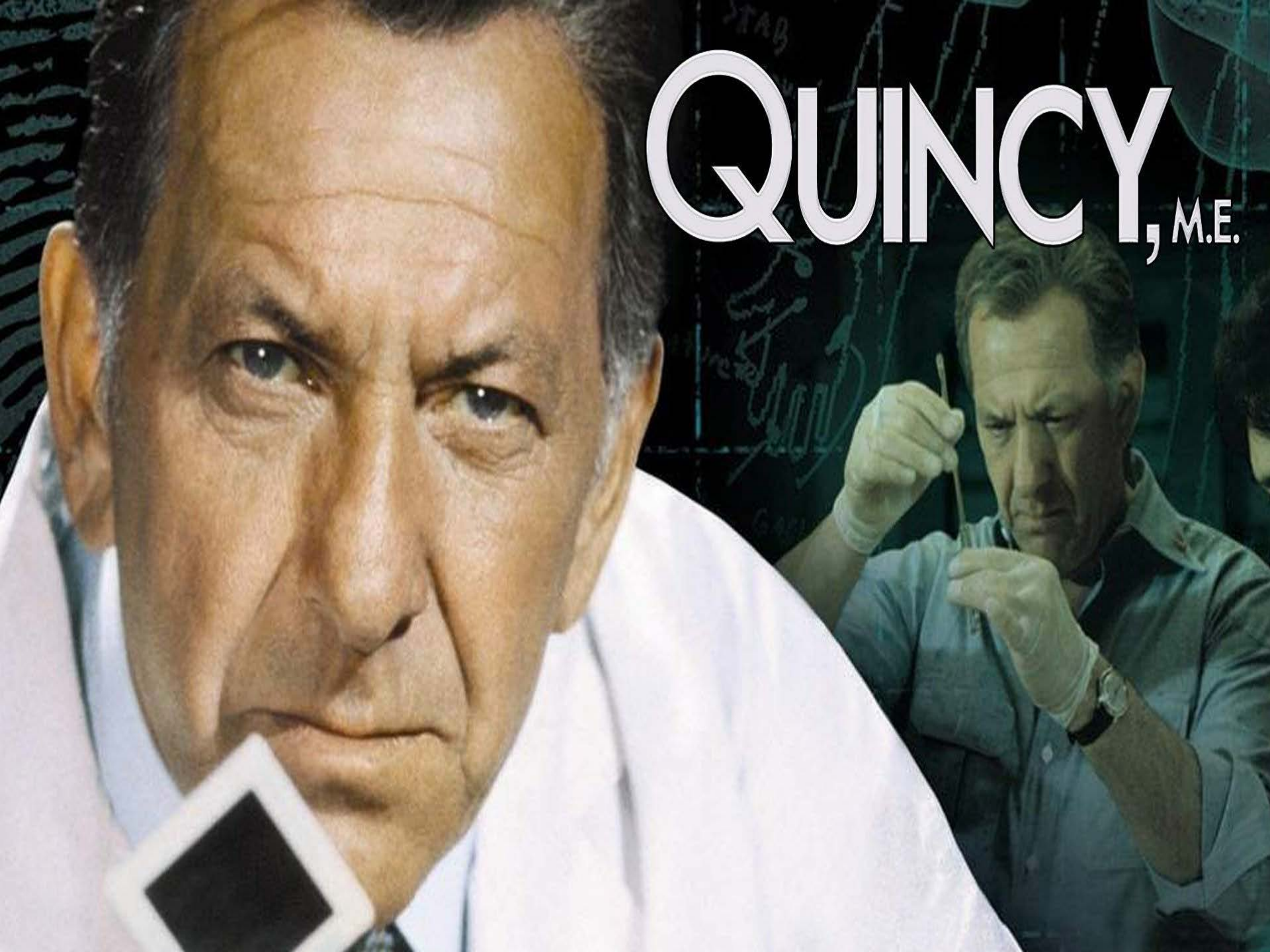
Orphan Drugs: overview of current issues

2.5.18

Michael S. Broder, MD, MSHS

What TV series was instrumental in the passage of the Orphan Drug Act?

For extra credit, what was the main character's first name?


QUINCY, M.E.

Orphan Drug Act of 1983

Covered drugs

that had “no reasonable expectation that…cost…will be recovered from…sales” (commercially non-viable) and are not patentable.

Amended in 1984 to

allow drugs for diseases affecting “less than 200,000 persons” (prevalence-based definition*) and remove non-patentability requirement.

US has no “ultra rare” vs “rare” distinction.

