The Endless Frontier?
Innovation, Sustainability and Tragic Choices in the Treatment of Cancer Diseases

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Cancer Real World. Milan, January 25, 2019

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INDEX

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1. The Endless Frontier
2. Innovation, Sustainability and Pricing
3. Targeting and Impact Analysis in the Wild

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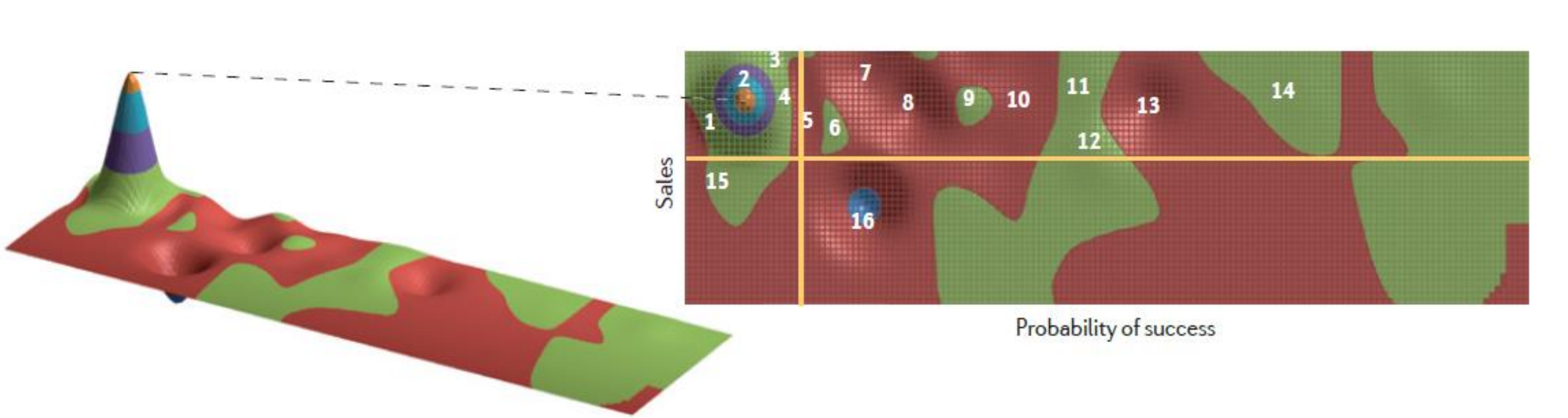
The Endless Frontier

nature REVIEWS DRUG DISCOVERY



1	A08A: Anti-obesity	**10**	C04A: Peripheral vasodilators
2	L01X: Cancer, monoclonal antibodies	**11**	J05B: Antivirals, others
3	N07D: Anti-Alzheimer's drugs	**12**	N02B: Analgesics
4	M01C: Specific antirheumatics	**13**	C02A: Anti-adrenergic agents
5	C01B: Anti-arrhythmics	**14**	G04D: Urinary incontinence; B02D: Blood fractions
6	A10B: Diabetes, excluding insulin	**15**	A16A: Other alimentary tract and metabolism products
7	J05C: Anti-HIV	**16**	C06A: Cardiovascular, others
8	C01D: Vasodilators		
9	N04A: Anti-Parkinson's drugs		

F. Pammolli, L. Magazzini, M. Riccaboni, (2011), "*The productivity crisis in pharmaceutical R&D* ", Nature Reviews Drug Discovery volume 10, pages 428–438

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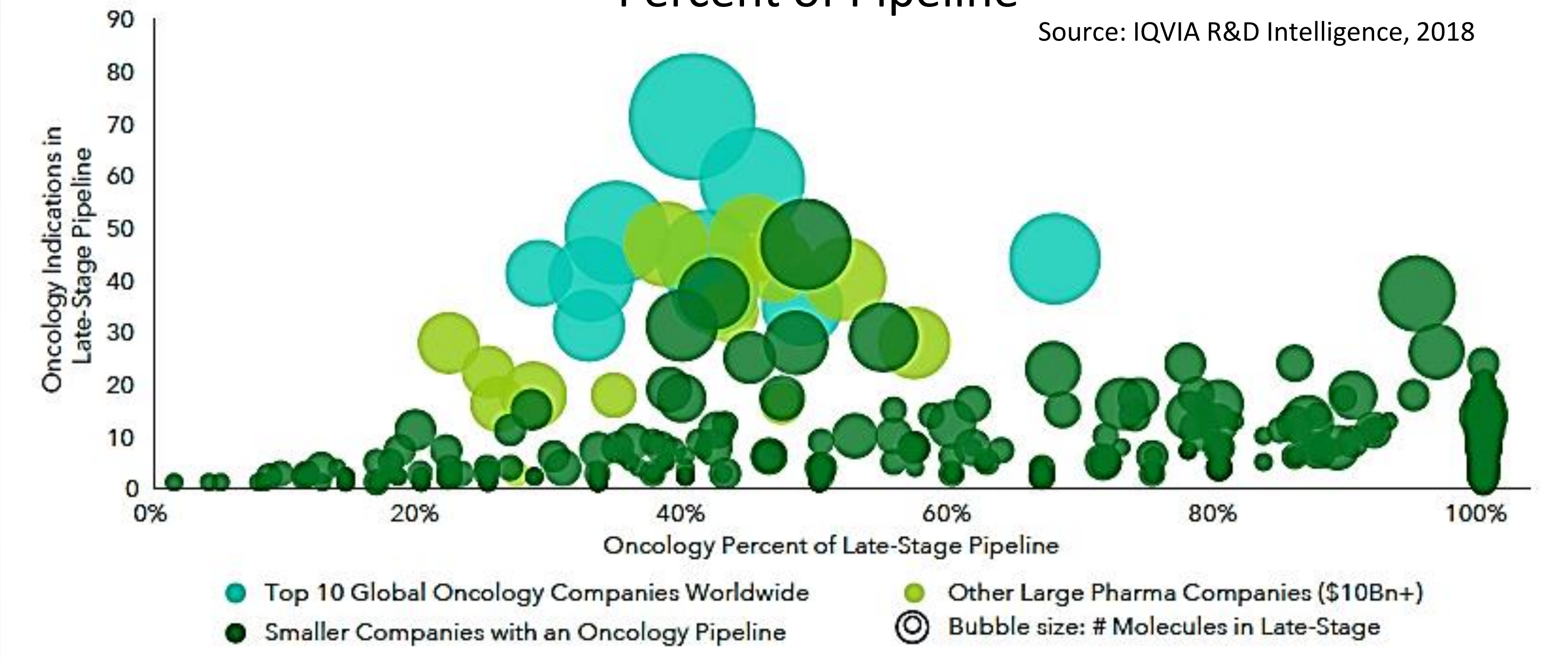
The Endless Frontier

Company Late-Stage Pipelines, Number of Oncology Indications and Oncology Percent of Pipeline

Source: IQVIA R&D Intelligence, 2018



- CAR T (*Chimeric Antigen Receptor T-cell*) Immunotherapy - **50** projects in clinical trials.
- Cell therapy, carrier cell therapy and stem cell therapy - **529** projects in clinical development
- Conjugated monoclonal antibodies - **188** projects in clinical development

