CALIFORNIA TECHNOLOGY ASSESSMENT FORUM℠

Novel Combination Therapies for the Treatment of Patients with Genotype 1 Hepatitis C

Public Meeting

December 18, 2014

CTAF Overview

- Core program of the Institute for Clinical and Economic Review (ICER), an independent non-profit research organization that evaluates scientific evidence on the clinical effectiveness and cost implications of medical interventions
- Goal: Help patients, clinicians, insurers, and policymakers apply evidence to improve the quality and value of health care
- Deliberation and voting by CTAF Panel – independent clinicians, methodologists, and leaders in patient engagement and advocacy
- Supported by a grant from the Blue Shield of California Foundation

Agenda

- **Public Meeting Convened** | 9:30 – 9:40 am
- **Presentation of the Evidence and Economic Modeling, Q&A** | 9:40 – 10:40 am
- **Public Comments** | 10:40 – 11:20 am
- **Q&A with Experts, CTAF Deliberation and Votes** | 11:20 am – 12:20 pm
- **Lunch** | 12:20 – 12:50 pm
- **Roundtable 1: Clinical Considerations** | 12:50 – 1:50 pm
- **Break** | 1:50 – 2:00 pm
- **Roundtable 2: Specialty Drug Payment and Pricing** | 2:00 – 3:30 pm
- **Roundtable Discussion and Best Practice/Policy Recommendations** | 3:30 – 4:10 pm
- **Reflections from CTAF Panel** | 4:10 – 4:25 pm
- **Summary and Closing Remarks** | 4:25 – 4:30 pm
- **Meeting Adjourned** | 4:30 pm
  - **Download meeting materials: www.tinyurl.com/ctafhepc2**

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Evidence Review

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December 18, 2014

I have no conflicts of interest.

Treatment of Chronic HCV Infection

- Rapid evolution of treatment for genotype 1
  - Pegylated interferon + ribavirin (PR) 2001
  - Boceprevir or telaprevir + PR 2011
  - Simeprevir or sofosbuvir + PR 2013
  - **Interferon-free DAA combinations 2014**
- Intermediate outcome
  - Sustained virologic response (SVR)
- Key patient oriented outcomes
  - Cirrhosis, hepatocellular carcinoma (HCC), liver transplantation, death

FDA: Treatment of GT1 with Single DAA Therapy

- Simeprevir + PR daily x 12 weeks
  - + 12 more weeks of PR for most
  - + 36 more weeks of PR for prior partial or non-responders
- Sofosbuvir + PR daily x 12 weeks
- Sofosbuvir + R daily x 24 weeks if interferon-ineligible

Single DAA Treatment for GT 1

- Good SVR12: 55% to 92%
- Many contraindications due to interferon
  - Psychiatric illness, autoimmune disease, advanced liver disease
- Many side effects due to interferon
  - Fatigue, fever, anemia, depression, anxiety

NEW DIRECT ACTING ANTI-VIRAL THERAPY

FDA: Treatment of GT1 with Dual DAA Therapy

- Harvoni (single pill combination of ledipasvir 90 mg and sofosbuvir 400 mg)
  - **12** weeks if treatment-naïve
    - **8** weeks if HCV RNA < 6 million IU/ml
  - **24** weeks if treatment-experienced
- Simeprevir 150 mg + sofosbuvir 400 mg daily
  - **12** weeks if no cirrhosis (naïve and experienced)
  - **24** weeks if cirrhosis (naïve and experienced)

Additional Multiple DAA Therapies Considered for the Treatment of GT1

- Daclatasvir 60 mg + sofosbuvir 400 mg daily x **12 - 24** weeks
  - FDA requested additional data
- 3D ± R: paritaprevir / ritonavir 150/100 mg with ombitasvir 25 mg in a single pill and dasabuvir 250 mg twice daily with or without weight-based ribavirin
  - FDA decision expected soon

EVIDENCE REVIEW

Four Subgroups within GT1

Treatment-naïve / non-cirrhotic 69%	Treatment-naïve / cirrhotic 9%
Treatment-experienced / non-cirrhotic 19%	Treatment-experienced / cirrhotic 3%

