE 1 RESURFACE 2*	1, 862	12	20	46
Risankizumab†	UltIMMA 1* UltIMMA 2 IMMhance	1,504	16	20	48
Certolizumab Pegol	CIMPASI 1 CIMPASI 2 CIMPACT*	1,020	16/12	20	46

*Placebo controlled trials with active comparators
†Phase III trials of risankizumab are only available in the grey literature

Placebo-Controlled Trials

All targeted immunomodulators had statistically significantly higher PASI 75, 90 and 100 responses compared to placebo

	PASI 75 (%)		PASI 90 (%)	
	Treatment	Placebo	Treatment	Placebo
Guselkumab	86-91	6-8	70-73	2-3
Tildrakizumab	62-66	6	35-39	1-3
Risankizumab	89	8	73-75	2-5
Certolizumab Pegol	75-83	4-12	43-55	0-5

Direct Comparative Trials: PASI 75 & 90 outcome

- ***Guselkumab was superior to adalimumab in two trials***
- ***Tildrakizumab and 400mg certolizumab pegol were superior to etanercept in one trial each***
- ***Risankizumab was superior to ustekinumab in two trials***

Trial/Treatment	PASI 75 (%)	PASI 90 (%)
VOYAGE 1 & 2		
Adalimumab	69-73	47-50
Guselkumab	86-91	70-73
RESURFACE 2		
Etanercept	48	21
Tildrakizumab	61	39
ULTIMMA 1 & 2†		
Ustekinumab	Data in confidence	42-48*
Risankizumab	Data in confidence	75*
CIMPACT		
Etanercept	53	27
Certolizumab Pegol 400mg	67	34
Certolizumab Pegol 200mg	61	31