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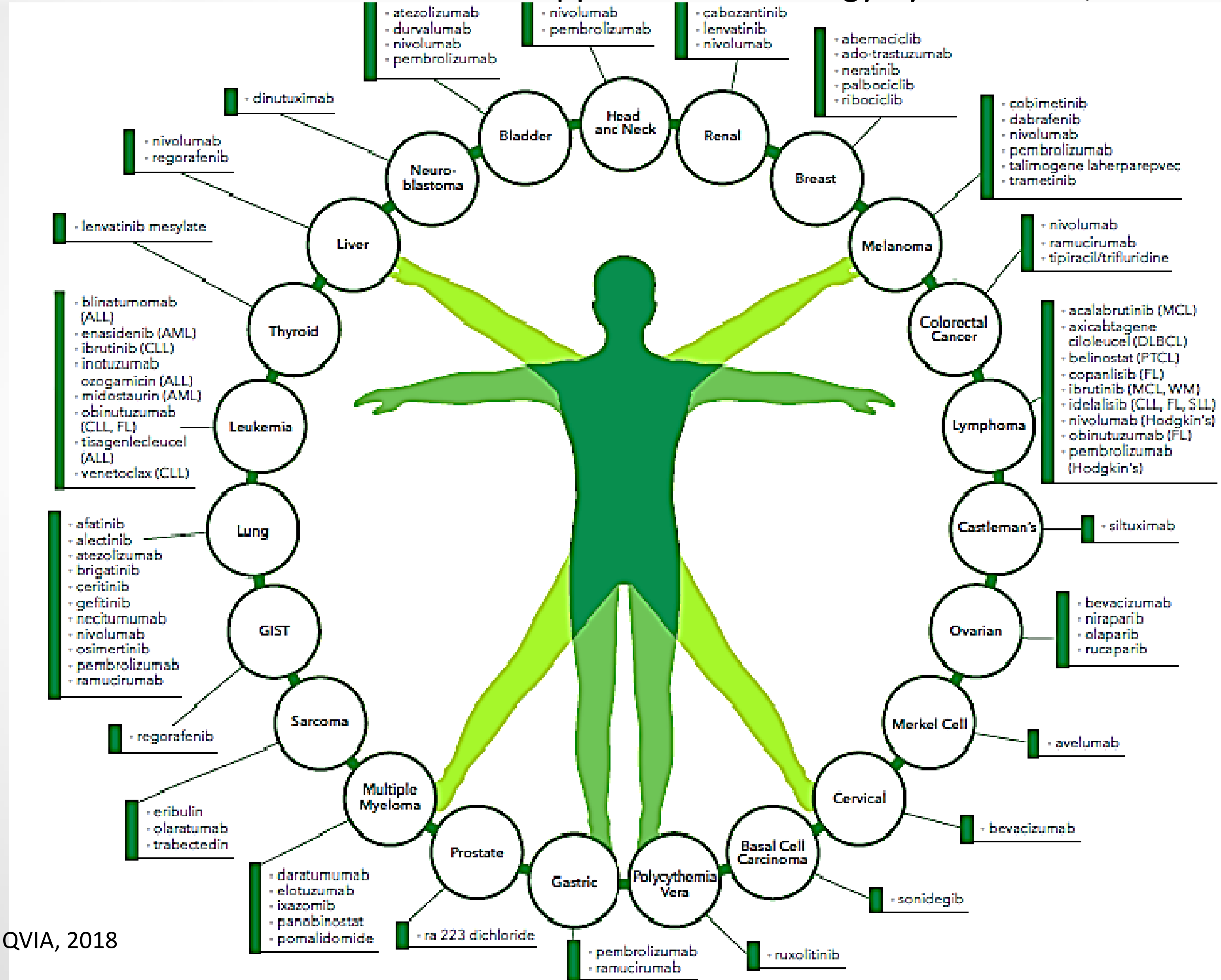
The Endless Frontier

New Active Substance Approvals in Oncology by Indication, 2013—2017



Data Source: IQVIA, 2018

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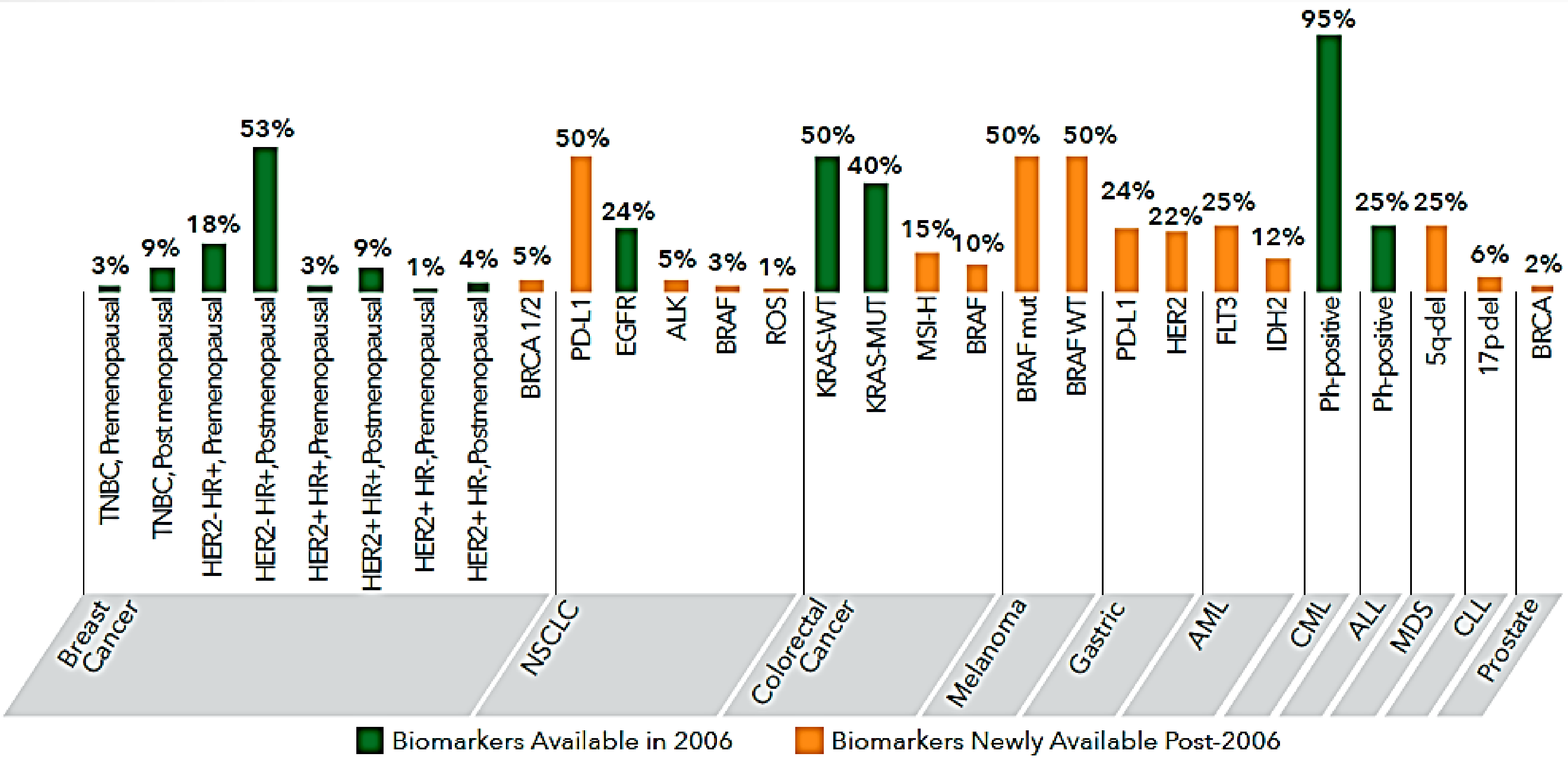
Patient Incidence of Positive Biomarker Results Per Cancer by Biomarker Availability, 2017



Source: FDA.gov and Drugs@FDA, Apr 2018; IQVIA, ARK R&D Intelligence, Apr 2018; IQVIA Institute, Apr 2018

