Content from the **No Patient Left Behind (NPLB) Fellowship** compiled by Avish Vijayaraghavan (Last updated 01/02/25)

- NPLB Fellowship organised by RA Capital, Elena Solopova, Peter Rubin, and Peter Kolchinsky (occasionally referred to as PK in these notes)
- General reference: The Great American Drug Deal by Peter Kolchinsky
- GCEA reference: Valuing the Societal Impact of Medicines and Other Health Technologies: A User Guide to Current Best Practices
- US healthcare reference: Health Policy 101 | KFF
- Live webinars from: Amitabh Chandra, Neelima Firth, Tess Cameron, Erich Scheller, Richard Xie, Peter Kolchinsky
- Other notes from the NPLB Slack channel

Biotech Social Contract and birds-eye view

Category	Details
Core Principles	- BSC = drugs go generic without undue delay + universal insurance with low/no OOP costs. - BSC not about "fair" price - that's hard to quantify. It's about whether a drug will go generic. - Key to innovation is offering high-enough reward. Price controls would kill innovation. - Key to getting value is ensuring all drugs go generic without undue delay. - Key to affordability is proper insurance. Reduce/eliminate high copays, deductibles, and other OOP costs. - **Don't need to choose between innovation and affordability.** Make them affordable or at least generic, then ensure more are made. Policy should based around this idea. - Biomedical innovation is a national strategic resource (for the US but also other countries with big pharma ecosystems). - Preserve market-based pricing for a patent-based exclusivity period & enact insurance reforms to lower OOP costs (MPI) - If we undervalue medicines, or fail to incentivise their development, we get fewer. Have to incentivise the first steps so people make full climb. Can't hold out for the ultimate product (e.g. cure for cancer), you have to incentivise the intermediary drugs too. - Point of brief patents: companies can make profits but need to innovate to continue.
Aligning stakeholders	- Industry aim: pharma should make profit from innovation not long tails of profits from old drugs. Clipping long tails impacts a few companies in near-term but keeps fundamental innovation engine going. - Policy aim should be: incentivise development of drugs, keep innovation going, keep the game (i.e. market) fair. - Investor aim: support industry, make money within 15y (30y maximum) so you can enjoy returns while alive. - Employee aims: contribute to science and drugs. Altruism doesn't need to be the motivation for employees but the underlying industry principle is noble: cheap drugs for everyone while maintaining innovation forever.
Broader economic benefits	- Society gets lots of benefits of drugs before they reach generic stage: people who need the drugs take the drugs and don't go to hospitals for surgeries, etc. - Drugs, unlike services, benefit from economies of scale i.e. higher the number of patients that need a generic drug, the less expensive it is to treat each one. Services require land which is in short supply, especially in cities. - Taxpayers contribute to innovation. Private sector pays society back in tax revenue and 40-50 new drugs every year.
Policy Challenges	- Need to understand policy change throughout entire ecosystem. - Why don't all drugs go generic? Patent evergreening, biologics are harder to create generics for. So need solutions against this. - Left doesn't believe in profits and patents, nor discuss insurance. Right can be too libertarian i.e. no social safety nets. Remember: Republicans don't charge out-of-pocket (OOP) for firefighters when a house is on fire… why should we for healthcare? - Public perception and response is a key market signal. Most dangerous thing for innovators is uninformed public → need to show the wins and the struggles of the industry.
Policy Solutions (more in-depth version in final table)	- Universal insurance with low/no OOP costs. - Contractual genericisation for biologics. - Patents. Appropriate scoping, policies allowing improvements but preventing evergreening, industry cooperation with generic manufacturers once patent expires. - Instead of standard cost-effectiveness analyses (CEAs), use generalised cost-effectiveness analyses (GCEAs) - you should do a GCEA yourself first before showing drug to other bodies like ICER or NICE. - EU has 20y patents and 10y patents for orphan drugs (i.e. rare diseases). Also has tougher laws around patent evergreening and pay-to-delay. - Need proper incentives for improvements (e.g. cure rate, mode of delivery, frequency of delivery). - Government can create market (financial need) where society needs one e.g. US govt stimulated drug dev for anthrax and smallpox by committing to buy disease from those who succeeded - - Why don't we see more investment in antibiotics? Knowledgebase higher than many other medicines but society doesn't pay much for them once developed and uses them sparingly. Govt now talking about enlarging reward for new antibiotics (e.g. in US, the Disarm Act) to encourage development.

Example of market effects: drugs for Hepatitis C Virus (HCV)	- Calculate value from convenience, side-effects, cure rate, cost/patient, cost/cure, number of patients treated - Hepatitis C treatment was $40k injectable drug with 40% chance of curing HCV i.e. $100k per cure. - That was a signal that the US would pay well for better drugs e.g. $50k for 50% chance of cure. - Several companies launched pills with 97% cure rates. - Price dropped from $80k to <$30k through competition - Curing HCV with drugs is 7x cheaper than managing diseases and that's before they became generics - Had the first HVC treatments been price-controlled, innovators and investors might not have bothered to develop better drugs. Same with drugs for HIV, blood pressure lowering, cancer, migraines, diabetes, etc. - Price controls would leave us burdened by diseases and higher costs. Even a credible ***threat*** of price controls can divert biotech investment elsewhere.