*Data obtained from grey literature

Network Meta-analysis

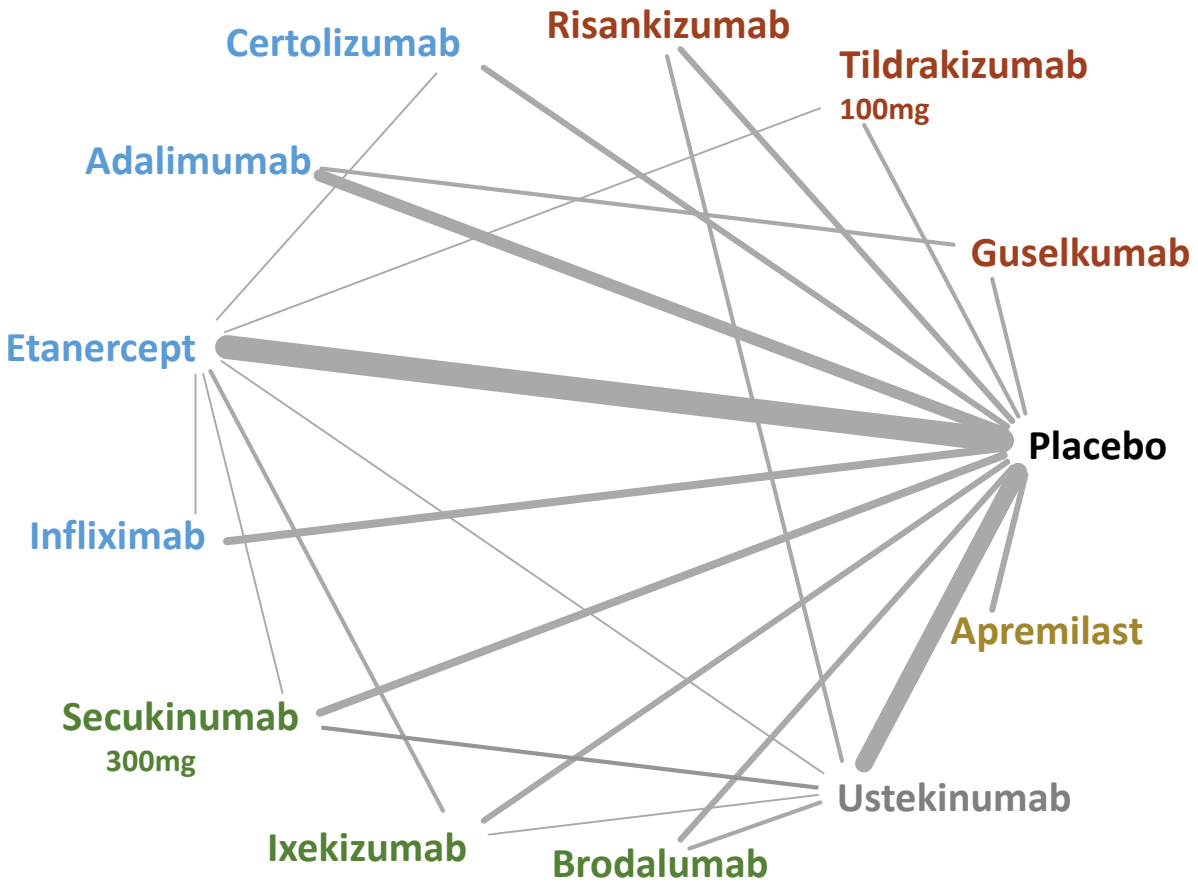
TNFα

IL17

IL 12/23

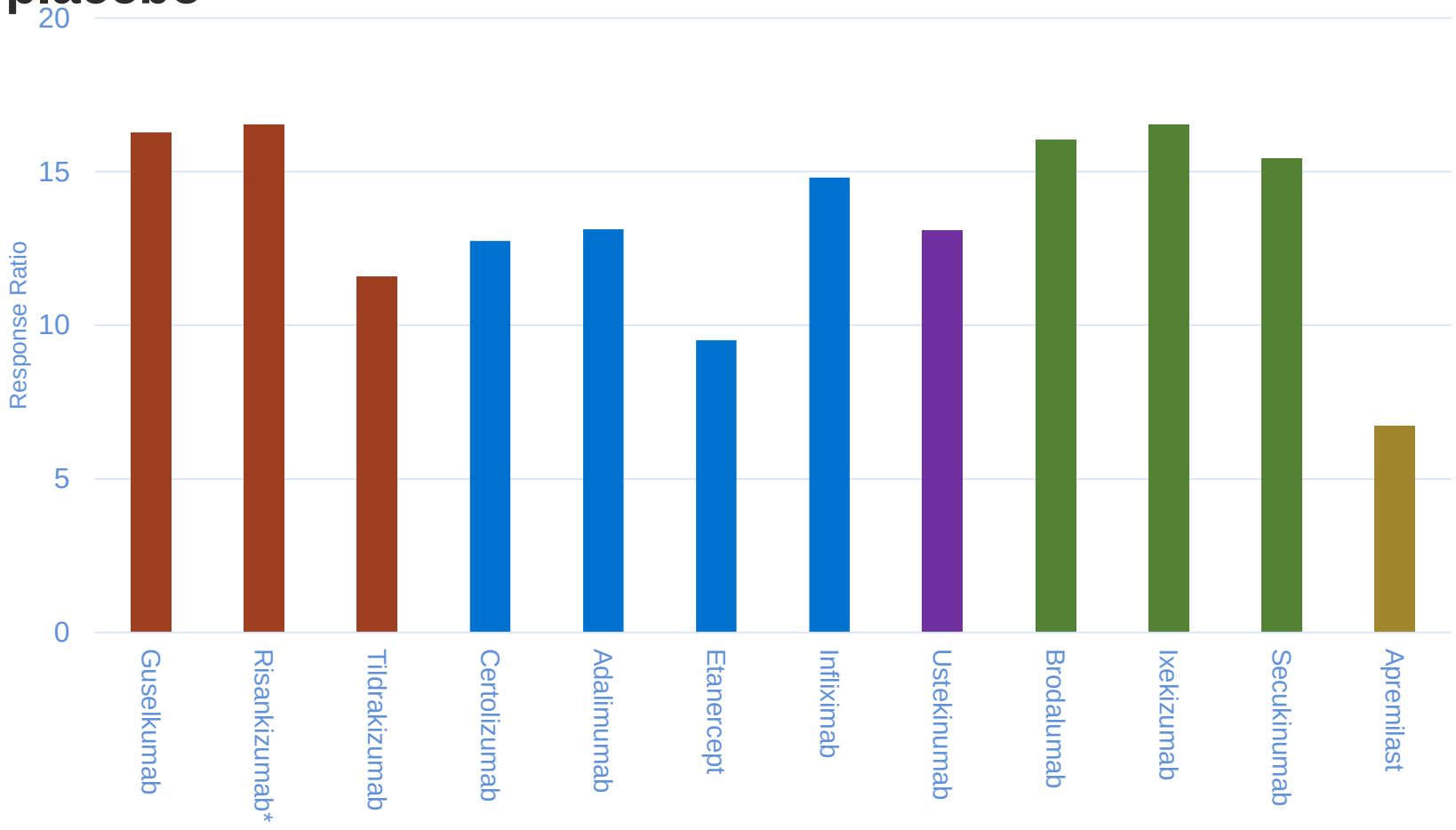
PDE-4

IL23



Network Meta-Analysis

RR of Achieving PASI 75 during induction relative to placebo



Other Outcomes: Direct Comparative Trials

Head-to-Head comparisons	Trials	N	PASI	IGA/PGA	DLQI
Guselkumab (vs. Adalimumab)	2	1,829	↑	↑	↑
Risankizumab (vs. Ustekinumab)	2	997	↑	↑	↑
Tildrakizumab (vs. Etanercept)	1	1,090	↑	↔	↔
Certolizumab Pegol* (vs. Etanercept)	1	559	↑	ND	ND

400mg certolizumab pegol (200mg certolizumab pegol not different to etanercept)

Statistically better (superior)	↑
Not significant (Comparable)	↔
Statistically worse (Inferior)	↓
Limited or no data identified	No data