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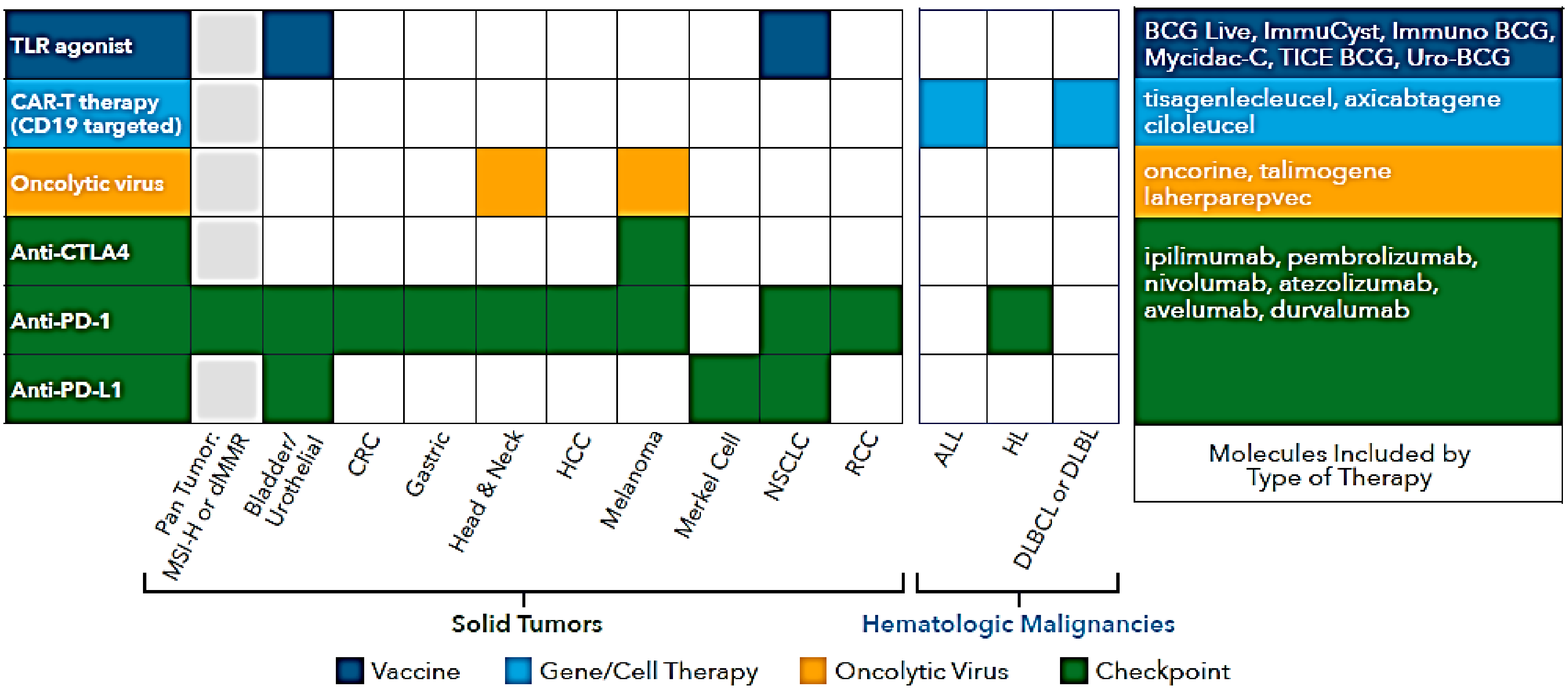
Approved Checkpoint Inhibitors and Next-Generation Biotherapeutics by Mechanism of Action and Tumor Type Approvals



Source: Tang J, Shalabi A, Hubbard-Lucey VM. Comprehensive analysis of the clinical immuno-oncology landscape. Ann Oncol. 2018 Jan 1;29(1):84-91. IQVIA Institute, Apr 2018

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1 The Endless Frontier

2 **Innovation, Sustainability and Pricing**

3 Targeting and Impact Analysis in the Wild

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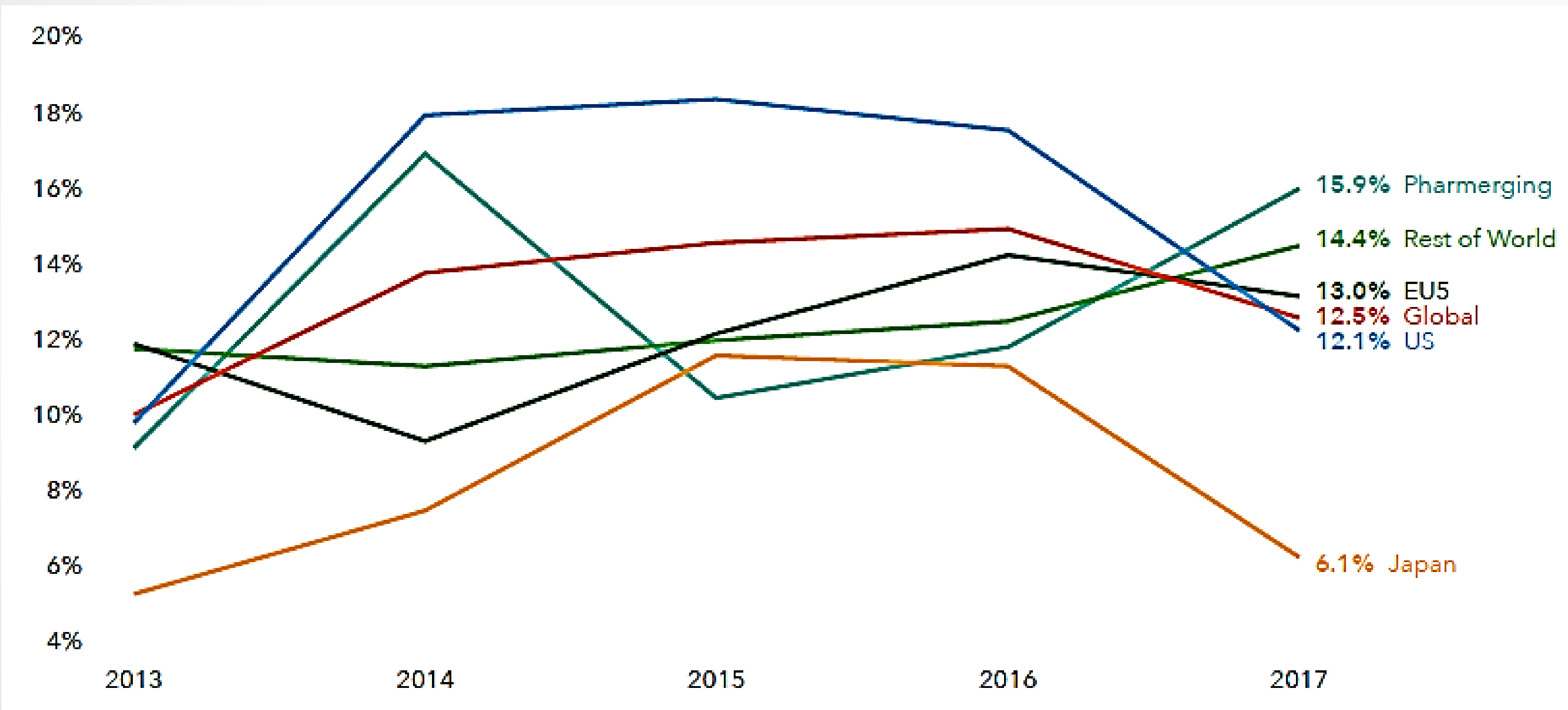
Innovation, Sustainability and Pricing

Growth Rates for Global Oncology Therapeutic Medicines Spending, 2013—2017



Data Source: IQVIA, MIDAS, Dec 2017

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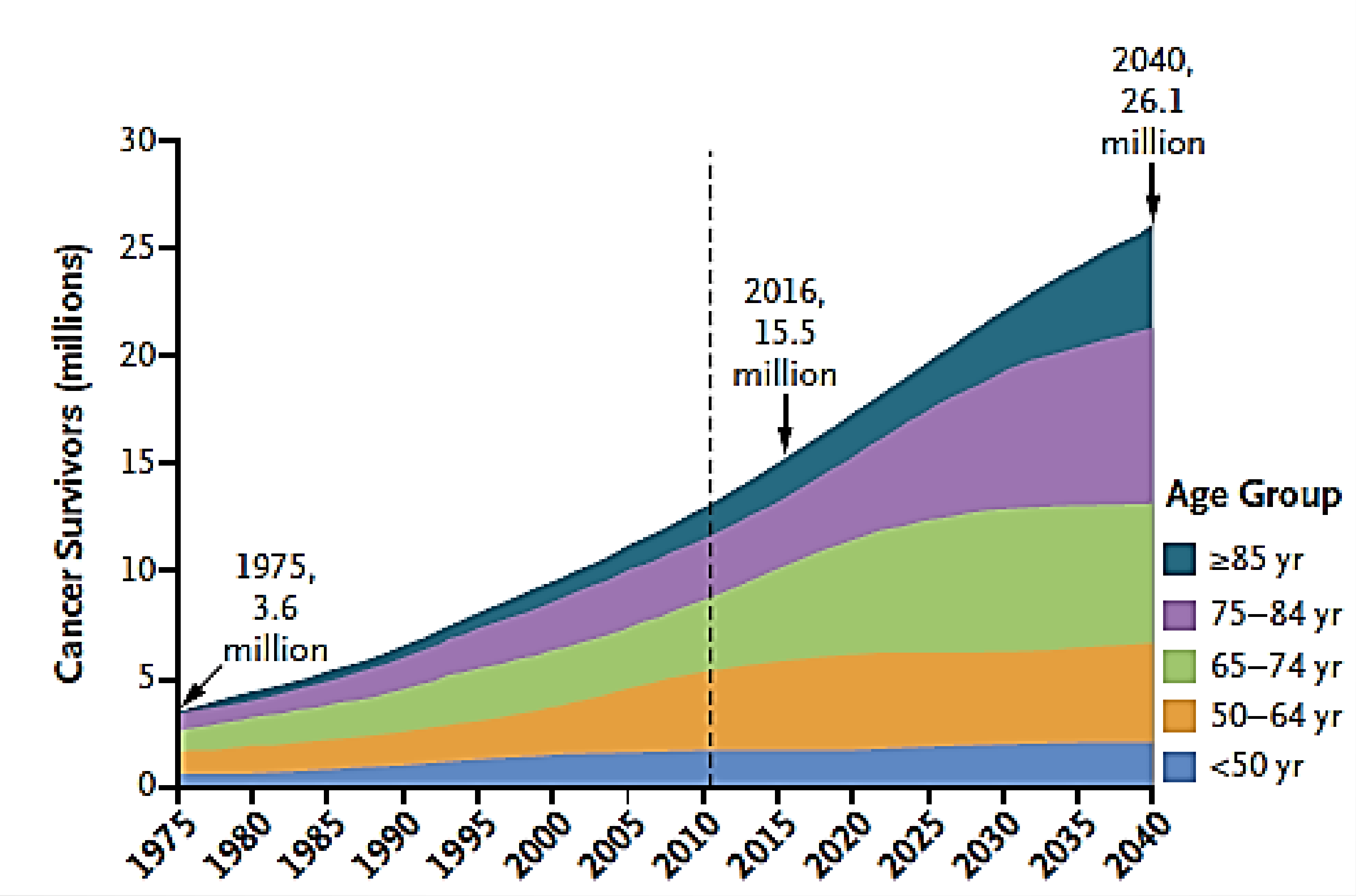
Innovation, Ageing, and the Welfare System