* roughly 65/100,000 in the US

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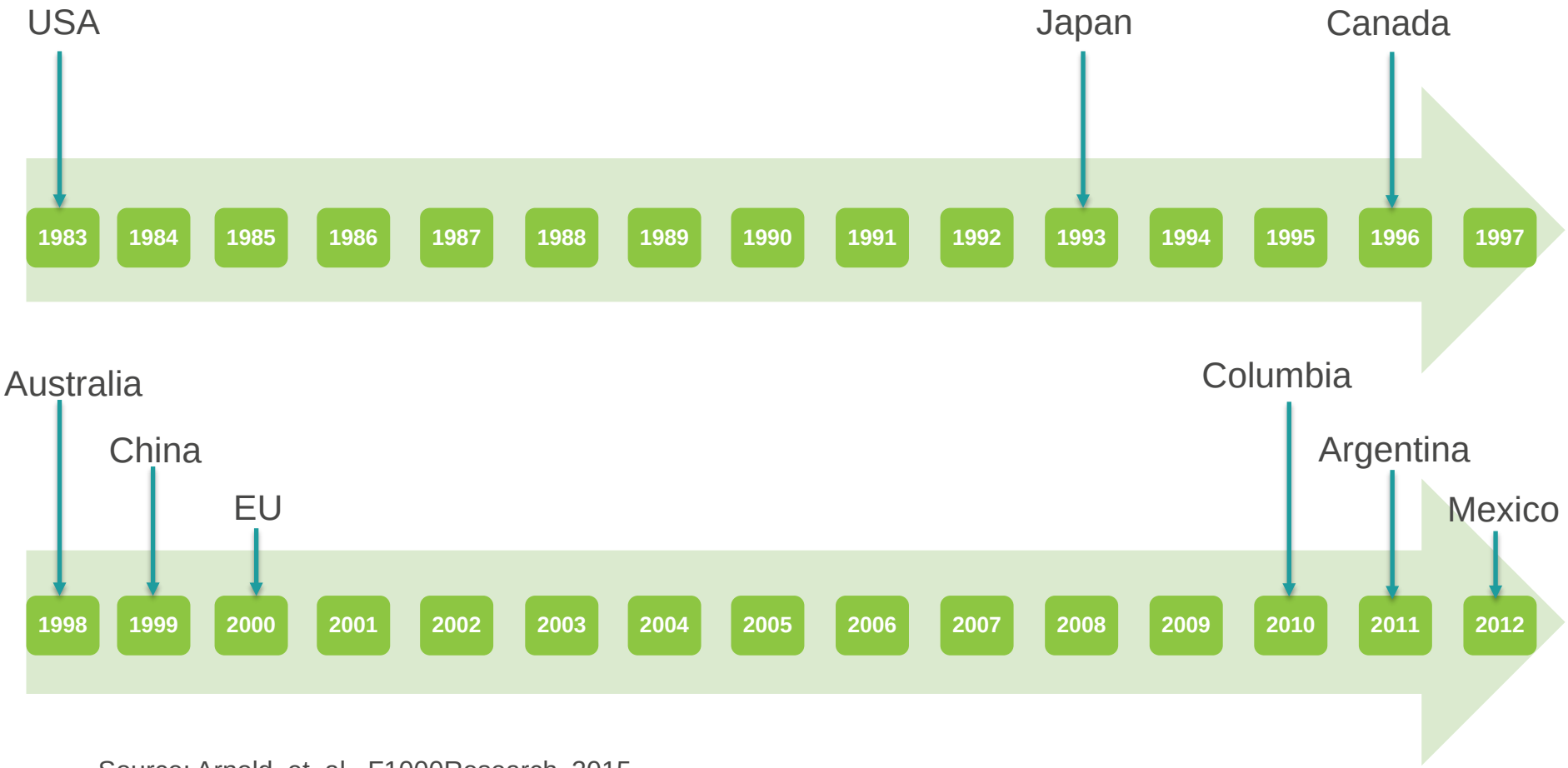
US led the way in orphan drug legislation