Pharma industry finances

Category	Content
Development process	- Starts from knowledge base (academics, NIH, past failures) - Early stage (discovery to P2 end): startups and VCs - Late stage (P3+): big pharma acquisitions - Regular funding needed from VCs and potential IPOs - Climbers of this development mountain are motivated by potential profits, investors motivated by higher chance of success i.e. higher knowledgebase so shorter climb.
Side note: R&D doesn't stop at approval	- Pre-approval R&D and post-approval real-world learning - Approval just means a drug will have a favorable benefit-risk profile for some patients. Over time we learn more. FDA approval is just a marker at which we switch from investors funding it to all of society (via premiums) funding it. Drugs can also evolve e.g. repurposed for new diseases or populations. - This idea should be communicated better to public. Public doesn't know about pharmacovigilance, medical affairs, post-approval safety studies, FAERs datasets. Often captured as selling, general and administrative expenses (SG&A) spending, not R&D spending.
Drug development costs	- Discovery: $15M - Phase 1: $30M - Phase 2: $200M - Phase 3: $400M - Costs include: hospitals, physicians, nurses, laboratories, safety boards, record keeping - Also unquantifiable human cost of developing a drug. Patients risk their lives and/or know they could end up in control group with a placebo.
Success rates	- Very few candidates make it to trials - Only 1/10 trial drugs make it to market - Only 1/100 trial drugs becomes a blockbuster - Investment return around 15% annually
Questions investors ask	- Innovators need funding. Investors need return on investment (RoI). - Innovator asks: "There are n patients with this disease, maybe x% will get treated with our drug, so with a price of $a, we expect peak sales of $b." - But investor asks: "At $b peak sales, the drug would be worth $c at launch. But it will take k years and up to $d in funding to get there." - Further investor questions: "How can you be sure patients will want it and doctors will prescribe it? How can you be sure insurance will cover it?"
How does pharma investing work?	- PNL on balance sheets. How companies are judged on earnings per share. - Discount rate arbitrage. Discount rate: discount between something over multiple years vs right now. These work with Net Present Values (NPVs). Reconsider 3% discount rate in valuations. - - A discount rate is higher than just inflation. It includes: inflation (money being worth less over time), risk (chance the future money might not come), opportunity cost (what you could earn by investing the money elsewhere, like in stocks or bonds). - Look at net present value (NPV) of idea vs NPV at time of approval e.g. investor puts in 5M with drug potential of 7B. - Investors representing $320B AUM and 665 drugs in development support R&D modeling changes → 1200 advocates urge IRA changes - Investing in just one drug is too risky, hence investors have portfolio where they need just one win. **Reward isn't just reward for one company, it's reward for the whole portfolio.**
Key challenges	- Patent expiration information hard to find - Forecasting biotech success is difficult - Balancing innovation incentives with accessibility - Investment requires portfolio approach due to high failure rates - Congress says to cut profits of winners but doesn't understand they subsidise rest of portfolio and that makes investment harder
Industry Scale	- Drug industry sales 2018: $344B (US), $1.15T (worldwide) - Profit margins range from 10-20%. Less than banks and software, similar to oil and gas. - 3% US workforce (4.7M people), 15M globally - Average US salary: $60k-80k (US median is $58.5k) - Why don't companies raise drug prices 10x if America is price-insensitive? - - Pharma execs and boards feel social pressure to justify prices. - - They can justify above-average salaries/profits but not record-setting. - - Given these limitations, total revenues of the drug industry can only be so high at this time.
Pharma stocks are not usually safe long-term investments…	- To avoid prices declining after patent expirations, big pharma often acquires lots of smaller similar companies to retain revenue. - Most (Pfizer, Merck, BMS, J&J) have underperformed S&P 500 over past 20y. - Exceptions: Lilly/Novo (weight-loss drugs) - Better as trading stocks (on order of years rather than days) than long-term holds - To be a long-term investment you'd have to have multiple blockbusters periodically, most likely in different areas so they are uncorrelated i.e. the pharma company itself is diversified.
Precarious nature of	- Industry makes 10-20% profit margins. It would only take a 20% drop in drug prices or 30% cut in US price alone to wipe out most profits.

pharma ecosystem	This would shrink the industry. - And yet, 20% decrease to drug prices per patient on a 20k/year drug doesn't even make it affordable. The price drops to 16k/year but it's spread over insurance payments → insurance payments are the thing that need changing. That's why we need insurance reform. - For the industry to continue to employ the people it does and attract investors to fund innovation, it will have to maintain its current revenues and profits. **Note: not saying we should charge more, but that we are at near-equilibrium.**

[How drug affordability and access impact investment decisions] (Erich Scheller, Investor at RA Capital)

Key elements required for an investment

- Ideal case for investors: lots of money quickly → this is possible for some industries like tech
- But biotech has long timelines because of hard manufacturing + clinical trials
  - Shorter adaptive trials and inexpensive manufacturing are good
  - Faster enrollment is good
- What makes investment worth it: larger market, higher diagnosis and treatment rate, fewer competitors, high adherence, higher price
- Probability of success based on: validated target, known/safe modality (e.g. small mols vs biologics), low placebo effect, clear biomarkers, high unmet need
- How understandable (perceivable) this all is (simpler is better; but not so unbelievably easy that anyone could do it): companies and products, proof-of-concept data, clinical trial data + trial design (objective endpoints, dose responses), publications, credible team

Some key terms

- What is it worth if it works (WiiWiiW): aggregate value generated over the lifetime of the drug (don't forget to discount for time!)
- Probability of Success (PoS): % chance that a drug will achieve its full value (WiiWiiW)
- Fair Value: what something should be worth today (WiiWiiW x PoS)

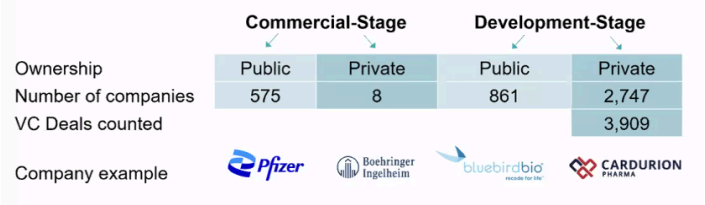
Discount for time

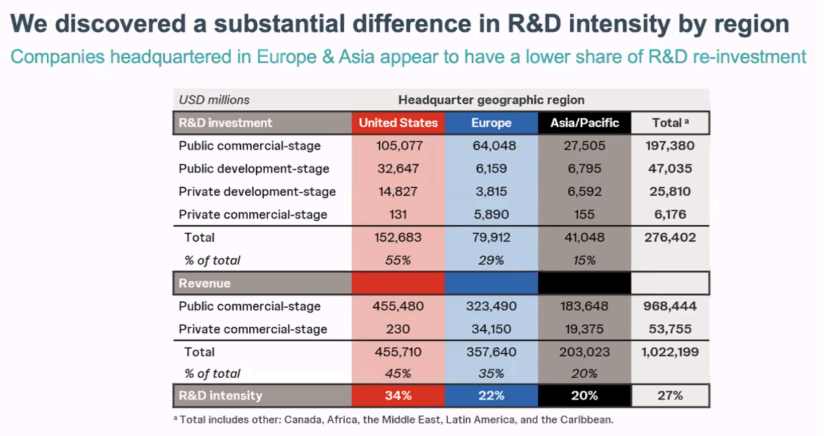
- Simply, a dollar tomorrow is worth less than a dollar today.
- Why? Because a dollar today can be invested (and start generating a return)
- And future dollars will be affected by inflation (or other uncertainty)

To determine WiiWiiW, we need to model: price of the drug, number of patients that are going to get the drug, how long that price will hold before the drug goes generic or negotiated down.

- All three of these are affected by affordability and accessibility of a drug for patients.
- Note penetration starts lower for first few years then increases and plateaus.
- Drug price can be negotiated such that there is a price cut
- Regulations put in place where drugs go generic so price will drop then
- High copays, prior auth or other impediments lower penetration as makes it harder for patients to get drugs.

Pharma industry finances from a global perspective

US pharma is the key market globally by far	- US dominates: 48% of all global companies, accounting for 55% of investments and 65% of development funding - Top 20 companies = 49.5% global R&D - R&D costs 5.7x larger than sales/marketing. DTC even less. - R&D intensity increasing over time which means drug dev is costlier than we thought
	[Slides from Amitabh Chandra] Four mutually-exclusive groups make up R&D system 