Cancer Survivors by Age Cohort



C L. Shapiro (2018), *Cancer Survivorship*, New England Journal of Medicine

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Innovation and Ageing: The Macro Constraints

<u>Population 65+ :</u>

2017: 22.3% (Germany: 21.2%, France:19.2%)

2040: 32.1% (Germany: 28.7%, France:25.6%)

Welfare expenditure, Italy

Demographics: higher life expectancy (+2 years)

AWG Risk: Higher health expenditure due to technological drivers

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Innovation, Ageing: The Macro Constraints

PAYGO Burden, baseline (Demography: EUROPOP2015 base scenario, AWG Reference scenario)

Italy: Current: 64.2% (*21.8% health+ltc*) 2040: 80.0% (26.4% health+ltc)

Demographic stress scenario (higher life expectancy)

2040: *80.2%* (*24.5% health+ltc*)

Innovation intensive stress scenario (Health)

2040: *81.4%* (*27.8% health+ltc*)

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Innovation and Ageing: The Macro Constraints

Total Health Expenditure as a function of GDP:

8.9% (OECD) (of which 71% funded through public expenditure, i.e. 6.3% GDP).

We project public health expenditure using age-class cost profiles and population projections and compute the average benefit cut required to keep the expenditure at the current level (as a % of GDP).

Costs are assumed to grow at the GDP growth rate.

	2020	2030	2040
Coverage Cut	2.9%	9.5%	15.3%

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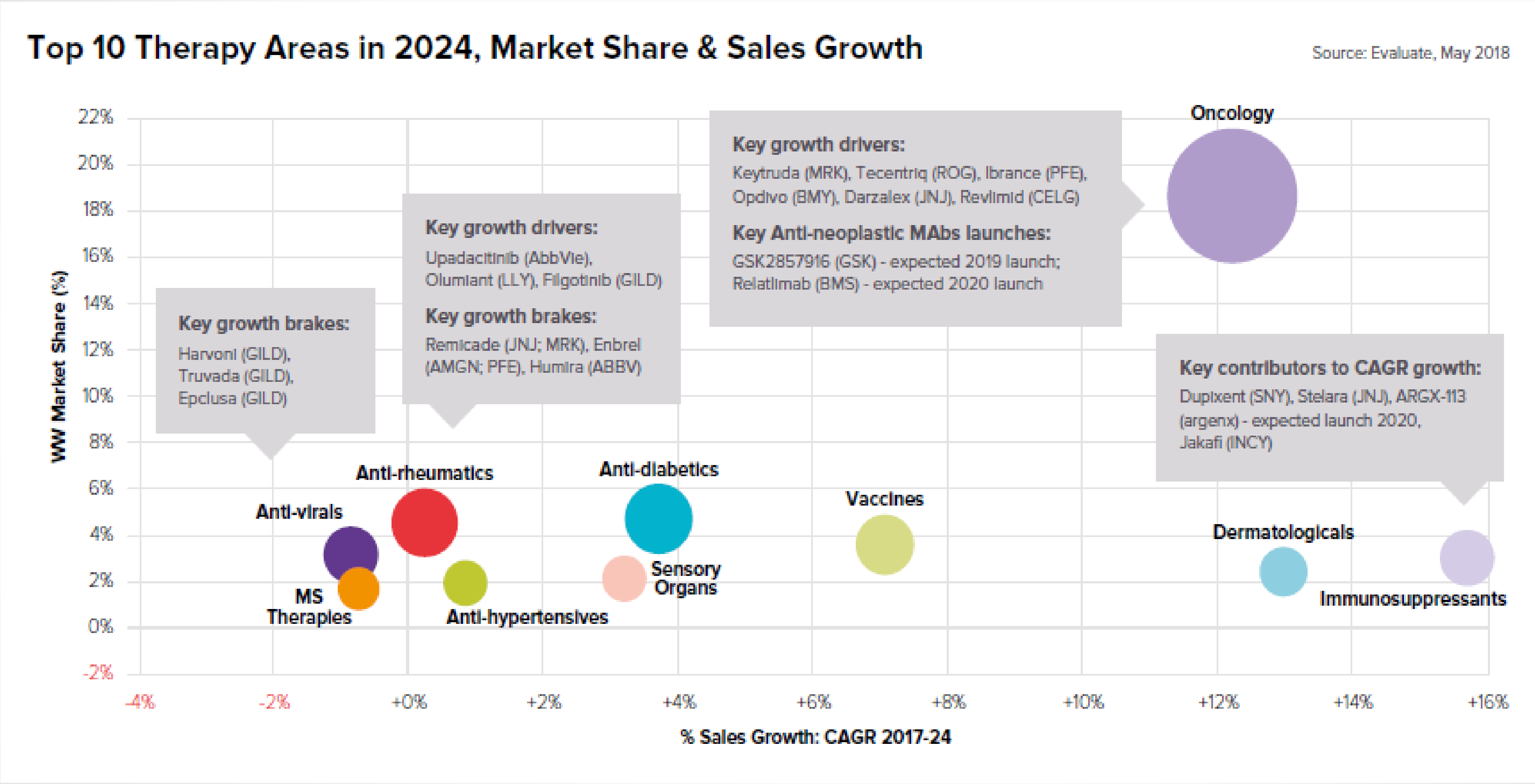
Back to Innovation and Sustainability