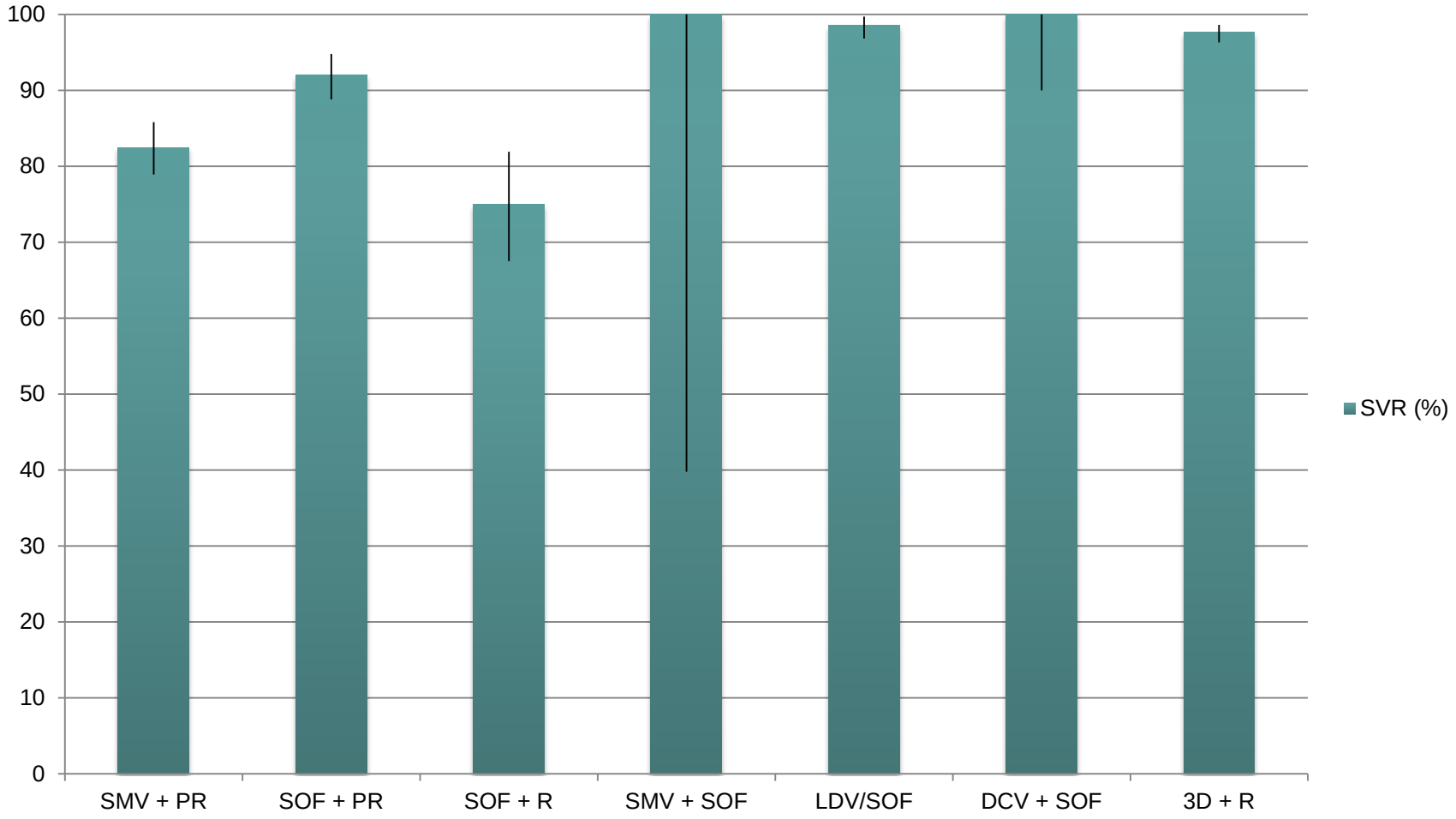
Methods

- Systematic review
  - Professional librarian; published reviews; manufacturers; experts
  - Phase 2 & 3 trial data on FDA-approved dose and duration
    - Exception to standard CTAF requirement for only published data to allow consideration of all data relevant to the topic
- Meta-analysis within 4 subgroups
  - No shared comparison group: precluded network meta-analysis (NMA)
  - SVR12 based on n randomized
  - Discontinuation rates included lost to follow-up, withdrew consent, never treated, and discontinuations due to adverse events (AEs)