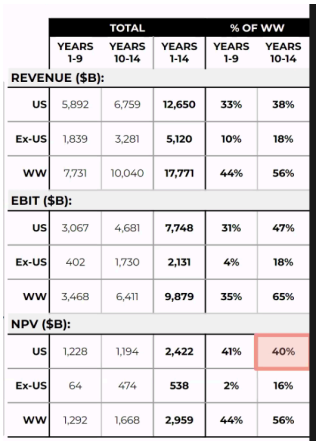
	Companies headquartered in Europe & Asia appear to have lower share of R&D re-investment (in table below)  **We discovered a substantial difference in R&D intensity by region** Companies headquartered in Europe & Asia appear to have a lower share of R&D re-investment *USD millions* — Headquarter geographic region R&D investment / United States / Europe / Asia/Pacific / Total [a] Public commercial-stage: 105,077 / 64,048 / 27,505 / 197,380 Public development-stage: 32,647 / 6,159 / 6,795 / 47,035 Private development-stage: 14,827 / 3,815 / 6,592 / 25,810 Private commercial-stage: 131 / 5,890 / 155 / 6,176 Total: 152,683 / 79,912 / 41,048 / 276,402 *% of total*: *55%* / *29%* / *15%* Revenue Public commercial-stage: 455,480 / 323,490 / 183,648 / 968,444 Private commercial-stage: 230 / 34,150 / 19,375 / 53,755 Total: 455,710 / 357,640 / 203,023 / 1,022,199 *% of total*: *45%* / *35%* / *20%* R&D intensity: 34% / 22% / 20% / 27% [a] Total includes other: Canada, Africa, the Middle East, Latin America, and the Caribbean.
US economic impact	- Society saved $2T from generic drugs over past decade - America paid $271B for branded drugs in 2018 - Potential $200B/year savings once current brands go generic - Long-term healthcare cost savings (20+ year timelines). New drugs benefit us and future generations.
International Pricing	- US pays more and is more reliable market - Europe is a fragmented secondary market i.e. pays less and is less reliable - Developing countries get large discounts, treated more as foreign aid - Example: Harvoni costs US $94.5k , France $50k, developing countries $600-900
Market dynamics	- Market-based pricing responds to ecosystem. It assumes everything is a negotiation and that patients will hold insurers accountable for representing their interests. - US market signals important globally. Harder to gain traction if US not on board with drug. - Understand market signals e.g. companies don't price a drug very high because perception will be ruined and government can act on this. - Industry profits ~10% of *global* branded drug revenues → 10% price drop globally (or 20-25% in US) would eliminate profit
Price Negotations	- US: Private insurance negotiates through PBMs - Public insurance (Medicare/Medicaid) not allowed to negotiate and initially pay wholesale price - Switches to average sales price after private negotiations - No point lowering drug costs if doesn't also reduce OOP costs - Other HICs: Monopsony power in Europe (e.g. NHS, IQWIG) allows them to negotiate to pay less. These countries are considered "free riders" because they get the benefits of American innovation at a lower price. Tariffs could be used here. - Some LMIC countries (e.g. India) are considered "free riders" because they reap the benefits of foreign R&D, but don't respect drug patents. This is different from other LMICs who simply cannot afford list prices and so get cheaper prices (as a form of foreign aid) but respect patents.
Gilead HCV case study	- Global Trial Strategy: >100 Harvoni studies worldwide. >1500 US and Western European patients but also 47 in Aus, 43 in Central America, 37 in Canada, 38 in Africa, 40 in China, 13 in India, 9 in Russia, 9 in Middle East. - Why? Most infected live in 91 developing countries. - Pricing structure: US: $94.5K, France: $50K, Europe: less, developing nations: $600-900 because Gilead allowed 7 Indian generics manufacturers to make. - Challenge: Western countries thought this was unfair. They don't import from cheaper countries because of intemational law and fear of being cut off from further supply. - Access mechanisms - - Regular market - - - Different prices by region, import restrictions and international law prevent abuse of cheap imports. - - - US negotiation is limited (UnitedHealthcare works for >100M people but they don't "walk away"), Europe has leverage because of single-payer systems and willingness to walk away. - - Compulsory licensing: legal override (if drug deemed necessary for poor nation) of patents for poor nations - - - Rwanda asked Canada to make their HIV drugs (for just Rwandan patients). - - - Rare because: trade relation risks (e.g. Thailand abused it and stopped after US sanctions), only works for small molecules that can be made easily and cheaply.
Challenges with international markets from investor perspective	- Slower sales ramp-up periods due to delayed approvals and coverage decisions so pay later with sales occurring closer to patent expiry. - Revenues can be high in international but profit margins are lower. Unfortunately, it's profit that incentivises investment in R&D, not revenues. And more accurately, it's the present value of those profits. - - Present value := core idea is that $1,000 today is worth more than $1,000 received a year from now because (1) can be invested to earn returns, (2) used to pay for immediate needs, (3) protected from inflation. - - Basically, the PV of a drug is higher in the US since the profits come more quickly. - Question to ask: "would any drug have ben invented if not for hope of US blockbuster sales?" Takes too long, margins too low, launch costs too high, commercialisation too hard (couldn't launch on your own, need acq), R&D costs as high, NPV too low or negative.

Tess Cameron, Investor at RA Capital

- Investors will look at revenue in a box like below

Revenue ($M)	Total			% of WW (US + ex-US)	
	Years 1-9	Years 10-14	Years 1-14	Years 1-9	Years 10-14
US	5,892	6,759	**12,650**	33%	38%
Ex-US	1,839	3,281	**5,120**	10%	18%
WW (US + ex-US)	7,731	10,040	**17,771**	44%	56%

- The red box in table above shows Y10-14 in US accounts for >⅓ of all revenues for a drug with $1.2B US sales and $1.8B global sales! The US market is extremely important for drug sales.
- Earnings before tax and interest (EBIT) will be a lower % value for each of above boxes obviously.
- If you make the patent time much shorter, for example, cut off the final 5 years, net present value (NPV) has a 40% decrease at time of approval (in image on right). This makes this drug uninvestable.
- US prices could halve and all other countries increase 300% to maintain profits. But would any countries accept that?
- Price AND volume are important.



	TOTAL			% OF WW	
	YEARS 1-9	YEARS 10-14	YEARS 1-14	YEARS 1-9	YEARS 10-14
REVENUE ($B):					
US	5,892	6,759	**12,650**	33%	38%
Ex-US	1,839	3,281	**5,120**	10%	18%
WW	7,731	10,040	**17,771**	44%	56%
EBIT ($B):					
US	3,067	4,681	**7,748**	31%	47%
Ex-US	402	1,730	**2,131**	4%	18%
WW	3,468	6,411	**9,879**	35%	65%
NPV ($B):					
US	1,228	1,194	**2,422**	41%	40%
Ex-US	64	474	**538**	2%	16%
WW	1,292	1,668	**2,959**	44%	56%

From cost-effectiveness analyses (CEAs) to generalised cost-effectiveness analyses (GCEAs)

Reference: Valuing the Societal Impact of Medicines and Other Health Technologies: A User Guide to Current Best Practices, Richard Xie webinar