Harms

- ***Induction: 10-16 weeks***
  - Serious adverse events rare: 2-4% (3% in placebo)
  - Any adverse effect: 46-58% (50% in placebo)
    - *Nasopharyngitis, upper respiratory tract infections, and headaches were the most common side effects*
  - Discontinuation due to AEs: 0.5-1.3%
- ***Long-term safety***
  - 48-52 weeks available data for guselkumab, tildrakizumab, and risankizumab
  - Types and patterns were similar to the placebo-controlled periods
  - Similar to other TNF-α therapies certolizumab pegol has a boxed warning for serious infection and malignancy based on it's longer term use in RA

Controversies and Uncertainties

- 16 of the 48 key trials are head-to-head comparisons
- Outcomes that patients said were important continue to be underreported
- Clinical outcomes based on short term data
- Subgroup data only for placebo comparisons
- No good evidence on choice of second line targeted immunomodulators

ICER Evidence Ratings – New agents

Treatment	Adalimumab TNFα sc	Etanercept TNFα sc	Certolizumab TNFα sc
Certolizumab pegol	C-	C (1)	-
Guselkumab	B (2)	C+	C+
Risankizumab¥	C+	B	C+
Tildrakizumab	I	C+ (1)	I

Indirect comparison Direct comparison ¥ Based on conference abstract

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Potential Other Benefits and Contextual Considerations

- All agents are administered SC except for apremilast (oral) and infliximab (IV)
  - SC may be less burdensome and has reduced complexity
  - Patients may favor the convenience of an oral drug
- New class of drugs that may offer new options for patients who did not achieve adequate control with the other agents

Public Comments Received

- Systematically include patient-reported outcomes (DLQI and others)
  - DLQI and other outcomes are reported when available. Outcomes other than PASI inconsistently reported across trials making cross-drug comparisons difficult. PASI relates closely.
- Add other subpopulations
  - No: Subpopulation analysis limited by available data. Evidence applicable to general patient population.
- Apremilast should not be viewed as part of the broader category of “targeted immunomodulators”
  - No: Apremilast is a targeted immunomodulator. Similar clinical use.
- Modify NMA methods, such as placebo adjustment
  - Scenarios and sensitivity analyses added that did not change the conclusions.

Cost Effectiveness

David Veenstra, PharmD, PhD

Professor

University of Washington

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Key Review Team Members

Nathaniel Hendrix, PharmD, PhD student (UW)

Disclosures:

We have no conflicts of interest relevant to this report.

Objective

Estimate the cost-effectiveness of targeted treatment strategies for moderate-to-severe plaque psoriasis in patients who have failed treatment with methotrexate, phototherapy, and/or topical therapy.

Drugs evaluated

Included in CUA

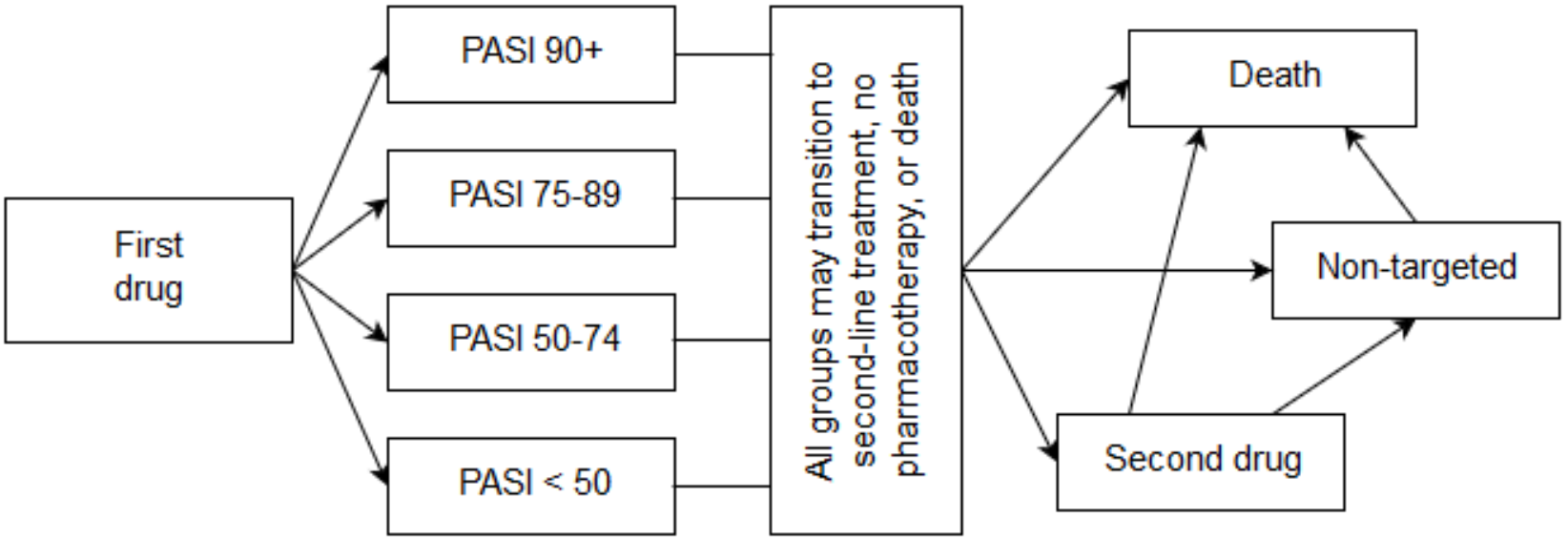
- Adalimumab
- Apremilast
- Brodalumab
- Certolizumab pegol
- Etanercept
- Guselkumab
- Infliximab
- Ixekizumab
- Secukinumab
- Ustekinumab