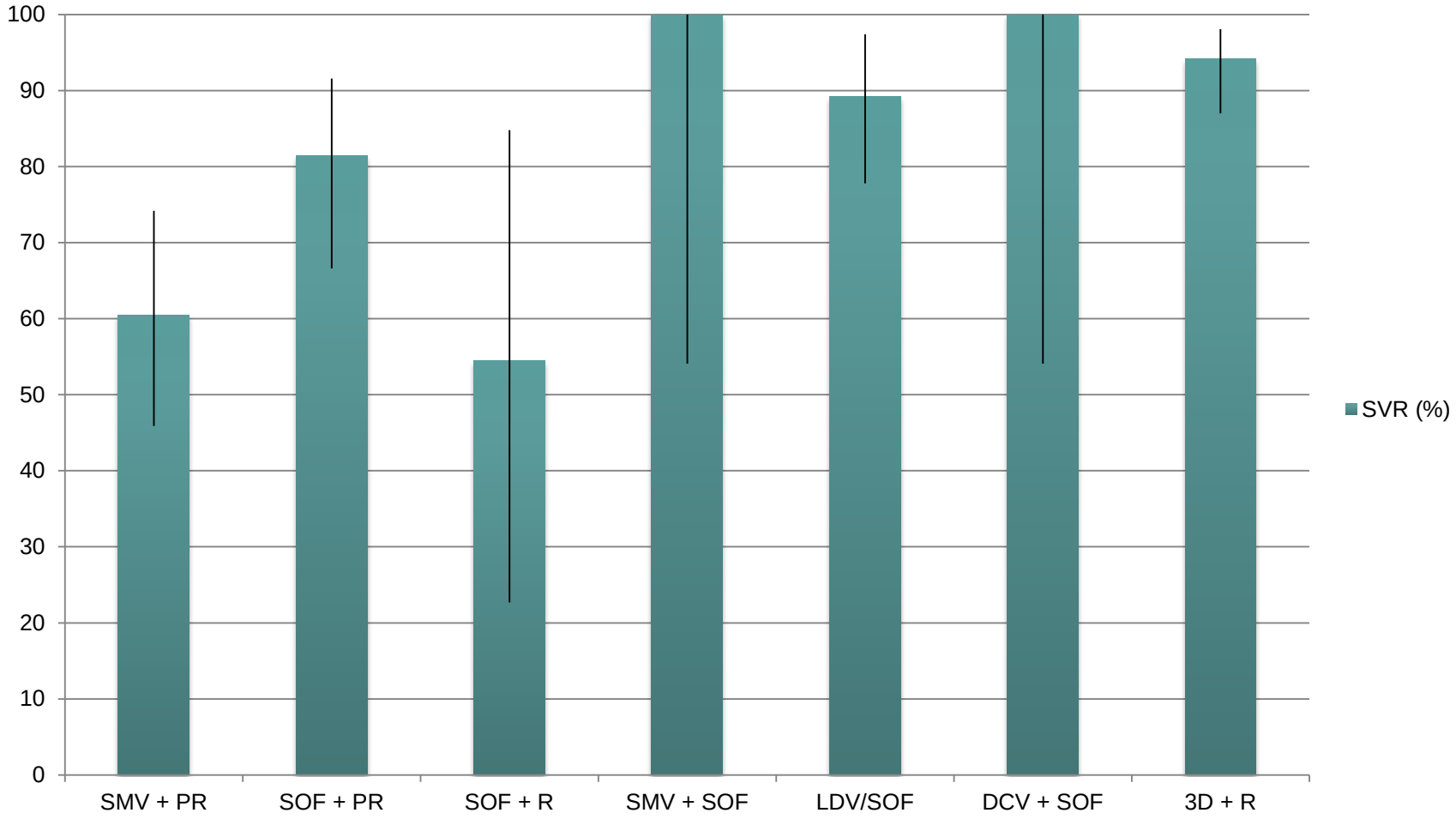
GENOTYPE 1

SVR IN EACH SUBGROUP

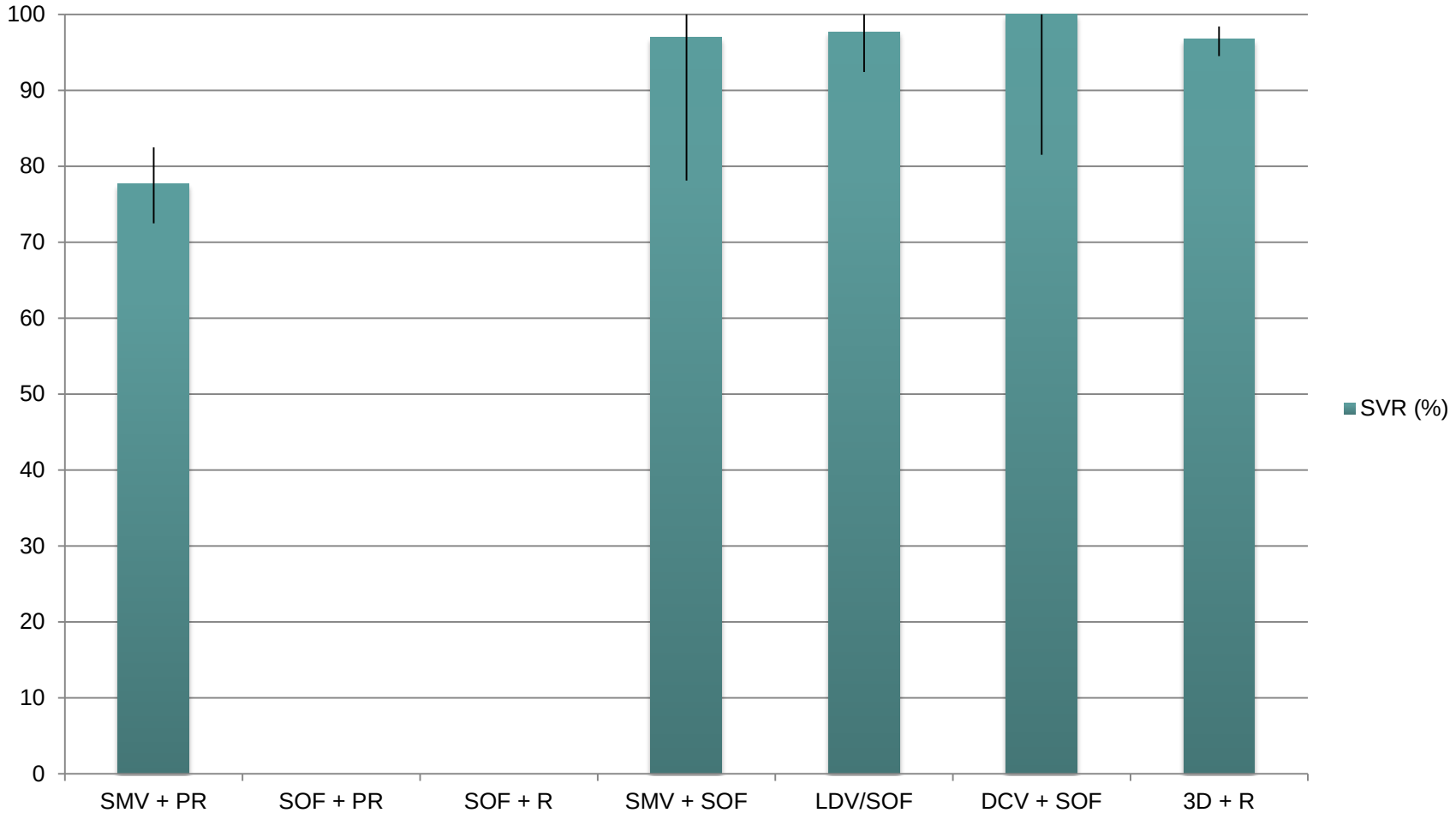
Treatment-naïve, Non-cirrhotic: SVR



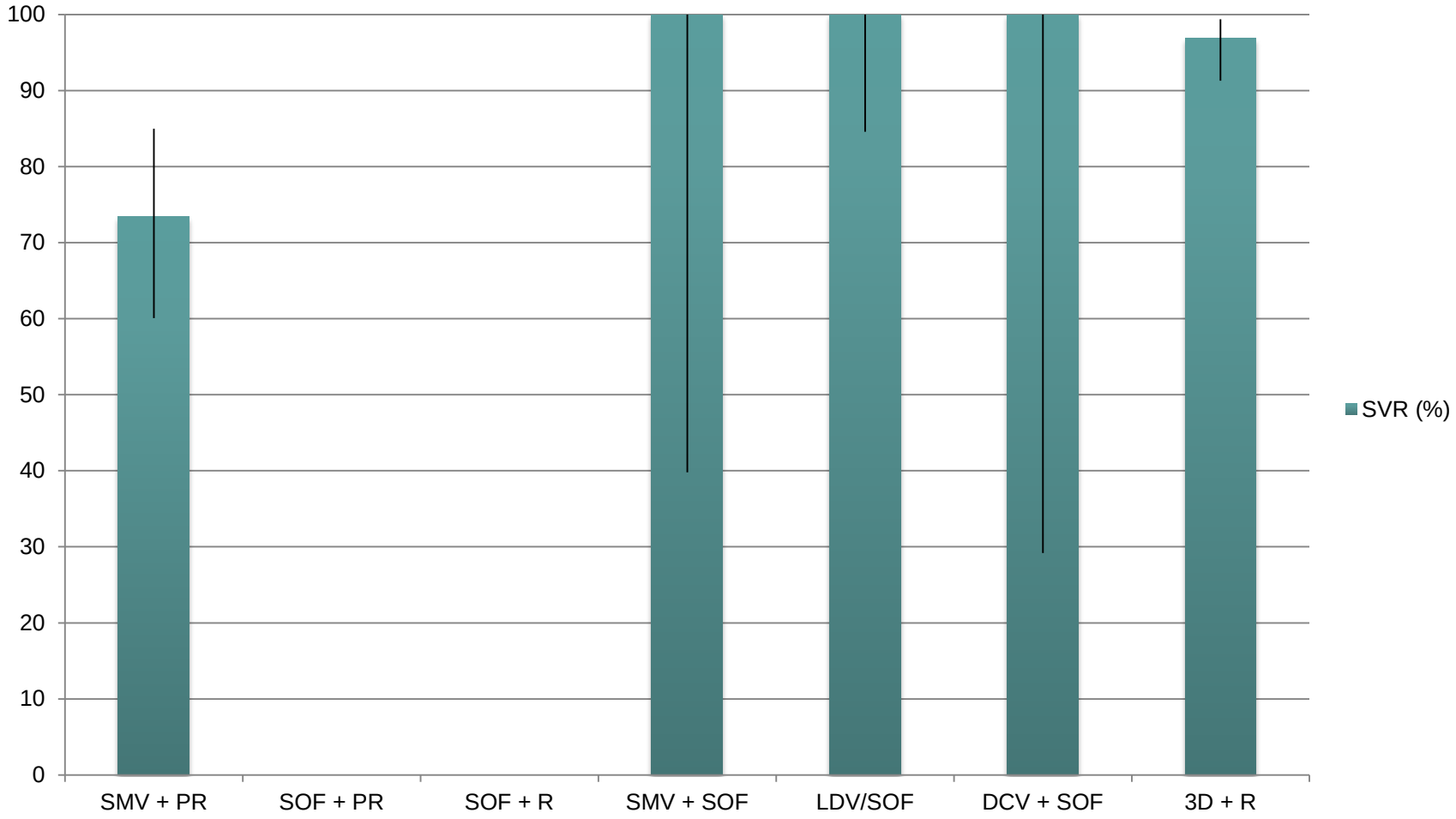
Treatment-naïve, Cirrhotic: SVR



Treatment-experienced, Non-cirrhotic: SVR



Treatment-experienced, Cirrhotic: SVR



GENOTYPE 1

HARMS OF TREATMENT

Adverse Events (AEs)

	SMV12 PR24	SOF12 PR12	SOF24 R24	SMV12 SOF12	LDV12 SOF12	DCV12 SOF 12	3D12 R12
N	781	327	566	28	539	41	1379
Flu	26%	16%	3%	NR	<5%	0%	NR
Anemia	12%	23%	9%	0%	0%	0%	3%
Rash	28%	18%	8%	11%	4%	5%	11%