Limitations of current CEAs	- CEA: doesn't consider price decrease after genericisation + context (i.e. marginal value of health improvement to those healthy vs disabled) + ignores scarcity - Normal CEA (used by ICER and NICE): QALYs gained, net costs, productivity, adherence-improving factors - Essentially, drug worth spending if QALY price per country >= incremental_cost / health_gains	
Issues with QALYs	- QALY differs for each person - QALYs can take earning potential into question which is dehumanising - Economists such as Uwe Reinhardt, Dana Goldman, David Cutler, Amitabh Chandra, Darius Lakdawalla, and Julian Reif, and patient advocates like Sue Peschin of Alliance for Aging Research have published on the harms of relying on QALYs and their flaws. But they are still used by organisations like ICER in the US and NICE in the UK. - Bottom line: math to calculate the full value of innovation to society has not yet been invented. Relying on any available agency to set prices for drugs would likely result in them being undervalued, and innovators don't work on what society doesn't value.	
GCEA potential	- Hard to appreciate new tech initially e.g. car, internet, statins. Rather not set the ceiling on this. - GRACE is one type of GCEA which adjusts for disease severity, disease risk, and dynamic pricing - Use a mix of health economics metrics like Quality Adjusted Life Years (QALYs) gained, reduction in healthcare utilisation (e.g., fewer hospital stays), and increased productivity (less time off work). - **Not just about money. Leaving smokers alone would mean they die earlier and save healthcare costs from treatment - which is a messed up way to do health economics! Value wellbeing where value less quantifiable i.e. paying whatever to treat or prevent pain, disability, untimely death.** - The point is not to judge whether treating any one patient with any one drug is worth it, but to ask whether we're making forward progress towards our larger goal of beating this disease. It's a portfolio-based view of risk. - If after 50y of high rewards and aggressive research, we find ourselves not much further along, we can revisit whether the threat and burden of Alzheimer's is just something we have to accept in our lives. But we're only just starting to crack the code of this disease. - For now, we believe that society has too much to gain to risk underpricing the hope of progress.	
GCEA Parameters		
Dynamics	**Scientific spillover**	Learning from experience (successes and failures) of developing and using a new drug
	Societal discount rate	Societal preference for health benefits that occur sooner rather than later, and defer costs into the future e.g. paediatric treatments and vaccines can accrue lots of benefits over time for a patient even though the treatment is a one-time event in the present period
	Option value	Drug helps someone stay alive for long enough to benefit from another drug e.g. first approved drug gives 1y benefit, next drug gets approved during that time and gives 3y benefit → patient's actual survival could be 3-4y
	Dynamic prevalance	Disease prevalence changes over time. e.g. hep C virus drugs being used will hopefully stop the virus spreading so less patients will have disease in the future, while Alzheimer's population is estimated to triple by 2050 as we live longer as a society.
	Dynamic net health system costs	- Effects of genericisation i.e. drop in prices once patent ends and generics introduced - To deal with genericisation and dynamic prevalence, recommended to use "stacked" cohorts that include impacts to current and future patients starting treatment → include (i) changes in price due to competition and generics entry (ii) changes in prevalence over time.
Uncertainty	**Value of knowing**	- Diagnostics helping create more targeted treatment plans i.e. knowing which drug to use - Even if diagnostic does not change decision-making, peace of mind is provided.
	Outcome certainty	- Say there is a drug that gives you 10% improvement in vision on average, but in practice it cures blindness for a few, improves it for some, and leaves some people blind. 10% (average outcome) is too simplistic to capture true outcome here. - This also changes based on patient preference. Some patients may not want to pay for the eye surgery and take the risk of it not working, and so may prefer to use glasses.
	Disease risk reduction	Look at risk of *future* patients developing this disease. Drugs developed now can reduce future risk. Related to dynamic prevalence.
Beneficiary	**Family and caregiver spillover**	Caregiver impacts: quality-of-life + emotional/physical health impact, productivity loss, non-healthcare costs (e.g. transportation costs, relocation costs, home renovation costs)
	Equity	Health benefits accure differently across heterogeneous patient populations e.g. if a new treatment comes out that affects all patients equally, it might actually be worth more to a segment of that population that is underserved (e.g. poorer population, minority popualtion) by the healthcare system
	Patient-centred health improvements	- Challenge: value assessment evaluates treatments at the population level, but treatment value may be unique for each person e.g. some people want extended survival, others want quality of life. - Use four principles: (1) capture individual patient preferences (2) capture quality-of-life and survival gains (3) health gains for those with more severe diseases should be valued more than identical health gains for less severe diseases (4) survival gains should not discriminate against the disabled e.g. don't value a life extension less if it occurs in a lower quality-of-life health state. - Getting the distinction between (3) and (4) is key: every *patient's* life improvement is valued the same BUT the same improvement for a more severe disease should be valued more.

Additional	**Productivity**	Common metrics of productivity loss: reduced productivity at work (presenteeism), reduced ability to go to work (absenteeism), unemployment due to disease, productivity loss due to premature death, productivity gains of life extension
	Adherence	- More patient adherence = more patients to benefit from treatment efficacy for longer durations. - Requires understanding how innovation might differ in real world vs in clinical trial setting. - E.g. long-acting injectable antipsychotic for schizophrenia taken every month preferred to having to take a pill every day, given the effect is the same. - Several things help: more convenient routes of administration, simpler dosing schedules, or combination treatments.
	Direct non-medical costs	- Part of family/caregiver spillover. Not generalisable and very specific to each disease. - E.g. parents of children with dyslexia incur higher education costs from tutors and other speicalised teaching - E.g. families with members with ALS will need wheelchair ramps and arm railings fitted in their houses
	Community spillover	- Useful for infectious disease treatments e.g. herd immunity from vaccines. Lack of this can lead to greater anxiety in rest of population. - Productivity impacts e.g. people who never got COVID were still impacted by closing of schools, business, etc.
Bottom line for biotech CEOs	- **Don't let anyone do CEA on your drug before you've published a GCEA** Practically, that means - Commission a GCEA 9 months before starting a registration study. Use crude inputs for values you believe your drug will offer + sensitivity analyses to identify variables that will make most difference and worth measuring carefully (e.g. drug reducing caregiver burden) - In parallel with registration study, measure all variables you care to include in GCEA - Upon completing registration study, update GCEA. In sensitivity analyses, show how ignoring GCEA factors would underestimate value of drug. - Publish GCEA before approval. Don't need to input intended price. Just show value below which price would be cost-effective. - When you finally launch drug and price, public will be surprised to see your market price is below upper limit on what GCEA showed as cost-effective.	
Is GCEA just another argument to charge higher prices?	No, because: - GCEA won't play as big a role because main signal comes from patients and efficacy (it's more to get your foot in the door rather than the defining factor) - Short timelines for payors and politics. Very hard to align that with long-term objectives of GCEA. - CEAs/GCEAs are defense mechanism for innovators to defend value of their medicines. But it probably won't be the key thing that moves the needle. CEA still hasn't fully made it in, let alone GCEA. Getting them in would improve things though.	
Challenges	- Lots of patient heterogeneity on value prioritisations - GCEA models aren't hard to make complex. The challenge is more working with the imperfect data that you have. - Results from one country may not generalise to others e.g. RCT results.	
Forthcoming from NPLB	GCEA best practice report, US GCEA calculator, ex-US GCEA calculator	