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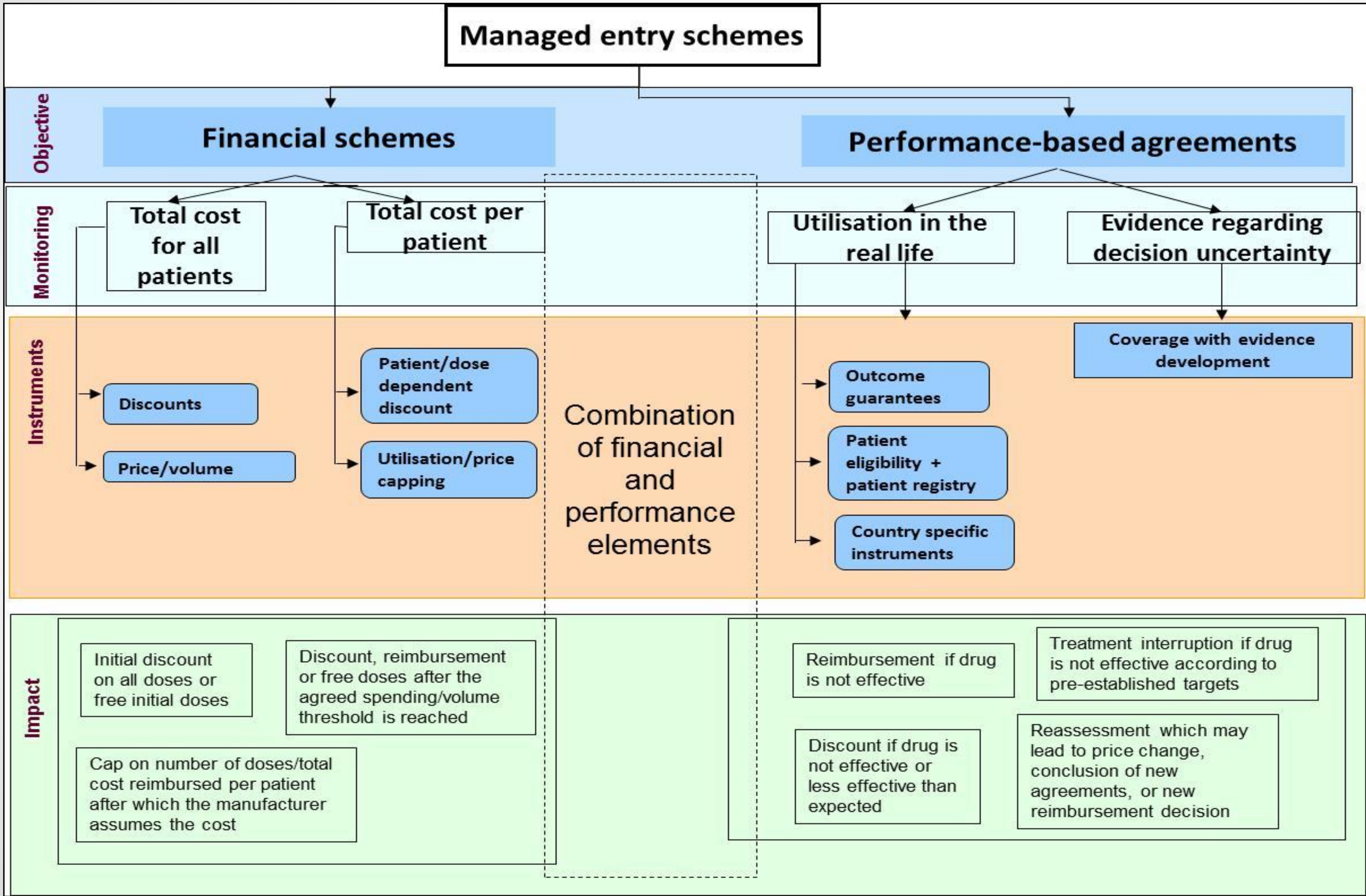
Back to Innovation: Pricing, Reimbursement and MEAs



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Back to Innovation: Pricing, Reimbursement and MEAs

Financial Sustainability, Risk Sharing, Payments by Results,

….but…

Real World Challenges

- Accelerated Adaptive pathways, Micro-level heterogeneity, Clinical guidelines vs. usage in specific patient cohorts
- Adjunctive therapies, Multiple indications, Combined therapies (e.g. ipilinumab + nivolumab in metastatic melanoma), Entry of new drugs
- Percentage of long term survivors (unknown ex ante)
- Duration of drug responses (unknown ex ante)
- Local and national formulary listing decisions; Off-labeling

Alternative solutions

Master and Margarita (Bulgakov) (e.g. broad equivalency classes, denial of breakthrough designations, rationing/coverage restrictions, delays …)

OR …

Data repositories to support ML+Causal modelling in real world to sustain payment by results, adaptive reimbursement, outcome based refund agreements, protocols in real world, socio-economic impact

AND …

Drugs Looking for Diseases, Medical Decision Making, Tragic Choices

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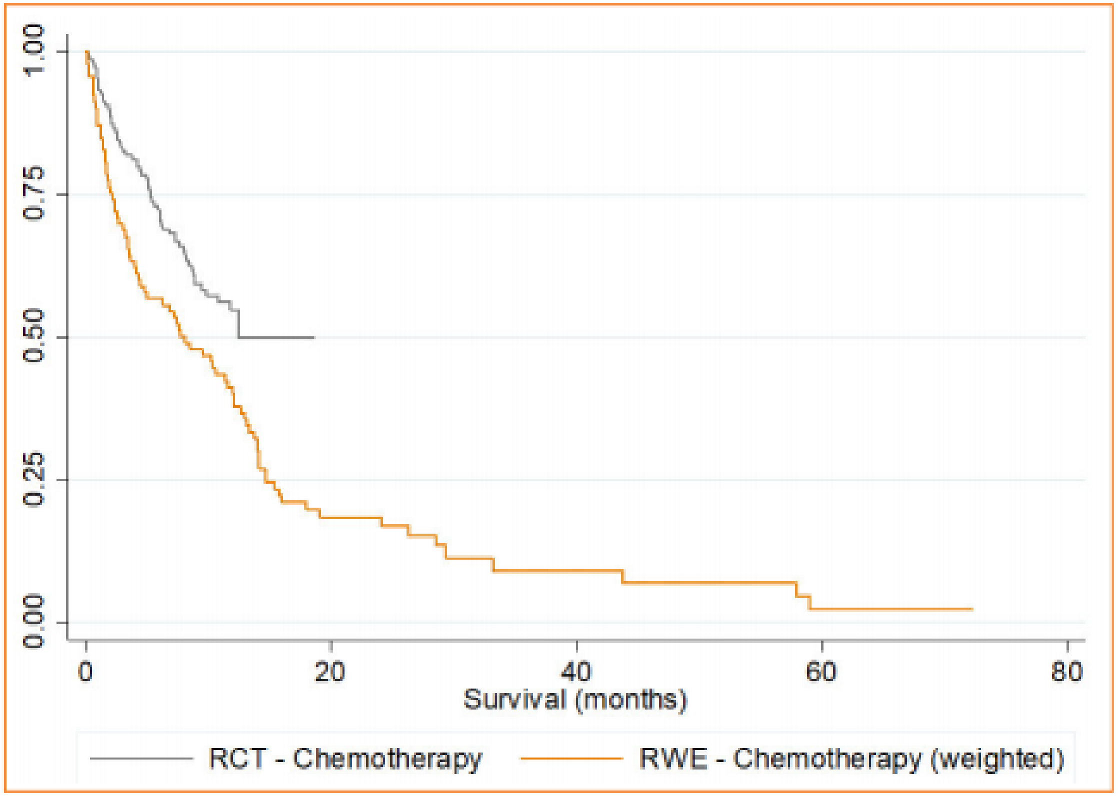
Targeting and Impact Analysis in the Wild

Causality in the wild:

- Age groups
- Ethnicity and gender variances
- Co-morbidity
- Concomitant drugs
- Lifestyle variances
- Differences in disease severity
- Varying levels of compliance
- (….)



X. Huang et al., 2018, "*Revealing Alzheimer's disease genes spectrum in the whole-genome by machine learning*", BMC Neurology

S. Mueller et al., 2017, "*Overall Survival In Patients With Non-small Cell Lung Cancer: A Comparison Of Clinical Trial Versus Real-world Outcomes Using A Propensity Score Reweighting Approach*", INGRESS

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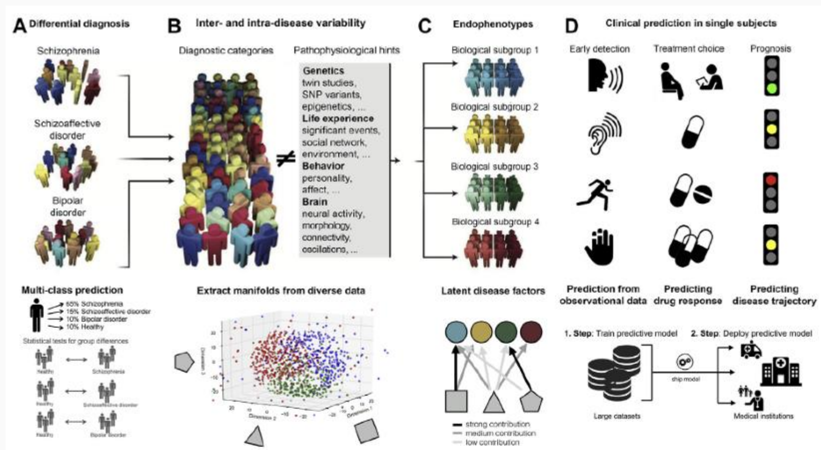
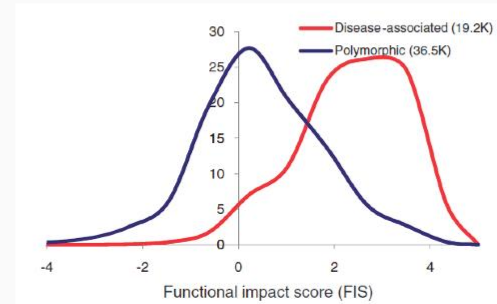
Targeting and Impact Analysis in the Wild