- Flu-like symptoms with P
- Anemia with PR or 24 weeks R therapy
- Photosensitivity rashes with simeprevir

GENOTYPE 1

SUMMARY

Limitations

- No direct comparisons, randomized or observational
  - Possible selection bias
- Intermediate outcome: SVR12
  - Imperfect measure of cure
  - Residual risk for HCC
- Small numbers studied
  - Great uncertainty around the estimates of SVR and harms
- Real world results likely not as impressive

Additional Studies Needed

- RCTs comparing therapies
- Large, well done observational studies
  - Real-world SVR
  - Comparing therapies
  - Uncommon AEs
  - Precise measures of AEs
- Special and under-represented populations
  - Co-infection: HIV, Hepatitis B
  - Decompensated liver disease, peri-transplant
  - African Americans, older adults, injection drug users

Key Comments Received

- Bristol-Myers Squibb
  - Recommend including daclatasvir regimens with ribavirin
  - Asunaprevir, but not daclatasvir, withdrawn from FDA
- Project Inform
  - Quality of life outcomes not included in evidence review
- Janssen
  - Simeprevir + PR data should be limited to those without the Q80K polymorphism
  - Phase 3 SMV + SOF OPTIMIST trials with results in 2015

Key Comments Received #2

- Gilead
  - ERADICATE trial (HIV/HCV co-infection): new results
  - Patients with decompensated cirrhosis in the ELECTRON-2 trial should be excluded from SVR estimates
  - Data on LDV/SOF + R for 12 weeks in treatment-experienced patients with cirrhosis at AASLD
- AbbVie
  - HCV-TARGET and TRIO real world data at AASLD
  - CORAL trial (HIV) now published in NEJM

Summary

- Multiple DAA therapy better than single DAA therapy
  - Moderate certainty
    - Greater SVR12 (>90%) with fewer side effects
    - Fewer pills, no injections
    - No direct comparisons
    - Small sample sizes in many subgroups
- Comparing the 4 multiple DAA therapies
  - Insufficient evidence to distinguish
    - No direct comparisons
    - Small sample sizes in many subgroups

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Care Value Analysis

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December 18, 2014

I have no conflicts of interest.

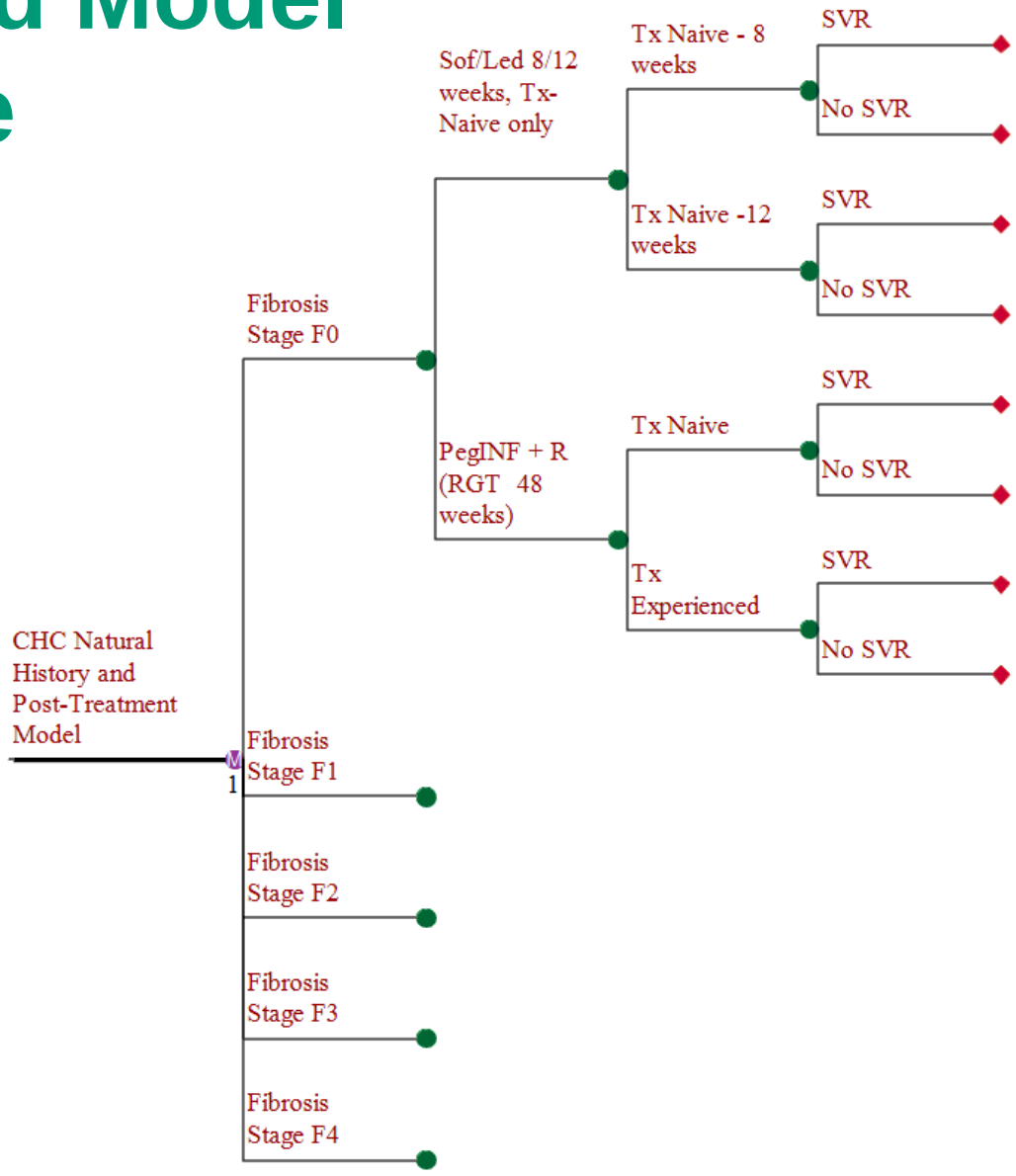
Research Questions

1. What are the outcomes and costs of newer treatment regimens:
   - When compared with previous interferon + ribavirin therapy?
   - When compared with each other?
2. What are the relative costs and health gains of waiting until patients reach more advanced disease (fibrosis stages F3, F4) versus treating a “prevalent cohort” of all fibrosis stages (F0–F4)?