Things perceived as bad by the public

Perceived bad thing	Wrongdoers	What happens/happened?	Is it actually bad?	Potential solutions / examples of solutions
Turing pricejacking the drug Daraprim	Shkreli / Turing Pharma (now Phoenixus), CorePharma	- GSK sold Daraprim ($1/pill) to CorePharma ($13.50/pill), who sold to Turing ($750/pill). Note that treatment course is 20-60 pills. - CorePharma could make generic but GSK would have dropped out anyway. - Turing bought for a high price indicating pricejacking. - To prevent generic competition, Turing exploited an FDA safety regulation to control Daraprim's distribution based on its side effects, similar to Jazz Pharmaceuticals' Xyrem (similar to date rape drug). This meant generics couldn't do bioequiv tests. - Current status: Turing (now Phoenixus) maintains Daraprim at $780/pill, generating ~$60M in 2019 sales with no generic competition, though patients pay less through rebates.	- **Kinda, but it's not common.** - Pricejacking off-patent drugs has minimal financial impact (<1% US drug spending) because drugs typically serve small markets and have modest prices. Often why single company offering them with no competition, even after patents expire. - Large companies sell rights to smaller firms who raise prices. - Patients pay less through rebates - Key insight: price hikes on low-revenue drugs yield minimal absolute returns compared to smaller percentage increases on blockbuster drugs (e.g., 500% increase on $1M drug (e.g. Daraprim) = $5M vs. 5% increase on $1B drug = $50M)	- Govt policy where drugs with no natural generic competition agree to sell at low but profitable price under purchase (being proposed for antibiotics) - Import generics from other countries when US prices rise, effectively merging US market with global market and minimising risk of shortages. Challenge here: FDA has to review generic quality which takes time. - Public perception: crucial to distinguish between unjustified price increases (e.g. Turing) from legitimate price adjustments that allow for profitability. As disease incidence decreases, prices might naturally rise to sustain profitability which should not automatically be labelled pricejacking.
Opioid Crisis	Purdue (also Teva, J&J, Mallinckrodt, Endo) + pharma distributors (McKesson, AmerisourceBergen, Cardinal Health), and pharmacies (CVS, Walgreens, Walmart)	- Purdue marketed drug they knew was dangerous as safer than it was, hid data that showed that, reaped revenues associated with non-medical use of product - Benefit-risk profile: addiction potential, what's on label, to whom it should be prescribed, how it's distributed. Requires balance. Opioids didn't have that balance. - Harm came directly (patient abuse) or indirectly (patients get addicted then cut off from access to prescription opioids and turn to illegal potent versions like heroin and fentanyl). - Some physicians prescribe things off-label. They understand the drug and its uses better. Off-label uses can become normal in the community and sometimes even make their way into medical guidelines, although no FDA approval.	- **Yes, extremely. The main culprits should be jailed.** OxyContin Timeline: Deaths - 1999-2020: 841,000 drug overdoses, 500,000 from opioids Development/Approval - 1995: FDA approved OxyContin (slow-release) - Preceded by MS Contin (immediate-release) - FDA assumed slower release meant safer Purdue's aggressive messed up marketing - Got broad pain management label from FDA which was a lie - Funded 5,000 conference attendees in 5 years - 20,000+ education programs (1996-2002) - Didn't do DTC on TV but did ads on pain-focussed consumer-facing websites - $5M medical journal ads (2001) - OC became $1B annual sales within 5 years - Would've been legal with proper disclosures (now required by Sunshine Act)	FDA/Regulation - REMS protocol added to make sure risk-benefit well-accounted for - Sunshine Act: required payment disclosure - Missed abuse risks despite MS Contin warnings Drug Development - Original issue: Easily abused via crushing/chewing (MS Contin was but not widely reported and OxyContin more widely prescribed) - 2010: Abuse-deterrent OxyContin released via hard shell and improved core to avoid injections - Other versions: Xtampza ER, abuse-resistant generics Impact & Solutions - Crisis shifted from prescription drugs to worse street opioids and the crisis there - 2010: Increased hep C from heroin - Modern drugs: Naloxone (counteracts effects if OD occurring), buprenorphine (milder so safely blunt cravings) - Future focus: Non-addictive pain treatments
DTC advertising	N/A	- Oldschool doctors don't like DTC advertising. - DTC is obv profit-driven (otherwise companies wouldn't do it) but does also have informational value that can lead to better patient outcomes. What's the point of a new invention if people don't know it exists and don't benefit from it? - Generics don't really get advertised. Want patients to know they're available. Society needs to make sure patients are aware of generics once standard DTC ads cease. - Challenge of saying we could pay a huge sum early on then force drug to go generic → removes incentives to invest in marketing and awareness to incorporate new medicines into standard of care.	- **When done with care, no.** - FDA originally shut it down. But after benefit-risk analyses, found that when done in accordance with regulations, it's a net benefit. - Has to be done carefully to avoid exploiting patient's lack of knowledge e.g. increasing their expectations which places strain on doctors to unexplain misinfo and makes that relationship worse. - Without DTC advertising, drug companies presume lower penetration, so fewer patients treated, so higher cost per patient. So proper DTC ads can lower OOP costs.	Awareness of disease is good. Example: - Mylan acquired EpiPen in 2018 and raised price 3-fold but did huge marketing and lobbying alongside funding non-profits + gave free EpiPens to schools - Grew EpiPens to $1b/y blockbuster by 2018 - Mylan so successful that we thought monopoly on epinephrine autoinjectors but was another cheaper one called Adrenaclick, whose manufacturer Impax (now Amneal) did little to promote it.
New drug denial: Zolgensma case study	Missouri Hospital System	- In April 2024, the insurance company of newborn twins denied coverage for Zolgensma, a one-time gene therapy treatment for their rare genetic disease, spinal muscular atrophy (SMA). - Twins' insurance policy thru Mosaic Life Care in St Joseph Missouri changed one day after the twins were born, removing coverage for Zolgensma. The family appealed the decision but it was denied.	- **Yes, but as long as the public can voice concerns, these issues can be solved eventually.** - The high prices don't look great but creating cell/gene therapies is hard and provide a lot of value to patients. Innovators should be rewarded for the risk/difficulty they take on.	- GCEAs (before classic regulatory bodies have the chance to do classical CEAs) to show true benefits of drugs over time - Partner with professional societies to include these drugs in guidelines - Real-world pilots to show performance - De-risk with value-based agreements.

An overview of the American healthcare system

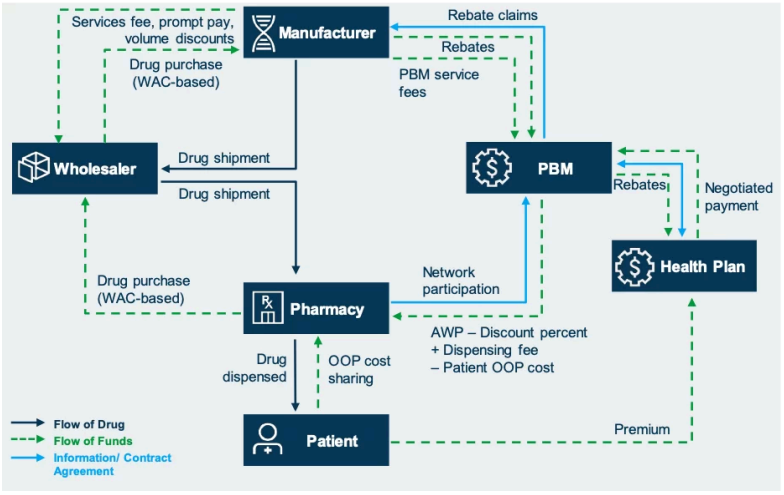
Health Policy 101 | KFF

(Note: Medicare and Medicaid are not socialised medicine because the doctors and hospitals are privately operated – govt pays them, but does not own or employ them.)