Source: Arnold, et. al., F1000Research, 2015

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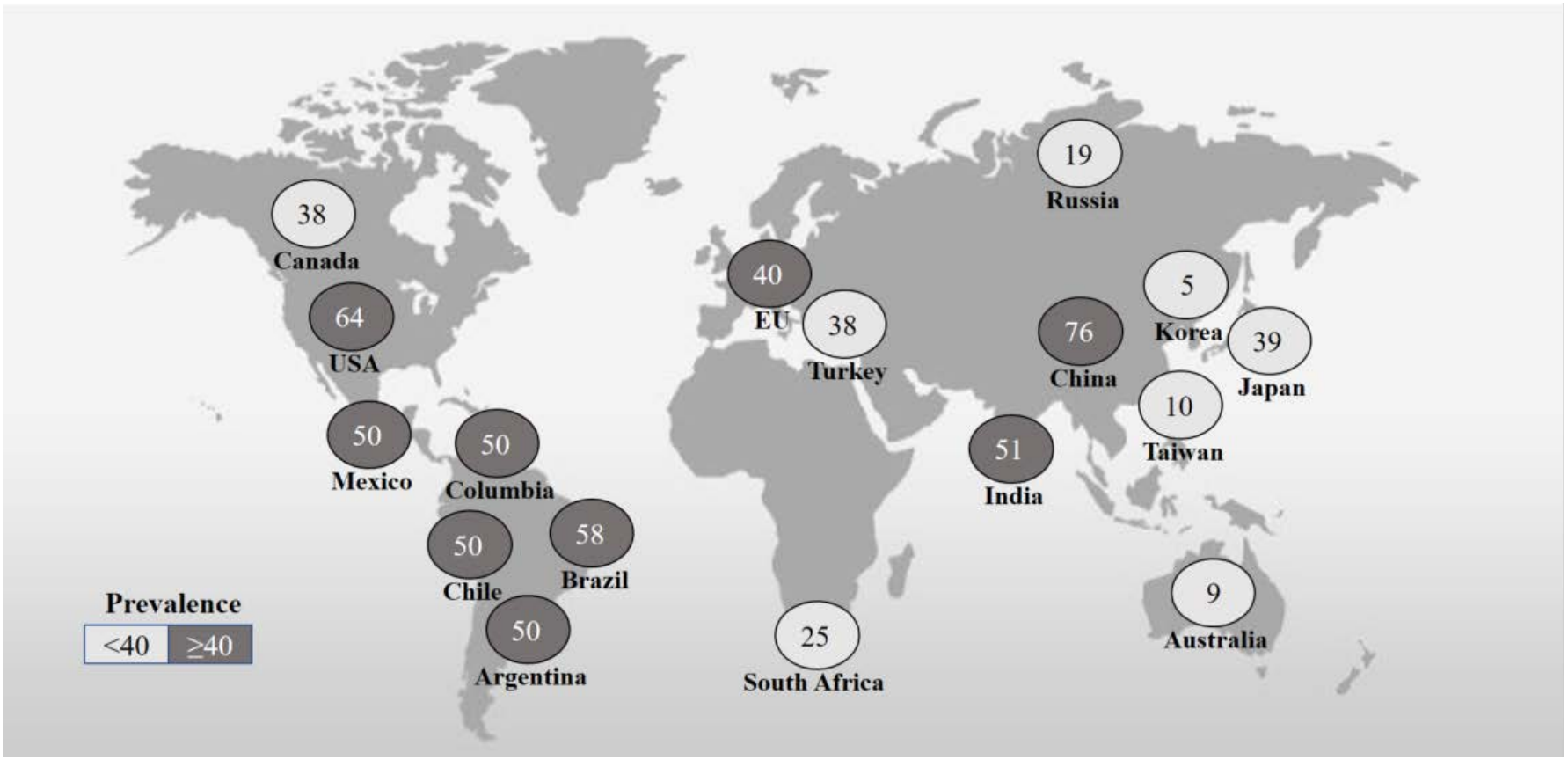
Most countries use a prevalence threshold around 40 cases per 100,000 population



Source: Richter, et. al., Value in Health, 2015

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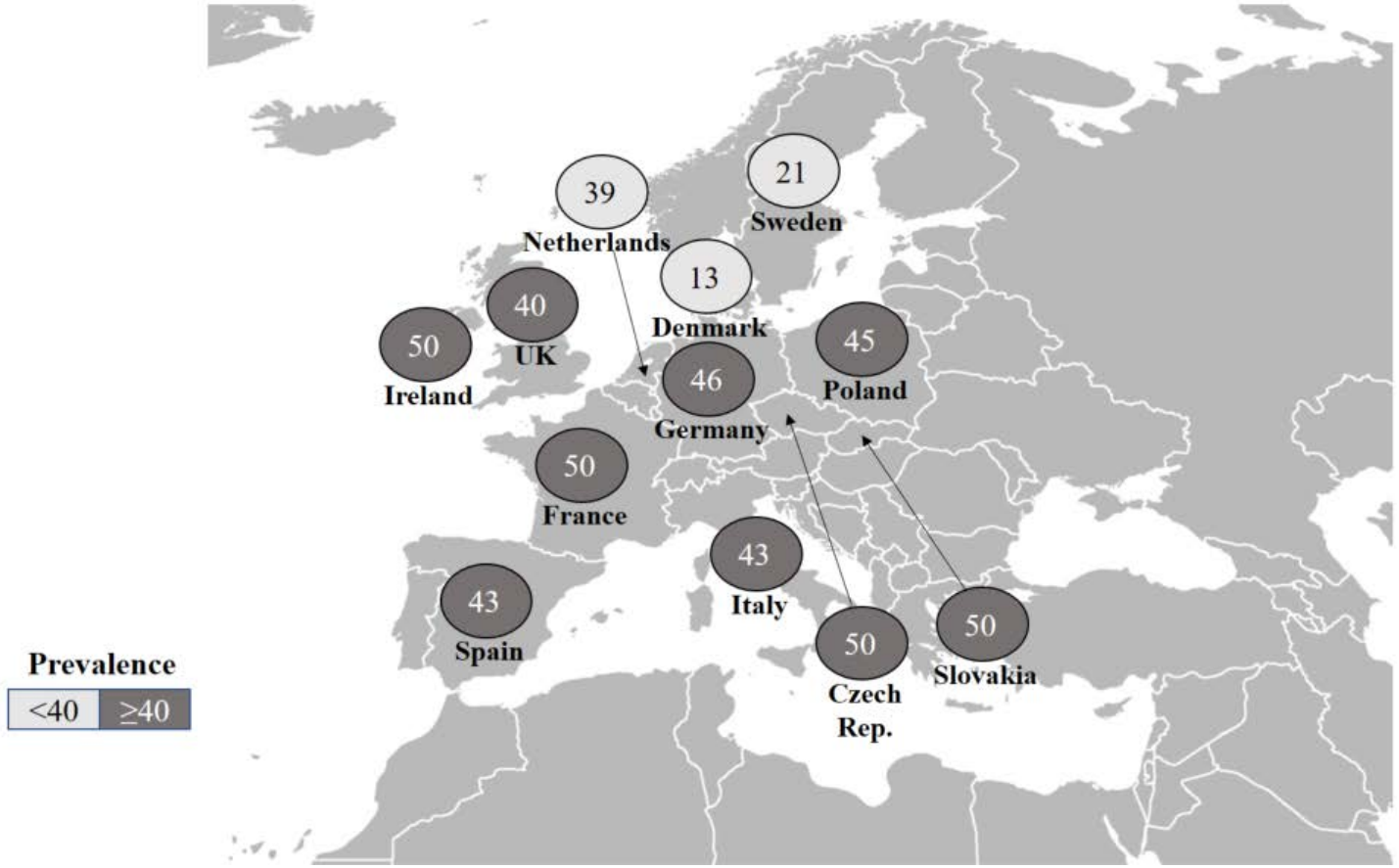
Most countries use a prevalence threshold of about 40 cases per 100,000 population