Threshold price only

- Risankizumab
- Tildrakizumab

Methods in Brief

Overall Approach



- Population assumptions: mean age 45, mean weight 90 kg
- Payer perspective
- Ten-year time horizon summing costs, QALYs, time spent in PASI 90+ health states, and time spent in PASI 75+ health states
- Discount rate of 3%

Key Model Assumptions

- Patients remain on first-line therapy during the induction period
- All discontinuation in the first year is accounted for by lack of effectiveness at the end of the induction period, except for infliximab
- Of patients discontinuing their first-line targeted treatment, 75% continue to a second-line targeted treatment
- Risk of death is based on age alone
- Subcutaneously administered drugs are given once in the clinic, then subsequently by the patient themselves

Changes since 2016 report

- Updated net prices
- Switched from class-specific to drug-specific discounts
- Changed source of utility weights
- Included calculation of time spent in PASI 75+ and PASI 90+ health states
- Used updated drug discontinuation data
- Made choice of second-line treatment dependent upon first-line treatment
- Did not include adverse events in the base case

Inputs: Treatment Sequence

Initial treatment strategy	Second-line treatment strategy
Guselkumab	Market basket average of all IL-17 drugs
IL-17 drugs	Guselkumab
Certolizumab and all other drugs	Market basket average of guselkumab plus all IL-17 drugs

Input: Effectiveness

- First-line targeted effectiveness derived from NMA results
- Second-line targeted treatment:
  - Assumed a 10 percentage point reduction in probability of achieving PASI 75 - 100, and a 10 percentage point increase in the probability of achieving PASI < 75.

Inputs: Annual Discontinuation Rates

	Year 1 during initiation	Years 2+
adalimumab	30%	5%
apremilast	63%	5%
brodalumab	13%	5%
certolizumab 200/400	31%	5%
etanercept	49%	10%
guselkumab	12%	5%
infliximab	21%*	10%
ixekizumab	11%	5%
secukinumab 300	17%	5%
ustekinumab 45/90	30%	5%

*An additional 35% of infliximab patients discontinue in the 1st year after initiation phase.

All second-line treatments discontinue at a rate of 15% per year.

Inputs: Dosing Considerations

- Certolizumab pegol
  - 50% receive 200mg dose, 50% 400mg dose
- Ustekinumab
  - 70% receive 45mg dose, 30% 90mg dose

Inputs: Drug Costs

Targeted drug	Maintenance cost per month
infliximab	$2,479
apremilast	$2,585
brodalumab	$3,044
ixekizumab	$3,140
secukinumab 300	$3,181
ustekinumab 45/90	$3,549
adalimumab	$3,641
etanercept	$3,643
guselkumab*	**$3,700**
certolizumab 200/400	**$4,213**

*estimated drug discount

Inputs: Quality of life weights

State	Utility weight
PASI 90-100	0.903
PASI 75-89	0.856
PASI 50-74	0.827
PASI 0 – 50	0.718
Non-targeted	0.660

Derived from mapping the PASI onto the EQ-5D – not based on treatment; average of five submissions to NICE (adalimumab, apremilast, ixekizumab, secukinumab, ustekinumab) (Pickard, 2016)