Inferences in the wild

- Clusterization of patients based on multiple features (co-morbidity, disease intensity, etc.)
- Machine Learning and RWE to support therapy choice and dosage

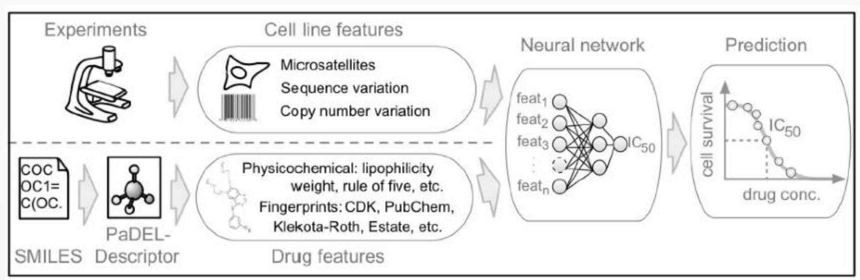




Reva et al., 201

ML methods to classify protein mutations as cancer-associated as opposed to common polymorphisms

Oncogenetic cell profiles and drug features: ML to assess drug efficacy in inhibiting tumoral cells



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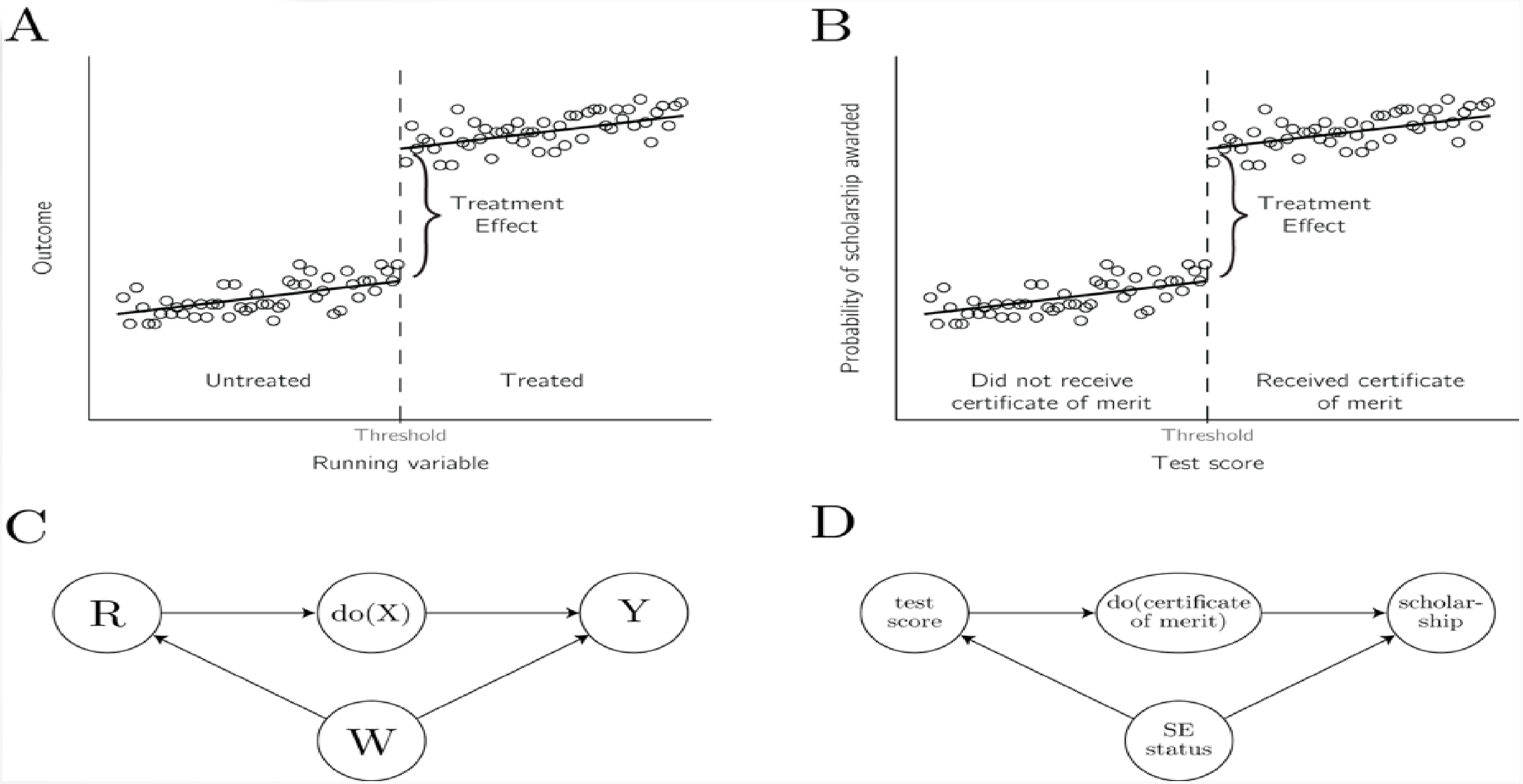
Targeting and Impact Analysis in the Wild



A) Schematic of a Regression Discontinuity Design analysis. The treatment is only administered if the running variable is above the threshold. The outcome (y-axis) is plotted as a function of a running variable (x-axis). The magnitude of the treatment effect, the difference in outcome at the threshold, is estimated using regression. **B) Schematic figure representing the analysis performed** in (Thistlethwaite D.L., Campbell D.T., 1960, "Regression-Discontinuity Analysis: An Alternative to the Ex-Post Facto Experiment", *The Journal of Educational Psychology*. 1960;51:309-17). Academic outcome (probability of scholarship) is plotted as a function of test score, and a discontinuity is seen at the cutoff for receiving a certificate of merit. Note that this figure is stylized and does not use the data used in the original analysis; it is intended only to demonstrate the approach. **C) Graphical model of Regression Discontinuity Design.** W are confounding variables; R is the running variable which determines the treatment along with the threshold; X is the treatment (independent variable) which is either administered (do(X)) or not administered (do(not X)) depending on R; and Y is the outcome (dependent variable) of interest. **D) Graphical model representing this analysis**. Socioeconomic status (for example) is likely to affect both test score and the probability of receiving a scholarship. Test score determines whether a certificate of merit is awarded, which in turn affects the probability of receiving a scholarship.

Targeting and Impact Analysis in the Wild

Venkataramani, Atheendar & Bor, Jacob & B Jena, Anupam. (2016). Regression discontinuity designs in healthcare research. BMJ. 352.