Methods – Inputs

- Population: US, 60 years old, prevalent mix of fibrosis stages
- “All payer” perspective: direct medical care and drug costs
- Lifetime time horizon
- HCV natural course
  - Without treatment or treatment failure
  - After successful treatment
- Costs: Drugs, ongoing HCV care, HCV complications
- Quality of life: Utilities (measures quality of life)
- Efficacy data: ICER systematic review

Simplified Model Structure



Outcomes

- Costs
  - Drug treatment
  - Costs from complications and sequelae (e.g., hepatocellular carcinoma)
  - Other ongoing HCV-related care (e.g., monitoring, treatment of extra-hepatic manifestations)
- Quality-adjusted life-years (QALYs) gained
- Incremental Cost-Effectiveness Ratio (ICER)
  - Difference in costs divided by difference in QALYs

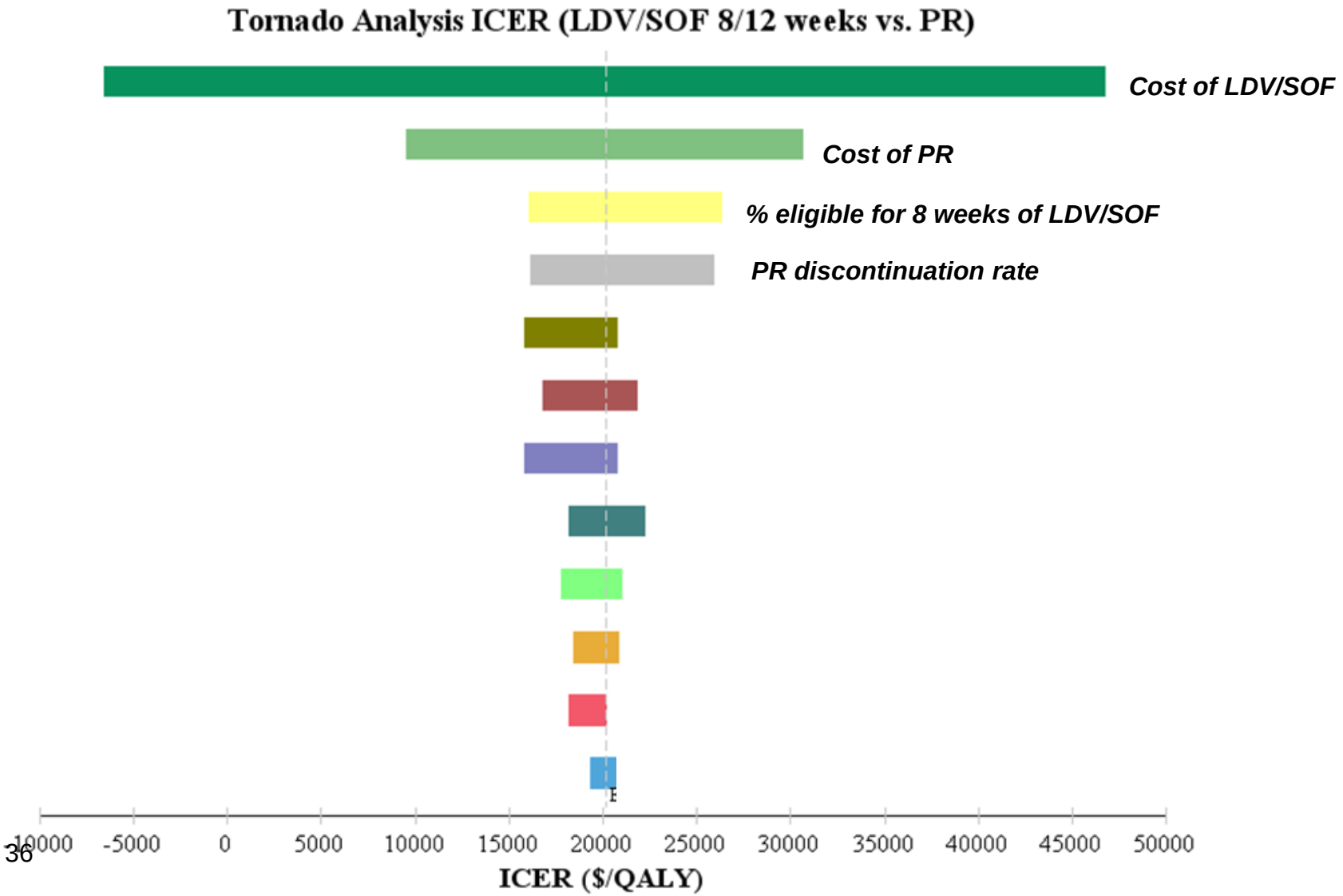
Results: Treatment-naïve

New treatments vs. PR					
Tx naïve, treat all		**Net cost**	**Effect (QALYs)**		**ICER**
LDV/SOF(8/12 weeks)	**$**	**28,451**	**1.413**	**$**	**20,132**
SOF + PR (12 weeks)	$	45,402	1.183	$	38,386
LDV/SOF (12 weeks)	$	46,079	1.475	$	31,234
SMV + SOF (12 weeks)	$	116,942	1.474	$	79,341
SOF + R (24 weeks)	$	123,972	0.655	$	189,160
Tx Naive, treat F3/F4		**Net cost**	**Effect (QALYs)**		**ICER**
LDV/SOF (8/12 weeks)	**$**	**16,853**	**1.057**	**$**	**15,940**
SOF + PR (12 weeks)	$	22,266	0.886	$	25,134
LDV/SOF (12 weeks)	$	32,218	1.101	$	29,257
SMV + SOF (12 weeks)	$	66,566	1.069	$	62,261
SOF + R (24 weeks)	$	66,635	0.455	$	146,472

Results: Treatment-experienced

New treatments vs. PR					
Tx exp, treat all		**Net cost**	**Effect (QALYs)**		**ICER**
PR (48 weeks)					
SOF + PR (12 weeks)	$	39,922	1.983	$	20,130
LDV/SOF (12/24 weeks)	**$**	**47,298**	**2.706**	**$**	**17,477**
SMV + SOF (12 weeks)	$	110,894	2.563	$	43,267
Tx exp, treat at F3/F4		**Net cost**	**Effect (QALYs)**		**ICER**
SOF + PR (12 weeks)	$	15,248	1.566	$	9,734
LDV/SOF (12/24 weeks)	**$**	**20,509**	**2.179**	**$**	**9,411**
SMV + SOF (12 weeks)	$	58,484	2.074	$	28,202