Source: Richter, et. al., Value in Health, 2015

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Benefits of orphan status have expanded

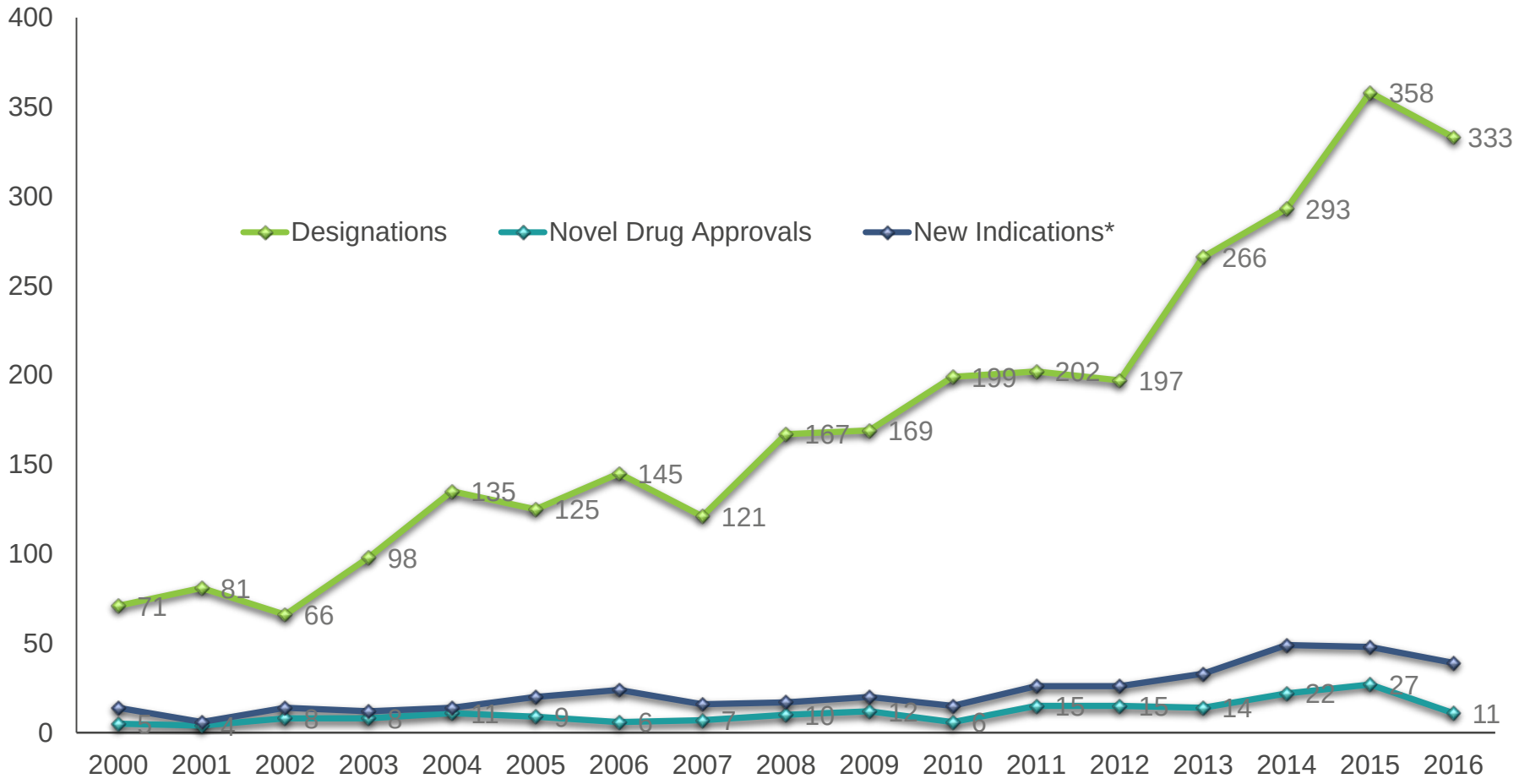
- As of 1985
  - 7 year exclusivity period
  - 50% tax credit for clinical R&D
  - Protocol development assistance
  - Various research grants/subsidies
- 2010 ACA added
  - Exemption from user fees ($2 million/submission in 2017)
  - Exemption from 340B drug discounting
  - Exemption from annual market-share fee ($4 billion for the whole market in 2017)
  - Dedicated FDA resources (frequently faster approval)