Results

Base-Case Results

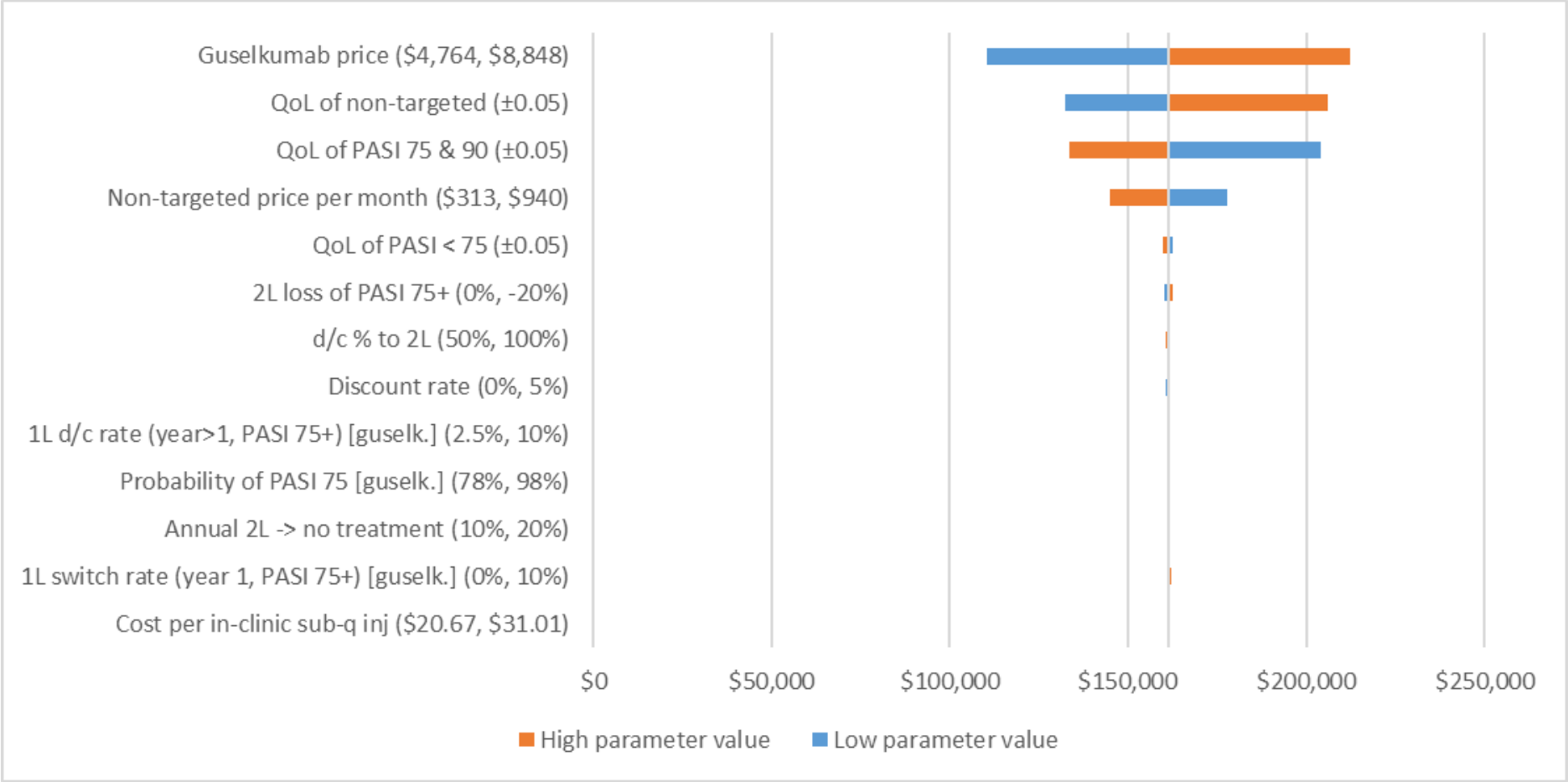
First-line Treatment	Total Cost	Total QALYs	Months spent in PASI 75+
Non-targeted treatment	$67,800	5.70	0
Apremilast	$215,000	6.79	53.5
Etanercept	$272,000	6.88	57.9
Infliximab	$238,000	6.98	62.5
Certolizumab pegol	**$341,000**	**7.16**	**73.5**
Adalimumab	$308,000	7.17	74.1
Ustekinumab	$315,000	7.17	74.1
Secukinumab	$305,000	7.34	82.4
Brodalumab	$289,000	7.39	84.9
Guselkumab	**$342,000**	**7.40**	**85.3**
Ixekizumab	$311,000	7.42	86.1

Base-Case Results: ICER vs non-targeted

First-line Treatment	Cost / QALY
Brodalumab	$131,000
Infliximab	$134,000
Apremilast	$135,000
Ixekizumab	$142,000
Secukinumab	$145,000
Guselkumab	**$161,000**
Adalimumab	$164,000
Ustekinumab	$169,000
Etanercept	$175,000
Certolizumab pegol	**$188,000**