Studies	Exposures	Type of assignment variables	Threshold rules	Outcomes
Clinical:				
Bor et al 2014, 2015[7 16]	HIV antiretroviral therapy	Therapeutic	Patients with CD4 counts <200 cells/mm^3 eligible to initiate early antiretroviral treatment in South Africa	Mortality, immune recovery, retention in clinical care
Almond et al 2010[13]	Neonatal intensive care	Therapeutic	Infants with birth weights <1500 g (designated very low birth weight) recommended for intensive care in United States	Infant mortality
Bharadwaj et al 2013[14]	Neonatal intensive care	Therapeutic	Infants with birth weights <1500 g (designated very low birth weight) recommended for intensive care in Chile and Norway	Child cognitive development, academic achievement
Geneletti et al 2015[15]	Statins	Therapeutic	10 year cardiovascular risk >20% as a guideline to initiate statins	Low density lipoprotein cholesterol
Jensen and Wust 2015[19]	Caesarean section	Calendar time	Changes in information and guidelines about efficacy of caesarean section starting 21 October 2000 in Denmark	Apgar score, physician visits, hospital admissions for neonates
Prevention and public health:				
Smith et al 2015[20]	HPV vaccine	Calendar time	Vaccines were available for select age groups after 1 January 1994	Cervical dysplasia and anogenital warts
Callaghan 2013[21]	Minimum drinking age	Age	Adults aged 21 or older can legally purchase and consume alcohol in United States	Mortality
Ludwig and Miller 2007[22]	Head Start program	Program eligibility	Counties ranked <300 based on historic poverty rates were eligible to receive federal Head Start	Child mortality
Chen et al 2013[23]	Air pollution	Geographic	Households north of China's Huai River received subsidies for high emission coal to heat homes	Mortality
Health policy:				
De La Mata et al 2012[24]	Health insurance	Program eligibility	People in households below a specific income threshold were eligible for Medicaid	Healthcare utilization among children
Wherry et al 2015[25]	Health insurance	Calendar time	People born after 1 October 1983 were eligible for more years of Medicaid coverage owing to rule changes	Hospital admissions among adolescents
Sood et al 2014[26]	Health insurance	Geographic	People living in predesignated districts were eligible to receive insurance, whereas those in neighboring districts were not	Mortality
Almond et al 2011[27]	Length of hospital stay	Clock time	Patients admitted after 12 am were allowed longer	Maternal and newborn

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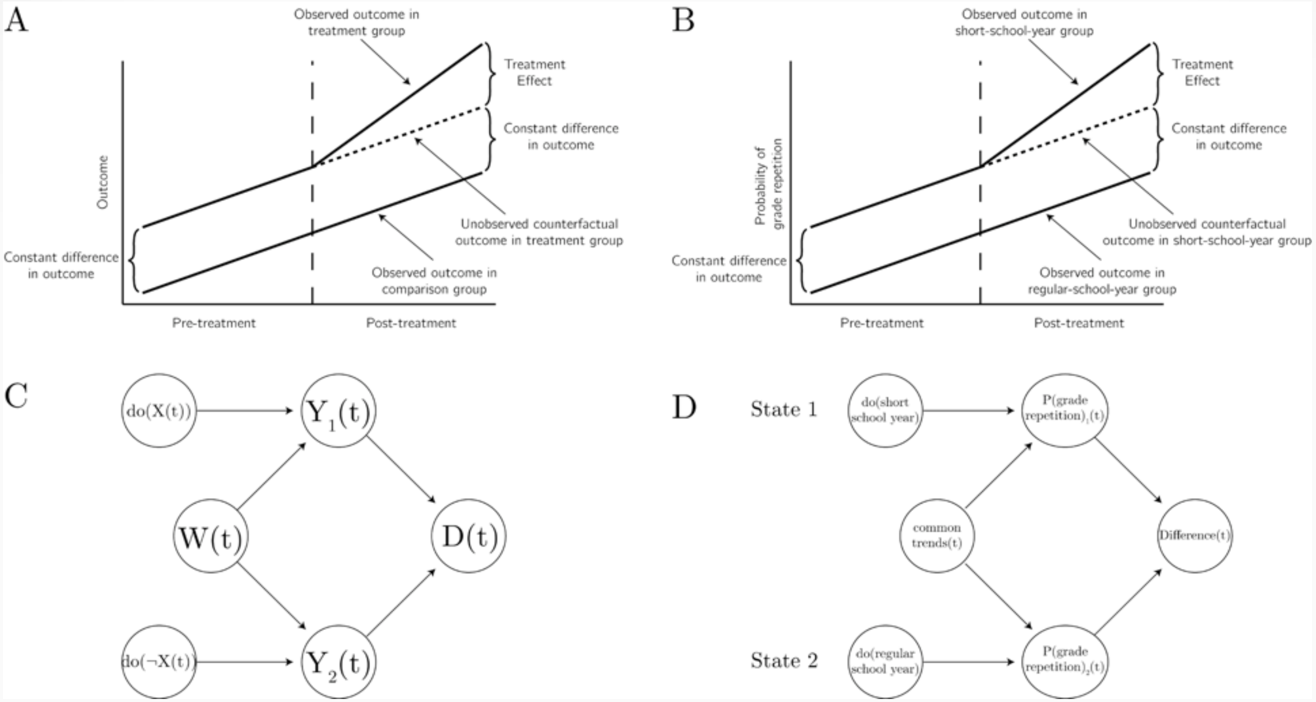
Targeting and Impact Analysis in the Wild



A) Schematic of a Difference-in-Differences analysis. The trend of two groups, treated and untreated, is plotted as a function of time. Before the treatment, the trends of the two groups should be parallel (a constant difference-in-differences). The treatment effect is estimated by the degree to which the trends diverge after the treatment is administered. **B) Schematic figure representing the analysis performed** in (Pischke J.S., 2007, "The impact of length of the school year on student performance and earnings: Evidence from the German short school years", *Economic Journal*, 117, 1216-42). Outcome (probability of grade repetition) is plotted as a function of time, before and after the implementation of the short school year in some states. The difference between State outcomes changes after the change in school year (i.e., there is an increase in difference in differences). Note that this figure is stylized and does not use the data used in the original analysis; it is intended only to demonstrate the approach. **C) Graphical model for Difference-In-Differences.** All variables are considered as a function of time, t. W are confounding variables; X is the treatment (independent variable) which is administered (do(X)) to population 1, and not administered (do(not X)) to population 2; Y1 and Y2 are the outcomes (dependent variables) for populations 1 and 2, respectively; D is the difference between Y1 and Y2 and is tracked over time**.** **D) Graphical model representing the analysis performed**. Common trends such as federal taxes and economic conditions are likely to affect the two States similarly. The short school year is implemented only in one State. The difference in outcome is calculated from the two States' outcomes.

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Targeting and Impact Analysis in the Wild

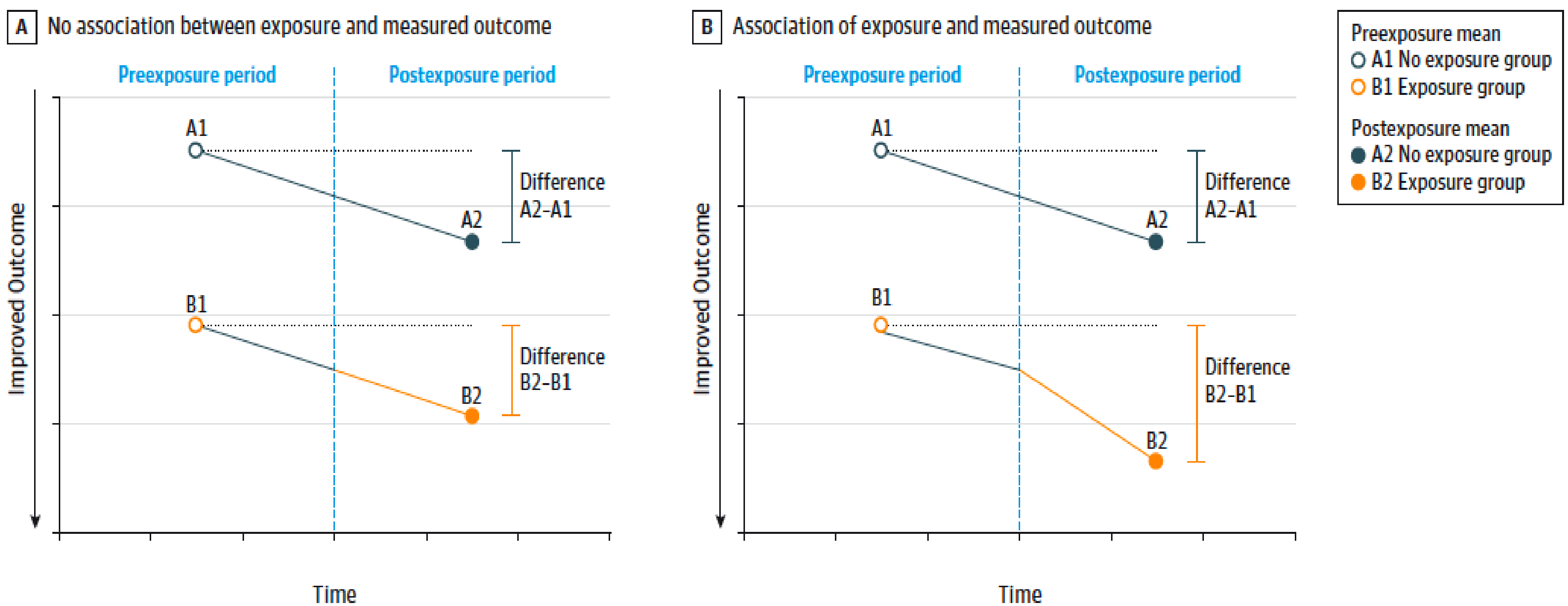
Clinical Review & Education

JAMA Guide to Statistics and Methods

Methods for Evaluating Changes in Health Care Policy
The Difference-in-Differences Approach