One-way Sensitivity Analysis: Treatment-naïve, Treat All



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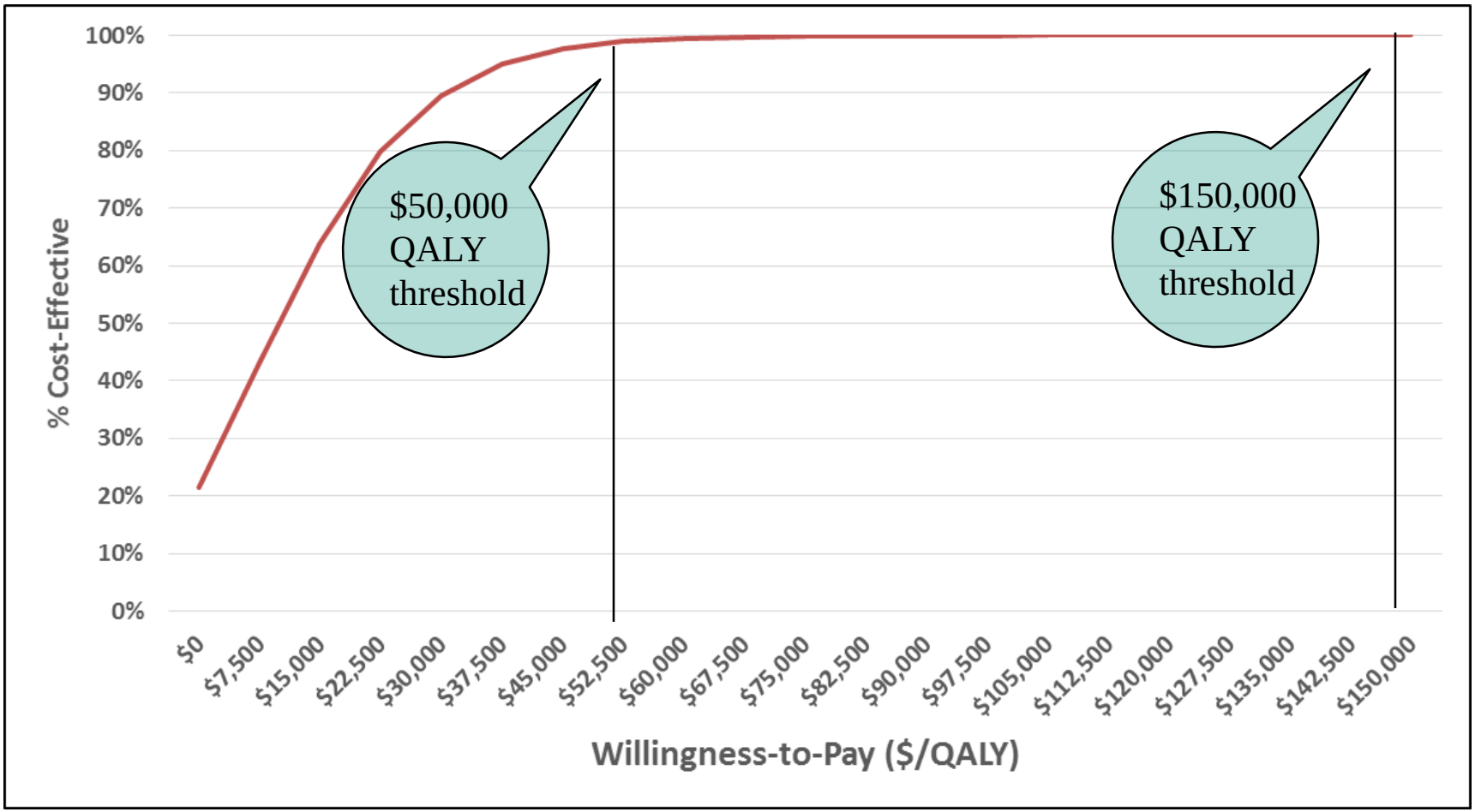
Probabilistic Sensitivity Analysis: LDV/SOF vs. PR, Treatment-naïve, Treat all



Results: Comparing "Treat all" with "Treat at F3, F4 only"

Treat All vs. Treat at F3, F4			
Treatment naïve	**Net cost**	**Effect (QALYs)**	**ICER**
PR (48 weeks)	$14,106	0.368	$38,282
LDV/SOF (8/12 weeks)	**$25,703**	**0.724**	**$35,484**
SOF + PR (12 weeks)	$37,241	0.665	$55,975
LDV/SOF (12 weeks)	$27,966	0.743	$37,663
SMV + SOF (12 weeks)	$64,482	0.773	$83,391
SOF + R (24 weeks)	$71,443	0.569	$125,577
Treatment experienced	**Net cost**	**Effect (QALYs)**	**ICER**
PR (48 weeks)	$12,432	0.228	$54,421
SOF + PR (12 weeks)	$37,105	0.645	$57,510
LDV/SOF (12/24 weeks)	**$39,221**	**0.756**	**$51,911**
SMV + SOF (12 weeks)	$64,842	0.718	$90,348

Why More QALYs in the "Treat all" Approach vs. Waiting Until F3, F4?

- SVR **improves quality of life** for patients with F0-F2 fibrosis scores
- SVR **reduces mortality** by reducing the number of patients progressing to F3, and extends life years

Depending on regimen, 55-74% of benefit of early treatment is from health status effect; 26-45% is from lower mortality.

Key Model Limitations

- Clinical trial data used; may not represent real-world results

Not considered:

- Reduction in transmission from successful therapy
- Risk of reinfection with HCV or SVR relapse
- Retreatment of patients who fail to achieve SVR – modeled only one course of treatment
- Co-infection with hepatitis B or HIV

Conclusions

- Under a wide range of values for price and effectiveness, LDV/SOF and SMV + SOF show cost-effectiveness ratios (ICERs) below commonly accepted thresholds
- Model appears to show that treating everyone rather than waiting until F3/F4 meets commonly accepted cost-effectiveness thresholds ($50,000 to $150,000 per QALY gained)

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Health-System Value Analysis

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December 18, 2014

I have no conflicts of interest.

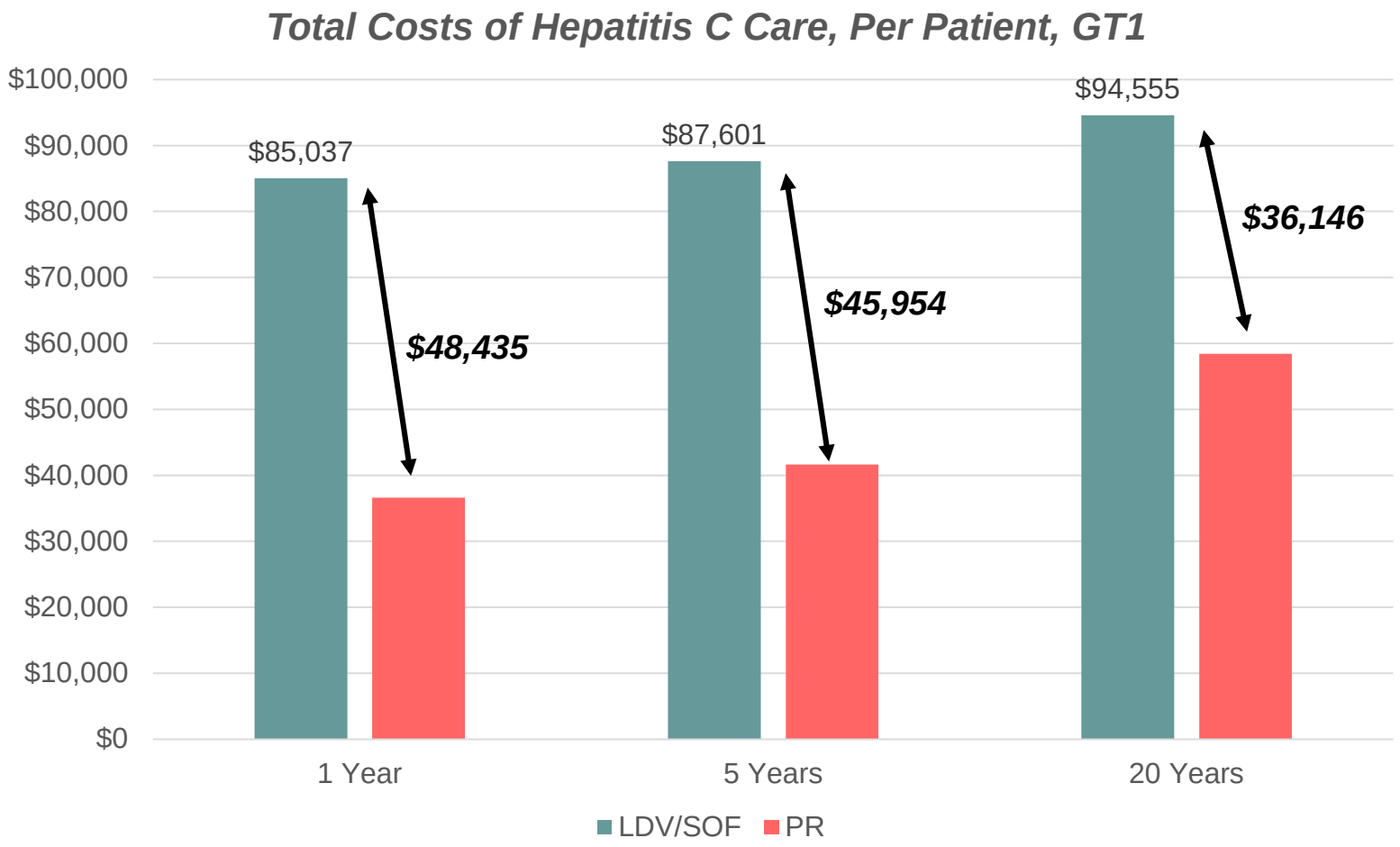
Health-System Value Analysis: 3 Components