Category	Medicare	Medicaid	Affordable Care Act (ACA, aka Obamacare)	Employer-sponsored insurance (ESI)
Established	1965	1972	2010	Been around for a while, dramatically expanded from 1940-1960
Populations served	65+ years (58M) and under 65 with disabilities (8M)	80M low-income people	Those without other coverage sources	164.7M non-elderly (60.4% of non-elderly)
Key demographics	Half had incomes below $36k and savings below $104k (2023)	Covers 1/5 people in US but important for certain populations: 2/5 children; 4/5 children in poverty; 1/6 adults; 3/5 non-elderly adults in poverty; 44% of non-elderly non-institutionalised disabled adults	Available to all, with subsidies based on income up to 138% of poverty level ($15,060 in 2024)	84.2M from own job; 73.8M household dependents; 6.7M covered as dependent by someone outside household
Coverage structure	State-administered. Four parts: - A: Hospital - B: Medical (outpatient) - C: Medicare Advantage - D: Prescription drugs	State-administered within federal guidelines	Regulated marketplace with private insurers	Private insurance through employers
Services covered	- Hospitalisations - Physician visits - Prescription drugs - Post-acute care - Nursing care - Home healthcare - Hospice - Preventative services	Varies by state	Essential health benefits as defined by ACA	Varies by employer plan and income - 84.2% for 400%+ FPL - 59.0% for 200-399% FPL - 23.9% below 200% FP
Cost structure	Funded by: - General revenues (43%) - Payroll tax (36%) - Premiums (16%) - Other sources	Joint federal-state financing. States have flexibility to choose populations and services	Premium assistance based on income	- Workers pay 17% (single) - Workers pay 29% (family) - Avg annual: $1,401 single, $6,575 family
Financial impact	- 12% of federal budget (vs Medicaid + ACA + CHIP = 11%) - 21% of national health spending (2021) - $989B total (2022)	16.6% (⅙) of healthcare spending	Varies based on enrollment and subsidies	Not govt spending but can put strain on employers and employees, particularly for workers with lower wages
Additional notes	Different plans: Humana, UnitedHealthcare, BCBS Plans, Others, Centene, CVS, Anthem, Kaiser Permanente, Cigna.	- Covers higher share of Black, Hispanic, American Indian or Alaska Native (AIAN) children and adults - Among non-elderly, nearly half of children are under age 19, 90% are PoC, 57% are female, 75% in family with full- or part-time worker	- Key goal: expand insurance coverage. - Did it by expanding Medicaid to people up to 138% of federal poverty level ($15k in 2024). - Improved uninsurance rates and lowered OOP costs but did not eliminate all	- Largest source of coverage for non-elderly US residents - 3.2% also covered by Medicaid / other public coverage and 0.6% have non-group coverage too

Challenges with insurance for patients

Category	Details
Insurance Types	- Medicare: 65+ years - Medicaid: below poverty line - VA: veterans - Employer-provided private (note: insurance not taxed so cheaper to do this vs paying employees more and telling them to get it) - Private insurance through exchanges
Insurance Dynamics	- Companies negotiate prices through PBMs - Medicare/Medicaid initially pay wholesale acquisition price, later switch to average sales price - Insurance should cover maximum to lower OOP costs - Main customers are healthy Americans who cover the insurance. - Companies profit most when people are healthy. So why don't they subsidise preventative care? They do encourage people to do the inexpensive stuff e.g. statins, contraception, annual checkups, blood pressure pills. But maybe not expensive moonshots for preventative care.
Weird incentives created by insurance	- 13% Americans uninsured (~45M), think it's now 9.5% (~25M) - Individual with subsidies pays £2.5k/year - Family of four at - - $50k income pays $3k/year with subsidies vs $17k without - - <$100k income (4x poverty line of 25k) pays $10k/year with subsidies - - >$100k income is ineligible for subsidies making them pay 17k - - 100k-105k is where maths gets weird - Many are fine though: 91% insured pay <$500/year in OOP costs - There is a federal law and other policies in place that protect a patient, from being billed from an out of network provider, while receiving services at an in network facility. - ⅓ Americans do not fill their prescriptions due to costs - Sometimes is cheaper for patients to buy drugs (generics, not new ofc) from pharmacy directly rather than via insurance. Mark Cuban's Cost Plus Pharmacy is famous for buying generic drugs from companies and selling to patients for a small markup, without the PBM middleman taking a cut. But for expensive drugs, need insurance to work properly. - PBMs create formulary tiers. Companies work to get their drugs into lower tiers or bundle with other drugs. But what can patients do? Look at insurance options (not a solution) or GoodRx (incomplete info).
What happens to uninsured?	13% Americans uninsured (~45M): not veterans, not poor enough for Medicaid, not old enough for Medicare, at a company with no insurance or not working. - These people can buy health insurance via state-run exchanges through which various insurers sell policies. - ACA also helps here. - They won't be turned away at hospitals but end up paying closer to list prices which can be astronomical. US isn't designed for people who are uninsured. - Can pay via installments (like post-hoc insurance) but will be a lot. And sometimes hospitals sell debt to collectors who will extract patients.
Economic impact of uninsured	US Healthcare Insurance System 2013 Data: - Uninsured costs: $25B out-of-pocket + $85B uncompensated care (unable to collect patient payment) - Government paid $53B to offset losses… which came from taxes so public still paid. - Administrative costs: $500B (2.4% GDP), 2x what Canada and Germany spend administering their healthcare systems
Cost Sharing Definitions	- List price = set by company - Net price = after insurance negotiations - Premiums: regular payments for insurance - Deductibles: initial amount before insurance kicks in - Copayments: flat rate paid for service covered by insurance - Coinsurance: when you still have to pay some costs of deductible, usually a % value - OOP max: if combined payment for deductibles, copay, coinsurance goes above this within a year, rest paid by insurance company - Reinsurance: basically insurance for insurance company - **Why deductibles, coinsurance, and copays (collectively called "cost-sharing")?** - - Encourage responsible behaviour and not expose yourself to unnecessary risks because they have insurance. - - Lower incentive to get check for everything. Can weight different health services based on necessity. - - Also higher deductible means lower premiums and vice versa. - - For insurance companies, it's a way to transfer risk back onto patients. That's bad.
	An example. You have an insurance plan with a $2,000 deductible, 20% coinsurance, $100 copay for a doctor's visit, and an out-of-pocket maximum for $4000. You get into an accident that requires surgery; the hospital bills your insurance company for $10,000. This means you've gotta pay $2,000 to cover your deductible. Of the remaining $8,000, also you have to pay 20%, or $1,600, as coinsurance. You have five followup appointments with the doctor to see how you're recovering. However, the fifth appointment doesn't require a copay, because it's above your out-of-pocket maximum.