…but orphan exclusivity is less important

Exclusivity category/legislation	Exclusivity period
Orphan Drug Orphan Drug Act, 1983	7 years
New molecular entity Hatch-Waxman Act, 1984	5 years
New formulation Hatch-Waxman Act, 1984	3 years
Innovator biologic Affordable Care Act, 2010	12 years
Pediatric exclusivity FDA Modernization Act, 1997	6 months
Qualified infectious disease product FDA Safety and Innovation Act, 2012	5 years
Single-enantiomer products FDA Amendments Act, 2007	5 years

Source: Healthy Policy Brief: Pricing Orphan Drugs, Health Affairs, 2017

Orphan designations and approvals 2000-2016



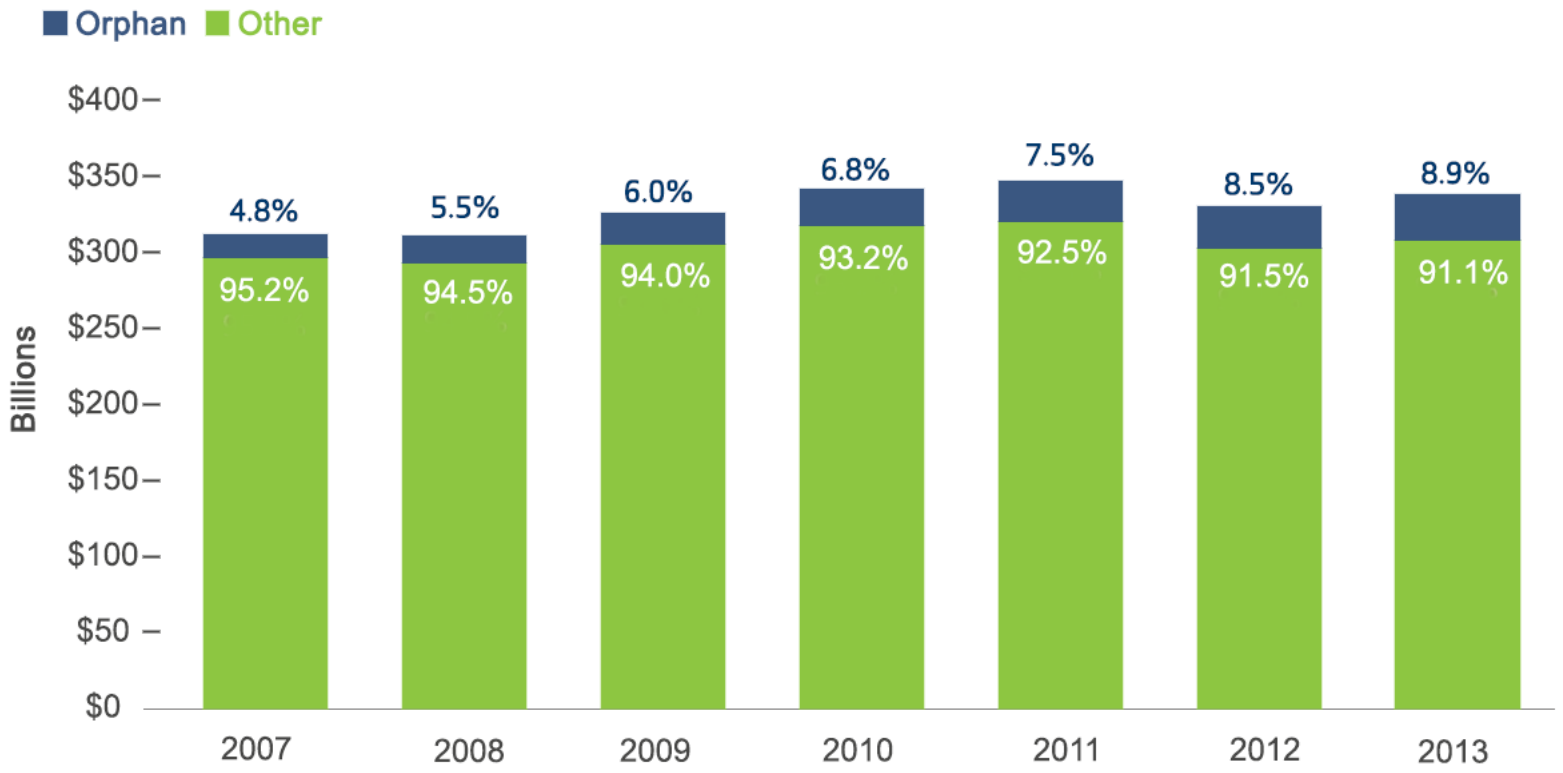
*novel drugs, new indications for orphan drugs, and new orphan indications for non-orphan drugs

Source: US Food and Drug Administration (FDA) website

Concern about (un)intended consequences

- Growth in numbers of orphan drugs/indications
- Growth in cost to the system
- High prices
- Face validity/gaming
- Lower evidentiary standards