- Clinical outcomes/total costs at 1, 5, 20 years after treatment initiation in hypothetical cohort
  - Based on outputs from cost-effectiveness analysis
- Budgetary impact of new therapy for GT1, 2, and 3
  - Extrapolated to size of California Medi-Cal/Dept of Corrections population
  - Budget impact compared to costs for common Medi-Cal service provided
- Threshold policy analysis
  - Based on a 0.5%-1.0% “affordable” PMPM budget impact
  - Implicitly considered by some payers as the threshold at which short-term budget impact of a single intervention often requires some policy effort to avoid negative effects of high costs on patients across the health system

Cohort Analysis: LDV/SOF vs. PR, Treatment-naïve, Treat all

- Hypothetical cohort of 1,000 HCV patients at a prevalent distribution of fibrosis stages
- Followed for 20 years
- Compared to historical PR, LDV/SOF would prevent:
  - 150 cases of cirrhosis (55 decompensated)
  - 20 cases of hepatocellular carcinoma
  - 3 liver transplants

Cohort Analysis: LDV/SOF vs. PR, Treatment-naïve, Treat all

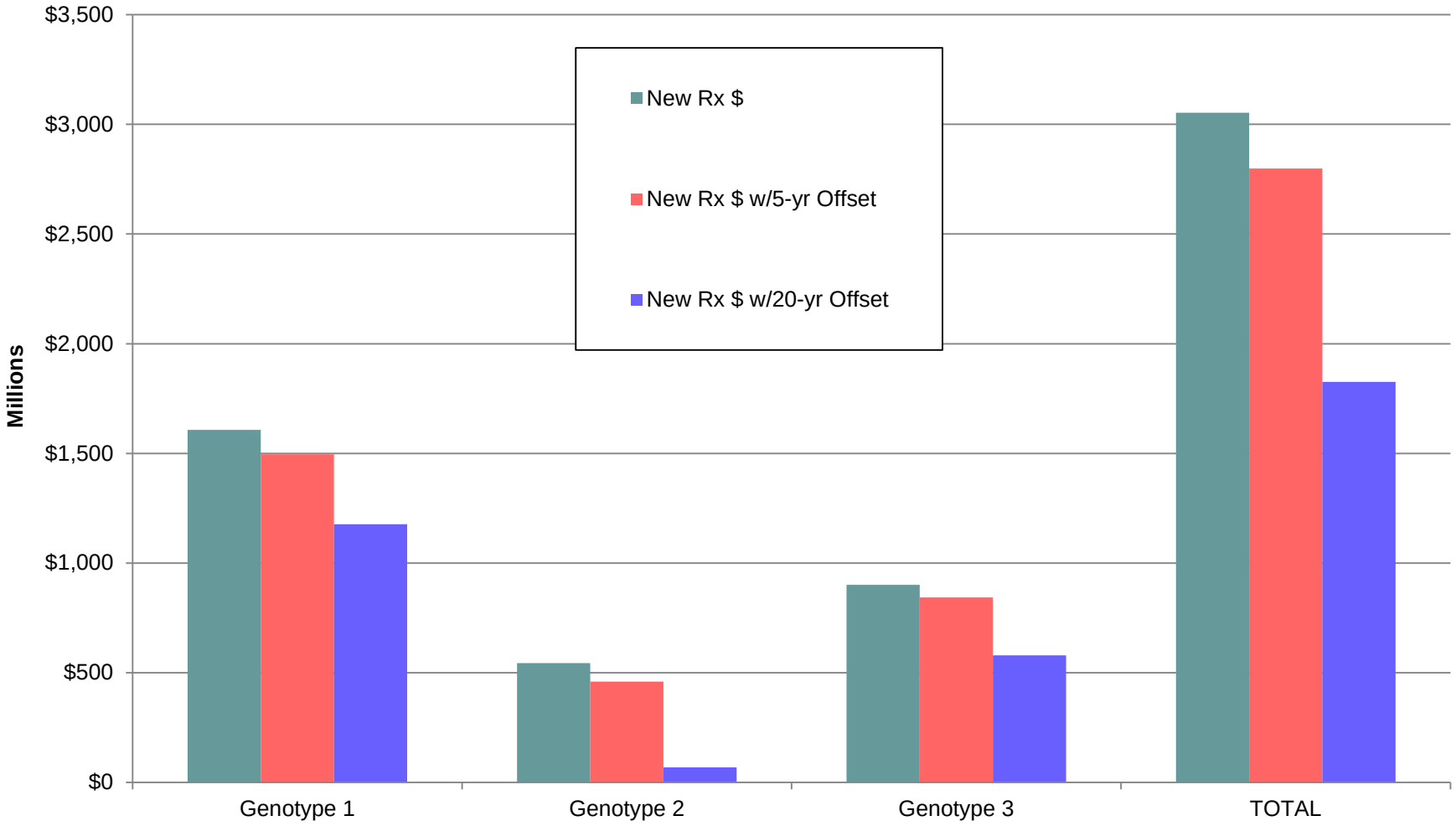


Budgetary Impact to Medi-Cal and Dept of Corrections

- Key Assumptions:
  - Candidate population: 93,000 with chronic HCV*
  - 50% of infected individuals aware of infection and treated
  - Most effective new therapies for GT1 (LDV/SOF) as well as GT2/GT3 (SOF + R)
  - Presented as increased treatment costs over one year as well as with potential offsets after 5 and 20 years
    - Compared to cost of PR, weighted by % eligible for interferon-based therapy (60%)