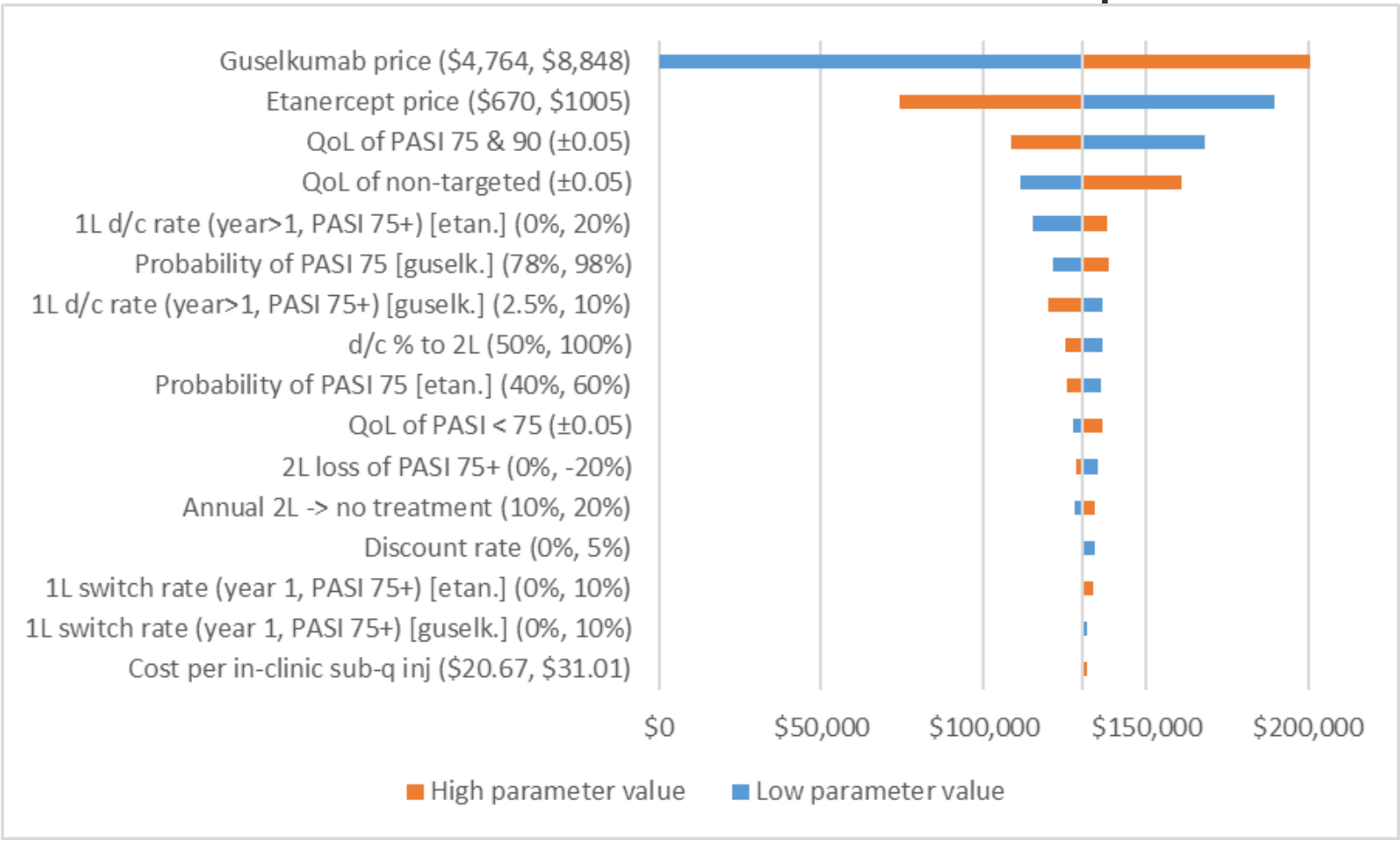
One-Way Sensitivity Analyses

Guselkumab versus non-targeted



One-Way Sensitivity Analyses

Guselkumab versus etanercept



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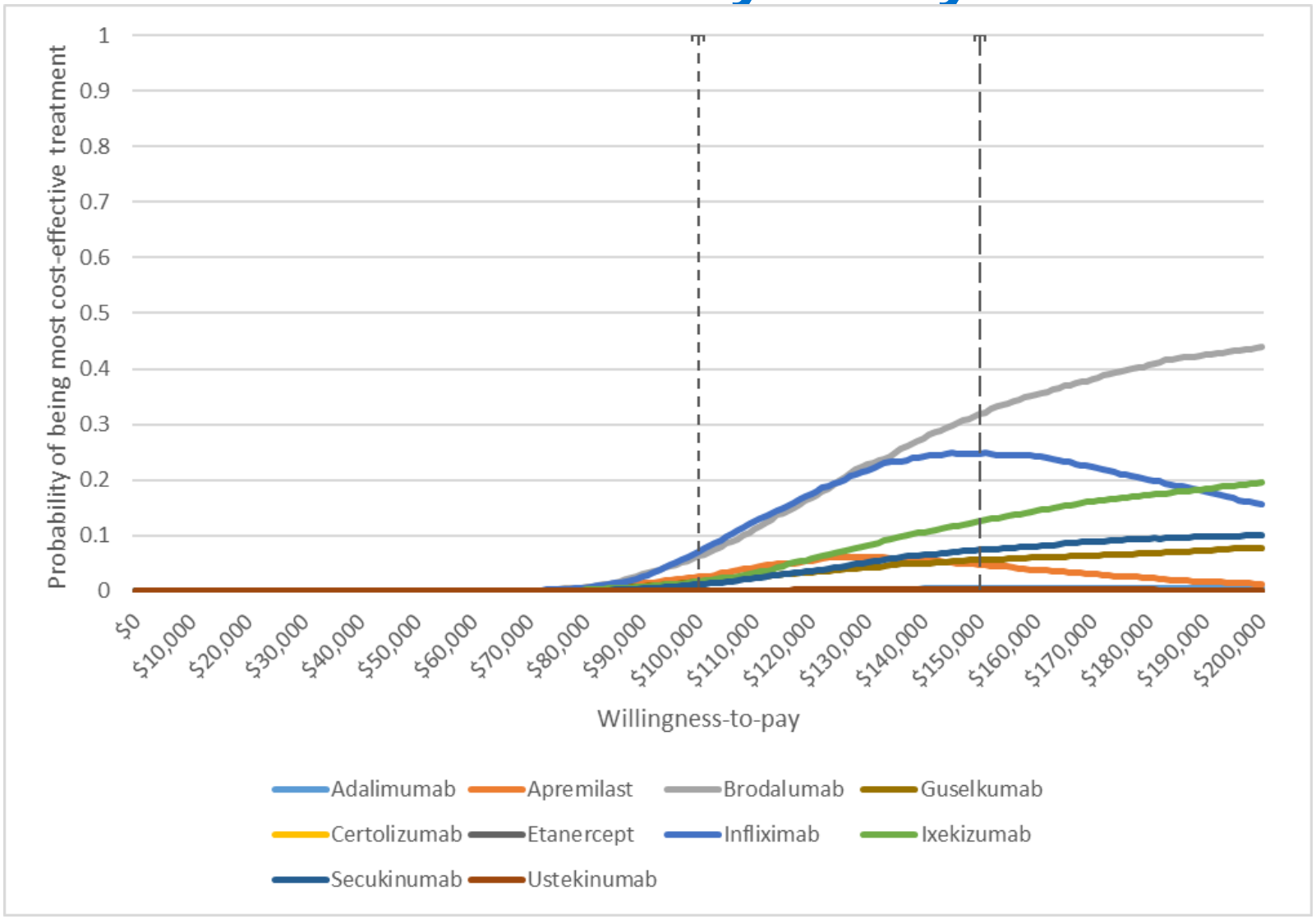
Comparison to etanercept shows comparison to step therapy
Guselkumab dominates at a unit price of $4,764