US pharmaceutical spending on orphan and other drugs



Source: Divino, et. al., Health Affairs, 2016

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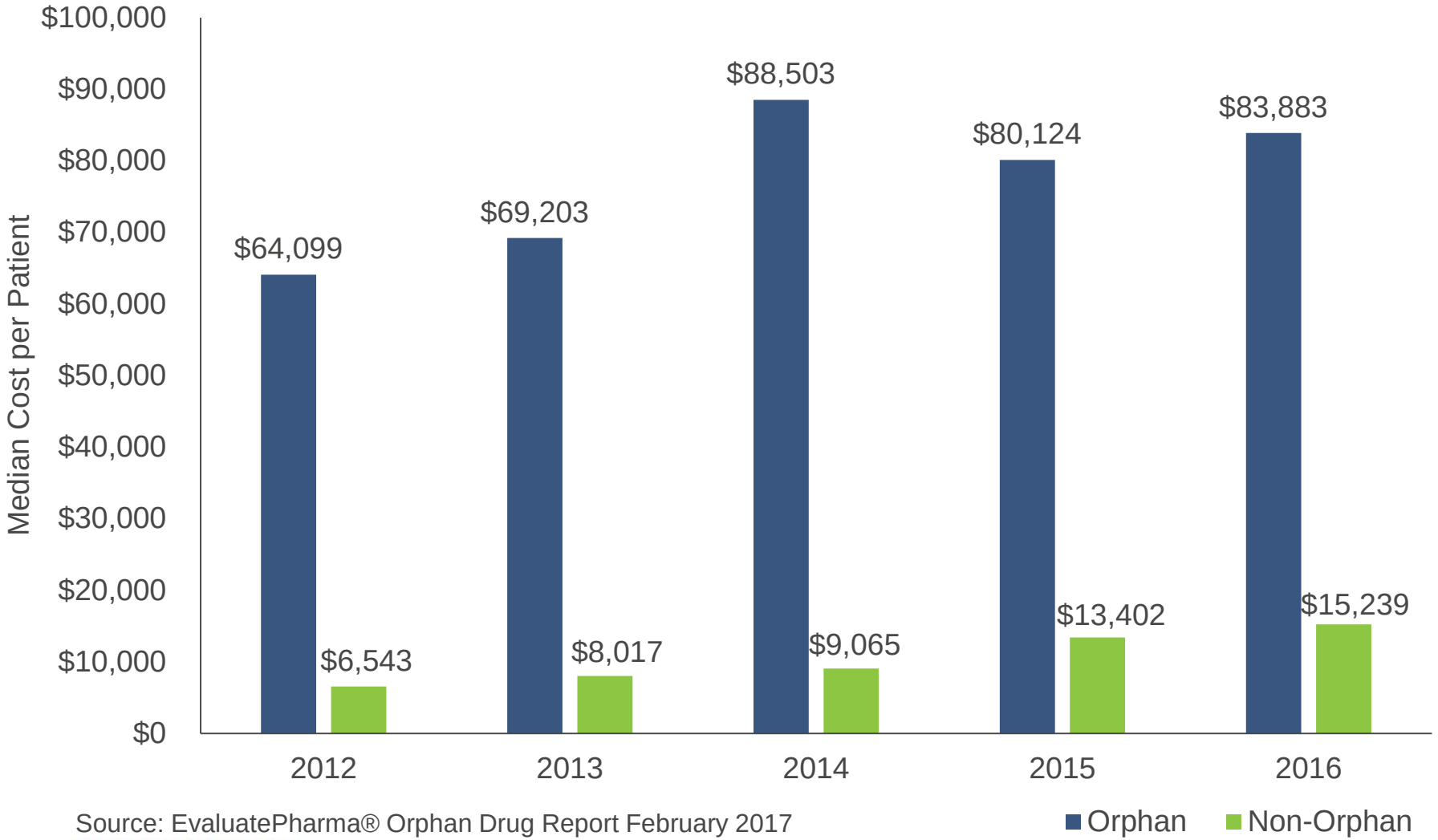
Median cost per patient per year (2012-2016)