* Express Scripts 2014. http://lab.express-scripts.com/insights/specialty-medications/state-governments-may-spend-$55-billion-on-hepatitis-c-medications

Budgetary Impact to Medi-Cal/ Dept of Corrections: All Patients

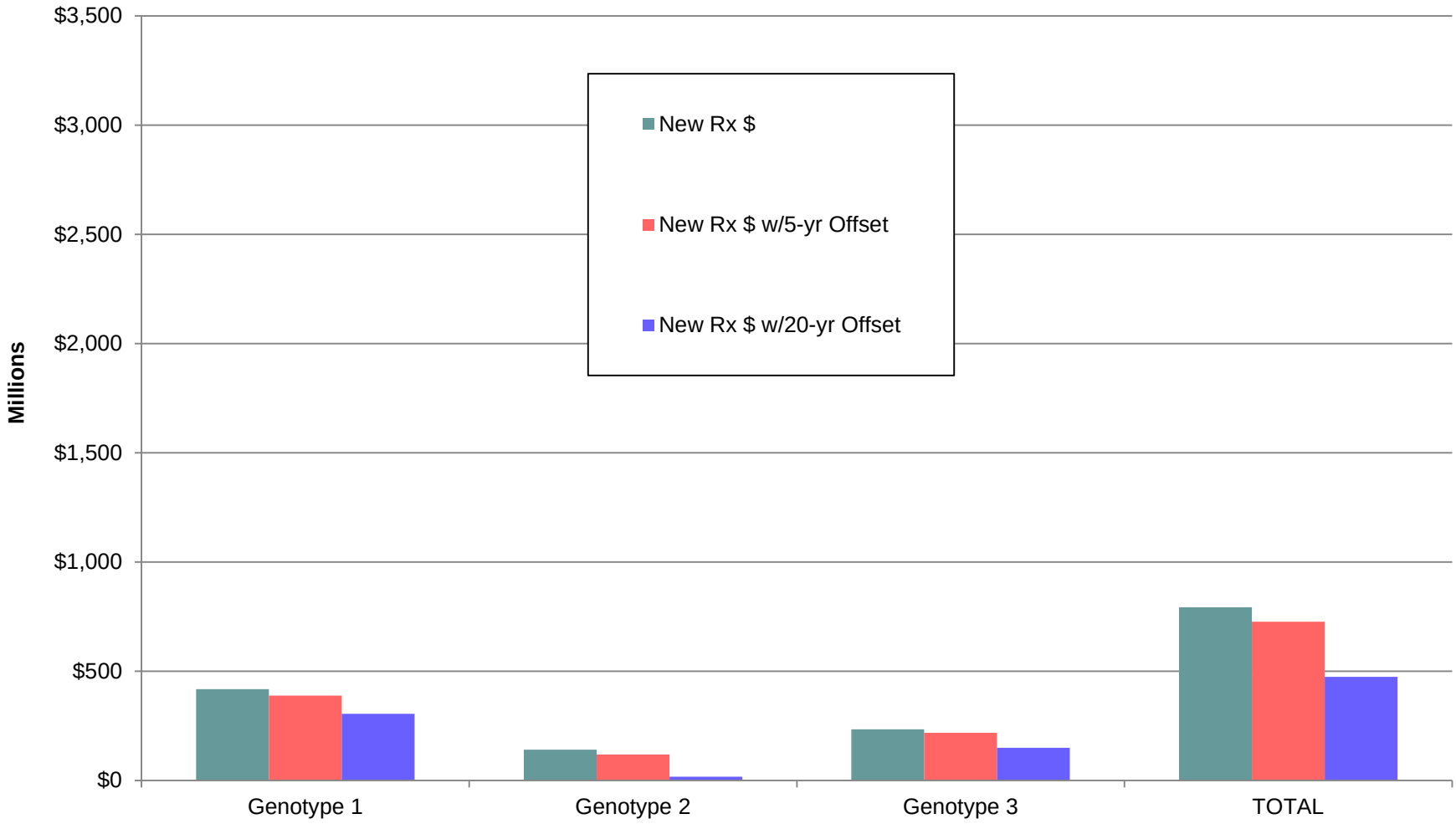


Budgetary Impact to Medi-Cal/ Dept of Corrections: All Patients

- First-year budgetary impact across the three common genotypes:
  - ~$3 billion ($33 PMPM)
  - 5% increase over current Medi-Cal base PMPM ($611)*
- Approximate Medi-Cal payment for well-child visits in established patients: $44
- Increased expenditure = ~70 million well-child visits
  - ~18 visits for each of the 3.9 million children currently enrolled in Medi-Cal

* DHCS, 2014: http://www.dhcs.ca.gov/dataandstats/reports/Documents/MMCD_Fin_Rpts/Medicaid_ACA_Expansion_Rates.pdf

Budgetary Impact to Medi-Cal/ Dept of Corrections: F3/F4 Only



Policy Threshold Discussion

- Assumptions:
  - Current Medi-Cal PMPM: $611
  - # of individuals with HCV GT1 in Medi-Cal/Dept of Corrections = ~65,000
  - 50% of infected individuals aware of infection and treated
- Cost of new therapy that would meet 0.5%-1% PMPM threshold: ***$34,000 – $42,000***

Policy Threshold Discussion (2)

- At current LDV/SOF prices, number of patients that could be treated with 8/12 regimen if expenditure increases held to:
  - ≤1% PMPM: ~16,500 (64%)
  - ≤0.5% PMPM: ~12,600 (49%)
- If treatment restricted to F3/F4, all patients could be treated at current prices and remain under 1% threshold (at 0.5% threshold, 91% could be treated)

Public Comments Received: Model

- Estimate of % with known infection (50%) too high… or too low
- Drug prices do not take mandated/supplemental rebates into account
- Complication/HCV care costs underestimated
- Models do not consider benefits of “treatment as prevention”
- More clarity needed around:
  - Medi-Cal PMPM calculation
  - Rationale for 0.5%-1.0% PMPM thresholds
- Incremental costs/budget impact should be compared to “new” standard of care (e.g., SOF + PR, SMV + SOF)

Summary

- LDV/SOF and other potential interferon-free regimens provide substantial clinical benefits over historical treatment
- Short-term budgetary impact to Medi-Cal/Dept of Corrections would be 5% PMPM under policy analysis of all eligible patients with known infection treated at current prices
- Limiting treatment to patients with F3/F4 fibrosis would allow all or almost all patients to be treated at current prices while remaining below 0.5%-1.0% PMPM budget impact
- Price of new drugs for HCV that would allow treatment of all infected individuals with known infection without exceeding 0.5%-1.0% PMPM increase: $34,000 – $42,000