Probabilistic Sensitivity Analysis



Scenario analyses

- *Inclusion of productivity cost offsets*
  - Reduced ICERs by approximately $20,000, and did not change ordering of drugs
  - Guselkumab: $133,985 (-12%)
  - Certolizumab: $166,162 (-13%)
- *Lower doses for certolizumab and ustekinumab*
  - Assuming similar effectiveness across doses,
  - ICERs are $129,000 and $130,000, respectively

Limitations

- No robust data on treatment patterns and discontinuation rates in the US for most drugs
- The 10% loss of effectiveness for second-line treatment data was derived primarily from observational studies
- Associations between specific treatments and patient utilities not well studied

Comments Received

- Monthly dosing does not capture the correct drug quantities
  - We recalculated monthly cost via average daily dose
- Include dose escalation in model
  - Dose escalation depends heavily on payer policies; for this reason and due to lack of data in the US setting, we have not included it in the model
- Include productivity cost offsets for clinical response
  - Included in a scenario analysis

Summary

- Guselkumab may be cost-effective at a $150K/QALY threshold
  - Primarily dependent on drug price discount
- Dosing for certolizumab pegol reduces its value in the general population
  - Cost-effectiveness may be favorable for patients eligible to receive the lower dose
- Value for tildrakizumab and risankizumab currently unknown due to lack of a published price
  - Threshold analyses suggest value-based prices of ~$25-$40K annually

Appendix

Threshold Prices (updated)

Intervention	Annual price of maintenance therapy	Price needed for $50k/QALY	Price needed for $100k/QALY	Price needed for $150k/QALY
Adalimumab	$43,700	$11,600	$25,700	$39,800
Apremilast	$31,000	< $0	$17,500	$36,600
Brodalumab	$36,500	$14,900	$28,200	$41,500
Certolizumab pegol	$50,600	$11,300	$25,500	$39,700
Etanercept	$43,700	$1,700	$18,500	$35,400
Guselkumab	$44,400	$15,400	$28,400	$41,500
Infliximab	$29,700	$2,600	$18,800	$35,000
Ixekizumab	$37,700	$14,500	$27,100	$39,700
Risankizumab	NA	**$14,700**	**$27,300**	**$39,800**
Secukinumab	$38,200	$13,600	$25,500	$39,400
Tildrakizumab	NA	**$9,200**	**$23,000**	**$36,800**
Ustekinumab	$42,600	$12,600	$25,200	$37,800

Risankizumab and tildrakizumab costs are calculated without laboratory monitoring.
Risankizumab and tildrakizumab assumed to be dosed at weeks 0 and 4, then Q12W, as in RCTs.

Public Comment and Discussion

Leah McCormick Howard, JD

Chief Operating Officer, National Psoriasis Foundation

Conflicts of interest:

- The National Psoriasis Foundation works with all the manufacturers that have a therapy in the psoriatic disease space, including AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Merck, Novartis, Ortho Dermatologics, Pfizer, Sandoz, Sun Pharma, and UCB. A full list of their funders can be found in their Annual Report.

Manufacturer Public Comment and Discussion

Brad Stolshek, PharmD

Director, Global Health Economics, Inflammation, Amgen

Conflicts of interest:

- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000
- Equity interests such as individual stocks, stock options or other ownership interests in excess of $10,000

Brad Stolshek is an employee and shareholder of Amgen.