Source: EvaluatePharma® Orphan Drug Report February 2017

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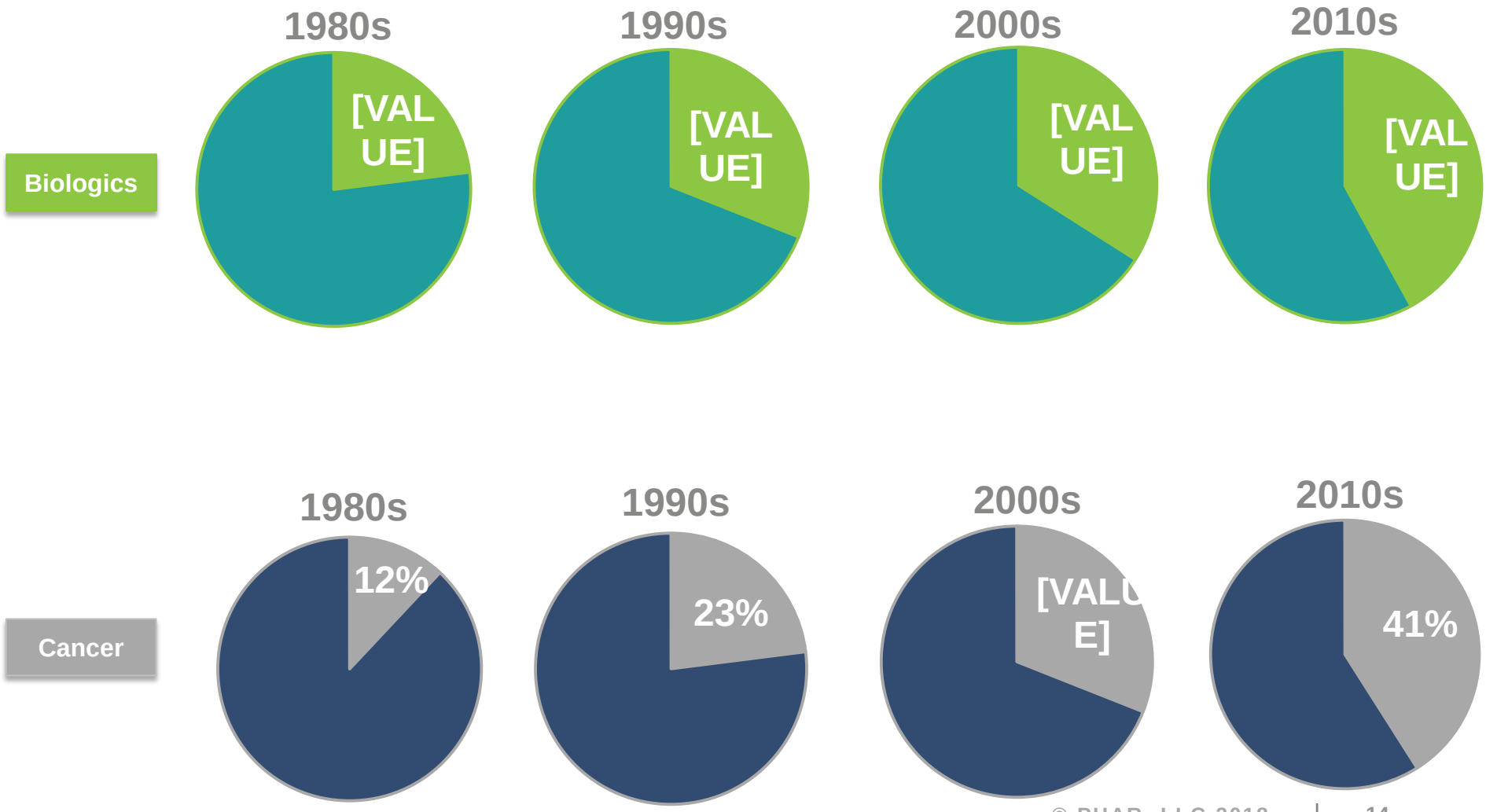
Biologics and oncology therapies have become a bigger proportion of orphan drugs



Source: US Food and Drug Administration (FDA) website

Monthly cost of oncology drugs 2009-2015 does not differ substantially by orphan status