Challenges	- Not all patients know they have the disease where there's a drug - Not all patients who know consult their doctors - Not all doctors know the drug to prescribe it - Even when prescribed, not all patients take it because they can't be bothered (treatment adherence) or insurance wouldn't cover (coverage issues) - If insurance does cover, copay/coninsurance/etc. might be too high - Side effects management - Copay assistance eligibility awareness
Pharmacy Tweaks	- Insurance plans have different formularies (formulary = list of medications approved as part of an insurance plan) - Utilisation management controls affect generic options - Rx coupons offered by manufacturers as subsidies to encourage use of their drugs i.e. branded drug with coupon might be cheaper than generic at a pharmacy - GoodRx enables pharmacy/cost comparison and became big because of this - Prior authorisation means that a health provider needs to get approval from a patient's health plan before moving ahead with a treatment/medication.
PBM Role	- How did they arise? As number of branded drugs expanded, there was more negotiation for discounts. Some insurance co's did better at this and started offerng their services (to reduce admin costs for insurers), serving as PBM. Eventually, one spun out as standalone company (e.g. Express Scripts). - PBMs have become increasingly associated with insurers to the point they're indistinguishable. - **Basically, they negotiate drug prices with pharma companies, amongst a few other things.** - Top 3 control 80% of market (Express Scripts, CVS/Caremark, OptumRx) - Top 3 manage drug benefits for 95% of Americans. - Serve half of US population - PBM provides 5 key functions: formulary design, utilisation management, price negotiation, pharmacy network formation, mail order pharmacy services. - - 5 formulary tiers from T1 (generics) to T5 (specialty drugs) - new drugs in T4, T5. - Market access control mechansims - - Formulary and formulary tiers - - Prior authorisation - - Quantity limits - - Step therapy i.e. try other drugs before this - - Precertification criteria e.g. companion diagnostic - - Limited access: available only in certain pharmacies
	
PBM good things	- Rebates = discounts the insurers or PBMs negotiate with drug manufacturers. - Realistically, being able to negotiate secret rebates is a useful tactic for playing drug companies off one another, as PBMs have done with Gilead, AbbVie, and Merck to drive down the cost of hepatitis C cures in recent years.
PBM issues	- Negotiate rebates with drug companies, but do keep portion of rebates. - Drug at low list price threatens PBM biz model so they encourage high public list price, charge you a lower price but also negotiate and profit the difference i.e. you pay copay on list price not net price which is messed up! - Negotiations done in private and based around classic sales tactic: "You're special so I'll give you a special price, but don't tell the other guy." - - Transparency is not the issue: They can do in private but insurance/PBMs shouldn't be allowed to charge high OOP costs for drugs nor charge list prices. - Why don't pharma companies bypass PBMs and sell directly to insurance companies? You'd be ostracised by PBMs but why does that matter?

	- - PBMs have grown and amassed wide influence. They are middlemen with wide bargaining power. The top three PBMs, Express Scripts, CVS/Caremark, and United's OptumRx, represent 80% of the PBM market and serve insurance plans covering half of the US population. - The overarching issue: PBMs are currently unregulated! This is now changing.
	Realistic good scenario. List price: 40k. PBM could negotiate to 30k and then takes commission of savings (20%) = 2k fees so you pay 32k. That's good. What actually happens. List price: 50k (as encouraged by PBM), PBM negotiates to 30k. So 20k saved but at 20% commission, they get 4k commission. PBMs can screw you over even though they look like heroes!
Rebate System	- List price vs net price after rebates - Patients pay copays on list price - PBMs profit from high list prices - Example: $10k list / $6k net, patient pays full $10k under deductible
What do insurers review when deciding whether to include in coverage?	- Obvious ones: efficacy, safety. - Inclusion in guidelines e.g. US Preventative Services Task Force or NCCN. - Paid subscription based-services that summarise data e.g. Hayes, ECRI - Human Technology Assessments (HTA) - primarily ICER in US - KOLs - theirs not the pharma co's - Competitor policies - quite important
Why are drugs the subject of cost-saving initiatives?	- System not good at absorbing cost of drugs that may have high upfront costs but tremendous downstream benefits e.g. cell & gene therapies, GLP-1's. - Easier to prefer low-cost vs high-value drug even though that's silly → HTA assessments like GCEAs can help - Lack of transparency around pricing - Many payors are publicly-traded and worry more about investors than those whom they serve
Frustration at pharma prices	- Drug OOP costs are about a ⅓ of total OOP costs. 3x higher than total share of branded drug spending as fraction of overall healthcare spending. - So OOPs skew people's perception of drug costs. - Still, drugs aren't majority of OOP costs. - For some patients, their only source is high OOP costs so frustration makes sense.

Biologics and value-based agreements

Generic Drugs	- 90% of all prescriptions in US - Cheaper due to commodity chemicals and copying - Minimal RCT requirements - Same labeling as brand drugs so pharmacists can substitute for branded drugs
Biologics Market	- $125B in US sales (2018), up 50% since 2014 - 55 blockbuster biologics ($1B+ sales in 2019) - Expected to exceed small molecule drug spending in a few years - 35 gene therapies + 46 cell-based therapies + 16 tissue eng candidates in P3
Challenge with biologics generics	Biologics are 4% (approx $6B) of all drugs but cannot go generic easily as generics hard to get approved (slower + complex) → prices stay high. - E.g., a price drop that took less than 12 months for the cholesterol-lowering statin Lipitor might take several years for the protein-based TNF-alpha inhibitor Humira. - Biosimilars exist which help drop price but not as much. - - EU biosimilar market is good - over 20 biosimilars in several drug classes - However, existing biosimilar legislation only applies to simpler types of biologics, e.g. enzymes and antibodies. No regulatory path for complex biologics like cell therapies
First solution: contractual genericisation	- Agree to lower its price to be close to the cost of production after patent expiry. - This is how biodefense industry is regulated. - - The government negotiates contracts with certain companies that manufacture vaccines for pandemic flu, smallpox, etc. - - These vaccines, while unnecessary under normal circumstances, might suddenly become necessary, so we need reliable supply. - - Government helps fund research + offers guarantees on purchasing certain number every year assuming FDA approval.

Second solution: value-based agreements

Drug	Description	Cost to payer	Potential financial benefit / ROI	Benefits
Luxturna	- First transformative gene therapy approved in US. - It is used to treat an ultra-rare condition causing blindness in kids. - Upon launch it was clear that all payors would have no choice but to cover this therapy.	No direct cost	Partial refund of 850k if visual improvement not achieved at 30-90 days and 30 months post-treatment.	- Demonstrates reputation to employers and others that payor is innovating around drug expenses. - Resulted in national visibility as the first value-based agreement for gene therapy. - First ever value-based agreement spanning multiple years. - Set expectations within industry for launch of all future gene therapies. - Resulted in HBS case study first taught in 2020 by Amitabh Chandra.
Zolgensma	- Priced at 2.1M, it's a one-time gene therapy approved for spinal muscular atrophy, a rare genetic neuromuscular condition present at birth. - Upon launch, was the highest-priced drug ever approved. - Insurers that initially attempted to limit coverage more narrowly than FDA label quickly expanded after being publicly vilified.	No direct cost	Partial rebate if durability of response not maintained for 5y.	- Demonstrates reputation to employers and others that payor is innovating around drug expenses. - Resulted in national visibility as the second value-based agreement for gene therapy.
Alunbrig	- Oncology drug to treat specific type of lung cancer. - Agreement calls for full refund of entire drug cost if patient does not remain on it for at least 3 months, presumably indicating lack of response or inability to tolerate.	No direct cost	Full refund of drug cost if criteria met, estimated annual cost is 173k.	- Demonstrate that both pharma and payor are managing oncology spend.