David L. Kaplan, MD, MS, FACP, FAAD

Clinical Assistant Professor, University of Missouri, Kansas City School of Medicine; Clinical Assistant Professor, University of Kansas Medical Center

Conflicts of interest:

- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000

Dr. Kaplan has been a speaker for AbbVie, Pfizer, and Celgene.

Voting Questions

WIFI Network: Student
Password: [Open Network]

0. How many stories is the tallest building in Vermont?

A. 8

B. 25

C. 11

D. 32

Patient Population for all questions:
Patients with moderate-to-severe plaque psoriasis for whom treatment with topical therapies, older systemic therapies, and/or phototherapy has been ineffective, contraindicated, or not tolerated.

1. Is the evidence adequate to demonstrate that the net health benefit of certolizumab pegol is superior to that provided by the other subcutaneous TNFα inhibitors (adalimumab and etanercept)?

A. Yes

B. No

2. Is the evidence adequate to demonstrate that the net health benefit of guselkumab is superior to that provided by all subcutaneous TNFα inhibitors (adalimumab, etanercept, and certolizumab pegol)?

A. Yes

B. No

3. Is the evidence adequate to demonstrate that the net health benefit of risankizumab is superior to that provided by all subcutaneous TNFα inhibitors (adalimumab, etanercept, and certolizumab pegol)?

A. Yes

B. No

4. Is the evidence adequate to demonstrate that the net health benefit of tildrakizumab is superior to that provided by all subcutaneous TNFα inhibitors (adalimumab, etanercept, and certolizumab pegol)?

A. Yes

B. No

5. When compared to non-targeted therapy, do newer treatments for moderate-severe plaque psoriasis offer one or more of the following "potential other benefits"? (select all that apply)

This intervention:

A. Offers reduced complexity that will significantly improve patient outcomes.

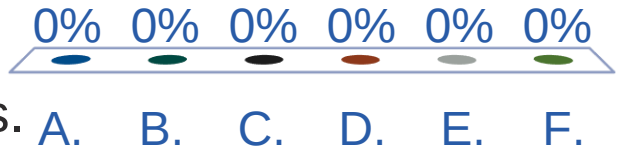
B. Will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.

C. Will reduce caregiver/family burden

D. Is a novel mechanism of action or approach

E. Will have a significant impact on improving return to work/overall productivity

F. Offers other important benefits or disadvantages.



6. Are any of the following contextual consideration important in assessing long-term value for money for the newer targeted immunomodulators? (select all that apply)

A. Intended for care of individuals with condition of high severity in terms of impact on quality and/or length of life

B. Intended for care of individuals with condition with high lifetime burden of illness

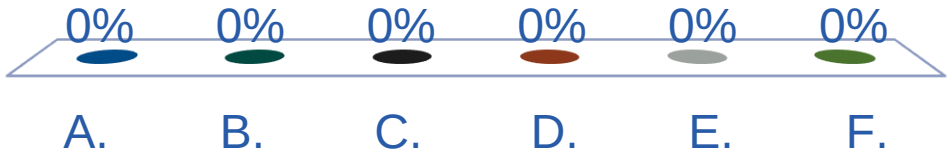
C. First to offer any improvement for patients

D. Compared to non-targeted therapies, there is significant uncertainty about long-term risk of serious side effects

E. Compared to non-targeted therapies, there is significant uncertainty about the magnitude or durability of long-term benefits

F. Other important contextual considerations.

_____

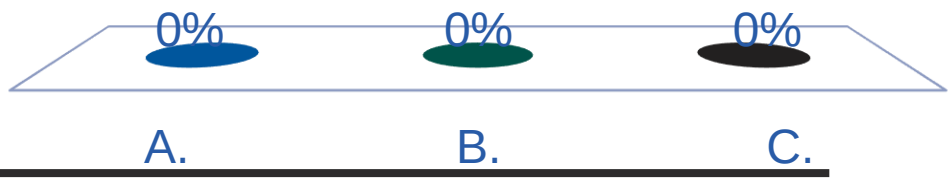


7. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of **guselkumab compared with non-targeted therapy?**

A. Low

B. Intermediate

C. High



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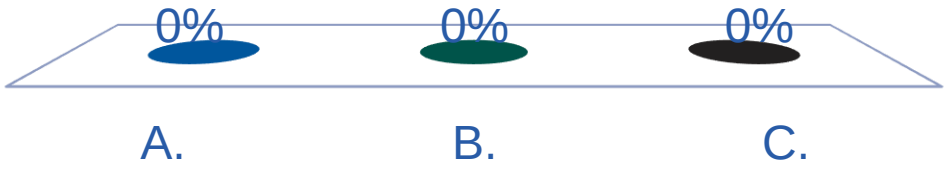
8. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of **certolizumab pegol compared with non-targeted therapy?**

A. Low

B. Intermediate

C. High



Expert and CEPAC Panel Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on/about August 2
  - Includes description of CEPAC votes, deliberation; policy roundtable discussion
- Materials available at

  https://icer-review.org/meeting/psoriasis-update/

Break for Lunch.

Reconvene at 1:00pm.