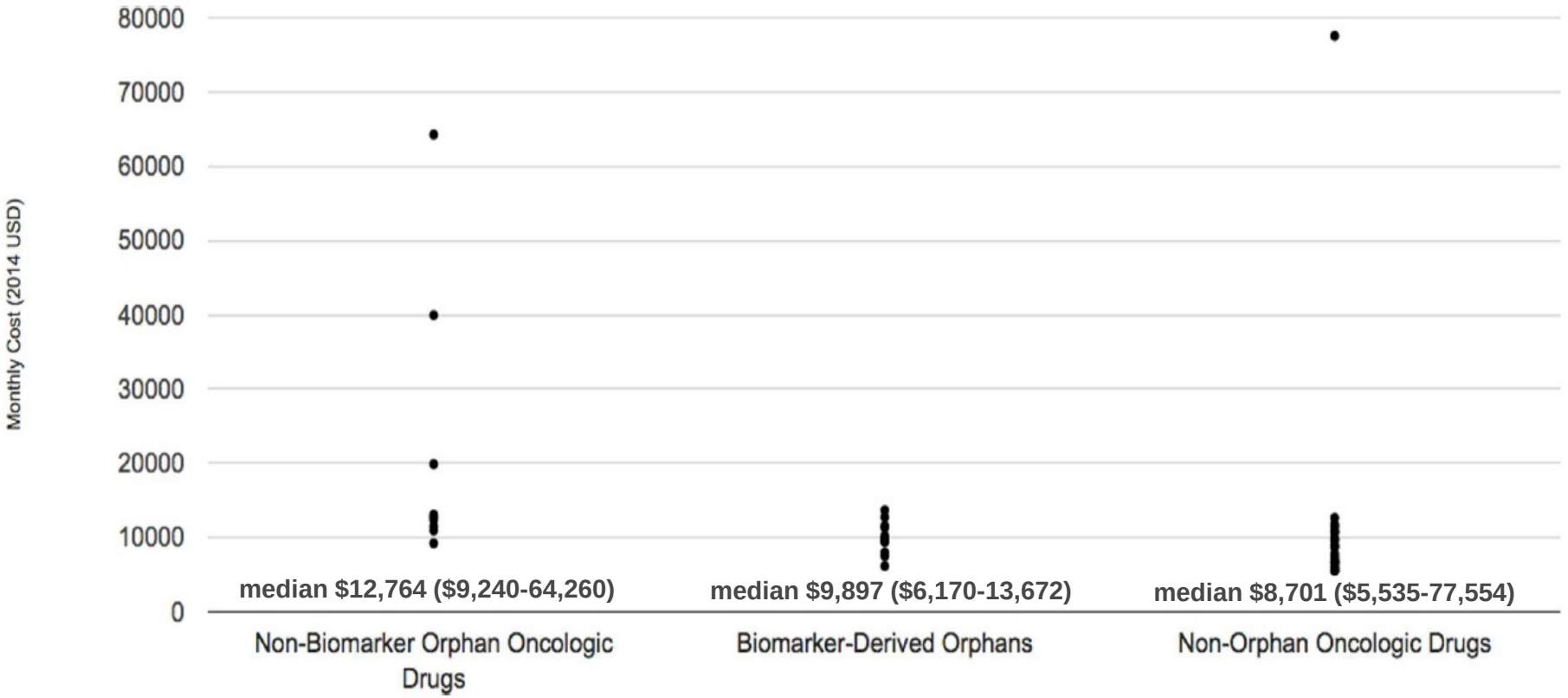


Fig 2. Monthly cost of three subgroups of oncologic drugs. See S1 Appendix for raw data used in these figures.

doi:10.1371/journal.pmed.1002190.g002

Source: Kesselheim, et. al., PLOS Medicine, 2017

What is an orphan?

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What is an orphan?

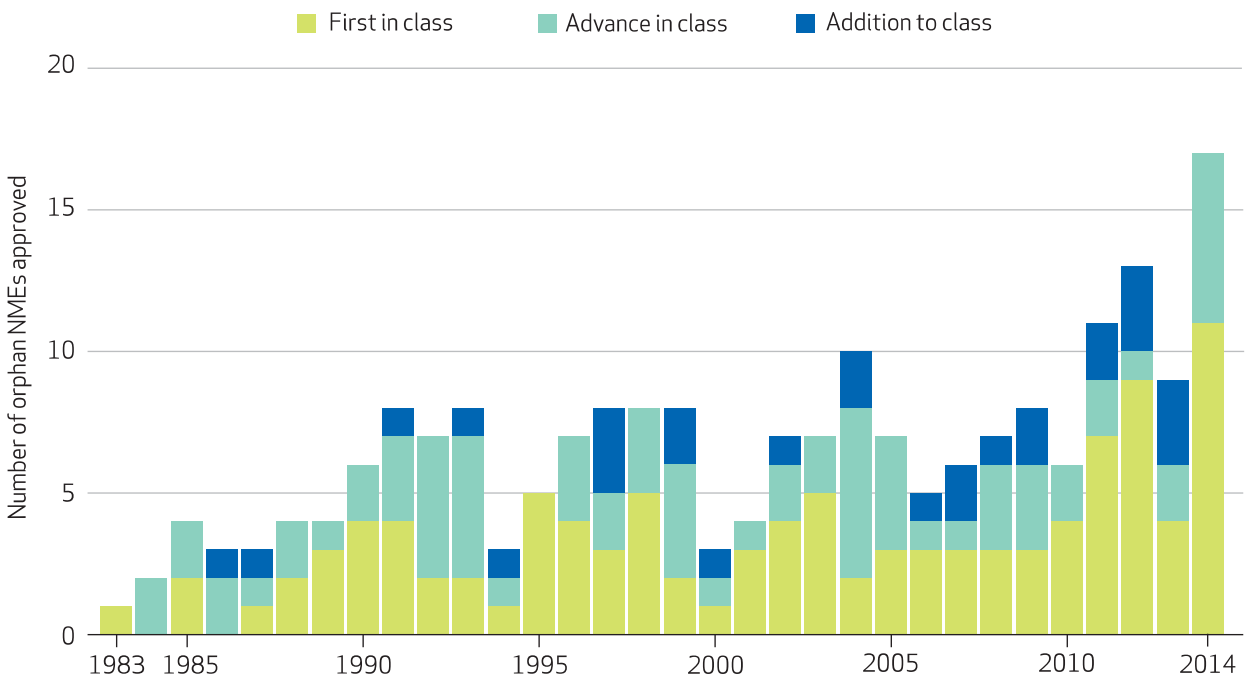
356 branded orphan drugs (1983-2013), and 64 had ≥1 non-orphan indication.

- Epogen is orphan for anemia in ESRD (n=80,000) but $2bn sales mostly off label
- Humira is orphan in JRA (n=50,000) but $8bn in sales mostly for non-orphan indications

Most orphan drugs are innovative

EXHIBIT 1

Number of orphan new molecular entitles (NMEs) approved, by year and innovation category



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Source: Miller Health Affairs 2016

Evidence standards probably lower for orphans

"orphan designation does not alter…regulatory requirements”--FDA

Neurology: 32% with an orphan indication had ≥ 2 placebo-controlled RCTs vs 100% with no orphan indication (Mitsumoto)

Oncology: orphan pivotal trials less often blinded (4% vs 33%), fewer patients (96 vs 290), less likely to be randomized (30% vs 80%) (Kesselheim)

All approvals 1983-2010: “flexibility” by FDA in 2/3 (90/135)

Source: Mitsumoto, et. al., Ann Neurol, 2009; Kesselheim, JAMA, 2011; NORD 2015

Summary

- ODA stimulated the development of certain types of drug
- Rare diseases now have more treatments
- More money (too much?) is made treating those diseases
- Conditions treated might differ from original conception
  - is cancer what Is this what Quincy (and Congress) had in mind?