Justin B. Dimick, MD, MPH; Andrew M. Ryan, PhD

Figure. Conceptual Illustration of a Difference-in-Differences Analysis for 2 Scenarios



Designing Difference in Difference Studies: Best Practices for Public Health Policy
Coady Wing, Kosali Simon, Ricardo A. Bello-Gomez
Annual Review of Public Health 2018 39:1, 453-469

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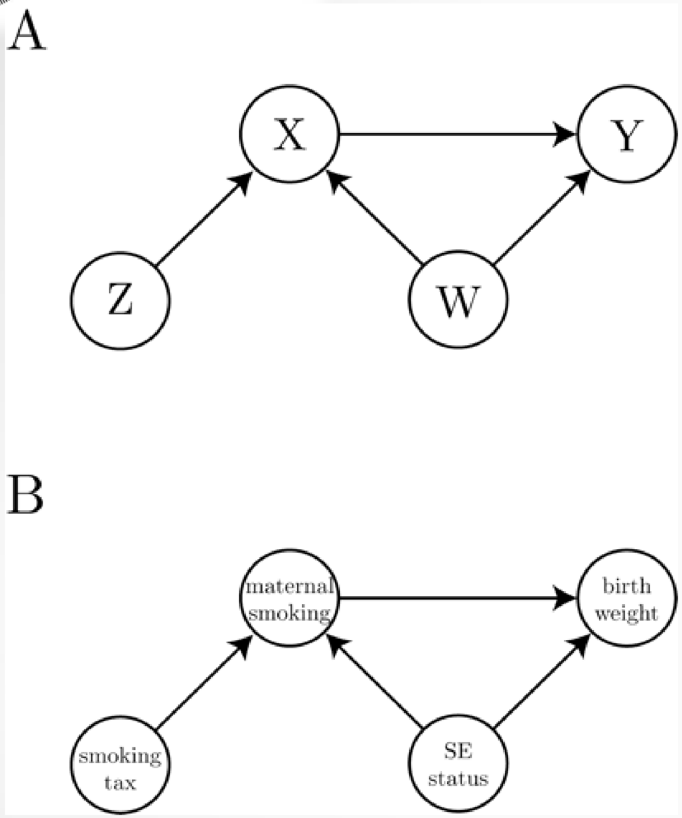


An instrumental variable (IV) is a variable, generally found in administrative data, that is assumed to randomize a treatment to estimate cause and effect relationships, thus controlling for known and unknown patient characteristics affecting health outcomes. An important (often heroic) assumption is that the IV randomizes treatment but does not directly affect the patient outcome.

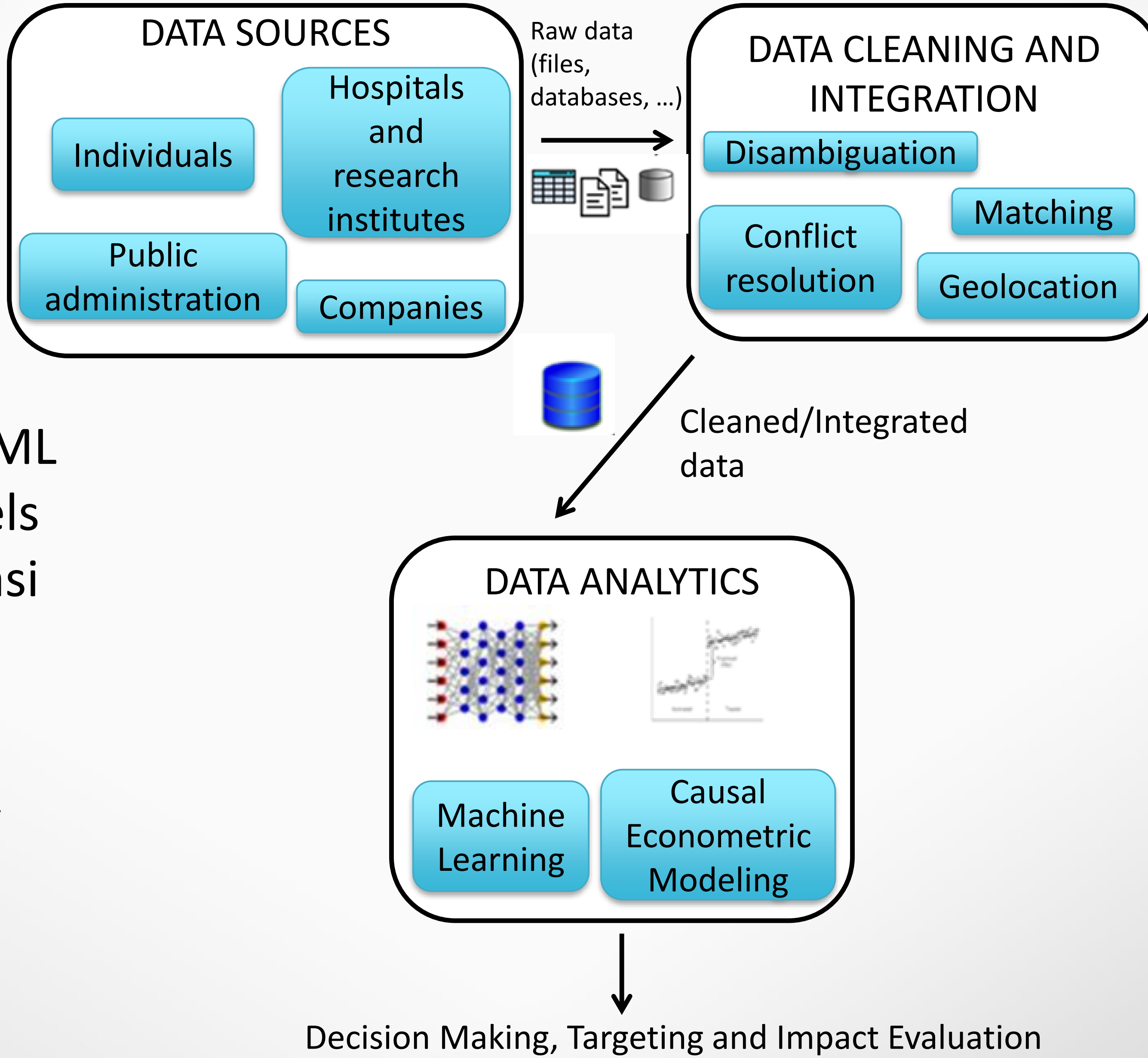
A) Graphical model for Instrumental Variables. W are confounding variables; X is the independent variable; Y is the outcome (dependent variable); Z is the instrument which only affects Y through its effect on X. **B) Graphical model representing the analysis performed.** Graphical model representing this analysis performed in (Evans W.N., Ringel J.S., 1999, "Can higher cigarette taxes improve birth outcomes?", *Journal of Public Economics*, 72, 135-54. Maternal smoking is thought to affect birth weight. But socioeconomic status (for example) likely affects both a mother's decision to smoke as well as the child's birth weight. A tax on cigarette smoking could affect maternal smoking but is unlikely to directly influence the birth weight, except through an effect on maternal smoking. Such a tax is therefore a good instrument to examine the effect of smoking on birth weight without being confounded by socioeconomic status

Inferences in the Wild: The Organization of Research

- Micro and population data from heterogeneous sources

- Combination of ML and causal models in real world quasi experimental settings

- Multidisciplinary data analytics factories



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Summing Up

- The Endless Frontier: Innovation, ageing, sustainability and *tragic choices* in health.

- Looking for a *Selective Universalism, designed around the evolution of individual needs over the life cycle*

- Causal inferences in real world to sustain Risk Sharing and Outcome-Based Dynamic Pricing Schemes. Data: A *Tragedy of the Anticommons* (M. Heller)?

- Adaptive Precision Therapies call for … Adaptive Precision Policies.

- ML and causal modelling for targeting and impact evaluation. The organizational challenge for research