Pros	Cons (of "standard" agreements)
- Opportunity to compete on things other than price - Shows confidence in the product - Aligns more with how physicians are compensated - Can align to new payment models (e.g. capitation, bundles) - Can remove restrictions by taking risk	- Parties cannot always agree on a starting price - Lack of clear cause-and-effect for many drugs - Insufficient patient population for some therapeutic areas and cost/difficulty in collecting data - Existing formulary designs may limit new opportunities - Concern around regulation and Medicaid "Best Pricing" requirements

Summary of takeaways

Main things to preserve the Biotech Social Contract (BSC)	1. Contractual genericisation (CG) to balance affordability with innovation 2. Incentivise upgrades with shorter regulatory exclusivity extensions rather than new patents 3. Proposal for how society can take over marketing from companies when certain non-standard products like EpiPen go generic 4. Caution with international reference pricing (IRP) - would paradoxically raise US prices. Reframe to focus on US payments and say other countries are subsidies. 5. GCEAs on drugs. And reinforce that drugs remove future hospitalisation spending.
Main policy aims	1. Cap/eliminate cost-sharing + ensure everyone has insurance. 2. Prevent pricejacking of sole-source generics e.g. (a) require samples to generic competitors and coordinate REMs, (b) guarantee purchase contracting (akin to CG). 3. Reform drug rebate practices s.t. PBMs can't profit by encouraging higher prices. 4. EU-style 10y exclusivity period (up from 5-7y) for any new drug approved in US that no longer has patent protection to incentivise that drug's development. 5. Creating market exclusivity extension voucher system to incentivise companies to upgrade drug labels of old generics. 6. Address opioid crisis by making addiction treatment more widely available and affordable and investing in non-additive drugs that treat pain. 7. Encourage other wealthy countries to contribute towards global drug dev industry by paying more for branded drugs.
What we can do	- Advocate for universal health insurance and capping OOP costs. - Public Domain Day for drugs. Generic drugs are most cost-effective aspect of healthcare. - Advocate for internal reforms to ensure drugs go generic. Acknowledge patent gaming and pricejacking and embrace reforms like CG. - Advocate for GCEAs.
Since book was written: IRA introduced	- The IRA's "Medicare negotiation" is akin to "contractual genericisation". Difference is that it kicks in after 13 years for biologics instead of PK's 15 years, which is ok, and doesn't include extensions for upgrades, which is a bummer but hopefully something we can fix in the future. - Major shortfall is that it kicks in for small molecules just 9 years after they launch, which is a harmful and weird thing to do for reasons we can discuss but that I've written a lot about. - And that law also included OOP caps, which is good. - Overall: IRA good bar small molecule penalty.
Policy notes	- Contractual genericisation at 2 * (production + distribution) price - Eliminate OOP costs - - Most people don't fake diseases, remove them. Could be offset by slightly higher premiums to save hospitalisation costs in long run. - - Do it in a smarter way e.g. try cheaper drug A OOP but if that doesn't work, know you're covered for more expensive drug B. - - Find ways to reduce costs elsewhere - - - Remove administrators. For every 1 physician, there are 10 non-clinical people (e.g. administrators) - a higher ratio than any other country. - - - Hospitals hire billing specialists to "up-code" invoices to maximise insurance reimbursement. Insurance plans hire similar people to "down-code" and minimise reimbursement. We pay for this coding arms race and no patients benefit. - Preventing claims denials - - Minimum loss ratio (claims paid / premiums claimed e.g. 75M/100M = 75%) already exists. Medicare gets 85% of premiums by law. Commercial plans subject to market but tend to similar zone. - - Improvements to step edits and prior authorisation - - Proposed solution: only use copays when nudging to alternatives is possible and ethical (e.g. don't do it if there is only one available drug with no alternative) i.e. minimise cost-sharing. - Value-based agreements - Flexible RCTs - - One big P2 and P3 rather than two P3s. Use RWE to help. - - Quicker ability to test existing drugs in new indications and/or new populations (defo for tests in other countries). - - Diseases with longer timelines need solution e.g. prodromal to development needs 5-10y trials vs current 2y trials. E.g. your patent gets extended. - Incentivise shorter upgrades via 6m extensions on patents. E.g. for testing drugs in children or small special pops, or to bring off-patent molecules to US market. - FDA could incentivise trials for generics well-suited to new uses. - - FDA already has priority review vouchers that can be earned when developing drugs for tropical diseases or paediatric conditions to speed up FDA review from 10m to 6m. - Incentivising certain areas. - - Already have The Orphan Drug Act of 1983 incentivises drugs for smaller orphan pops (<=200k). Gives longer patent + tax breaks, research subsidies, more open dialogue with FDA on how to develop the drug, accelerated review of app to launch earlier than usual. If a drug has no patent protection, the law grants 7y of exclusivity. That's not bad, though Europe is more generous, offering 10y of exclusivity to any new drug. - To help international ecosystem: - - **Remember: there is no American pharma or Europe pharma. There is only American-market-dependent pharma, and that's most of the innovation in the world.** Note that Novo is in Denmark and Denmark pays little for semaglutide. Roche is in Switzerland and that's too small a country to incentivise anything even if it pays pretty decent prices for novel drugs. The market that incentivises innovation is decoupled from where the innovation is done. So not only does Europe freeride in US market's incentives (ie willingness to pay) by enjoying the flow of new

	medicines at low prices, it enjoys the taxes it gets to charge the European giants and all the jobs. - - “A lot of American healthcare is an extractive industry. But these profits fund a lot of research and are the primary driver of commercial drug development on this planet, subsidising many health insurance systems around the globe.”
Useful analogies	- **Concept:** cost of drugs vs hospital services. **Analogy:** mortgage vs rent (“it’s a societal investment”). Drugs cost a lot during patent then drop in price drastically relative to cost of production once patents expire. Hospital services don’t genericise relative to cost of production, they increase in prices. Going further, drug upgrades = upgrading house. - **Concept:** drug development journey from discovery to market. **Analogy:** mountain climb (“it’s a long difficult climb”). Public+private basecamp, startup+VC till P2, startup+big pharma acquisition P3+. - **Concept:** replication of small molecule drugs vs biologics. **Analogy:** fine wine vs cocktail (“All drinks are not created equally”). Cocktails can be replicated easily, fine wines can’t. Small molecules are like cocktails, biologics are like fine wines. - **Concept:** drug pricing on patent vs off patent. **Analogy:** on patent like buying a ticket for a new movie at the cinema, while off patent is waiting to watch it at a lower subscription price on TV (i.e. generics via taxes). Issue is that US cinemagoers are subsidising the costs for all the TV-watchers in other countries. - **Concept:** the issues behind using international reference pricing. **Analogy:** reading books by borrowing from a library vs buying. "It would be like a guy who loves reading books borrowed from the library telling everyone who buys books that reading from the library saves money. Then one day, he will be reading books from the library with everyone else and wonder why there aren't any new books." The buyers keep the industry going i.e. US pays more and keeps the industry going for other countries who pay less.