@ATS RIS | RESPIRATORY INNOVATION SUMMIT

Breathing Innovation:

2nd Annual Report on the State of Respiratory Innovation's Industry and Investment

Dallas, Texas
May 17, 2019

Tim Watkins, MD, MSc, Executive Director of Clinical Research, Respiratory & Inflammation Therapeutics, Gilead Sciences
Cecilia Gonzalo, Partner, Oberland Capital

Agenda

Introductions

An Update on Major Developments in the Respiratory Space

VCPE and M&A Environment for Respiratory Companies

Tim Watkins, MD, MSc
Executive Director of Clinical Research, Respiratory & Inflammation Therapeutics

GILEAD

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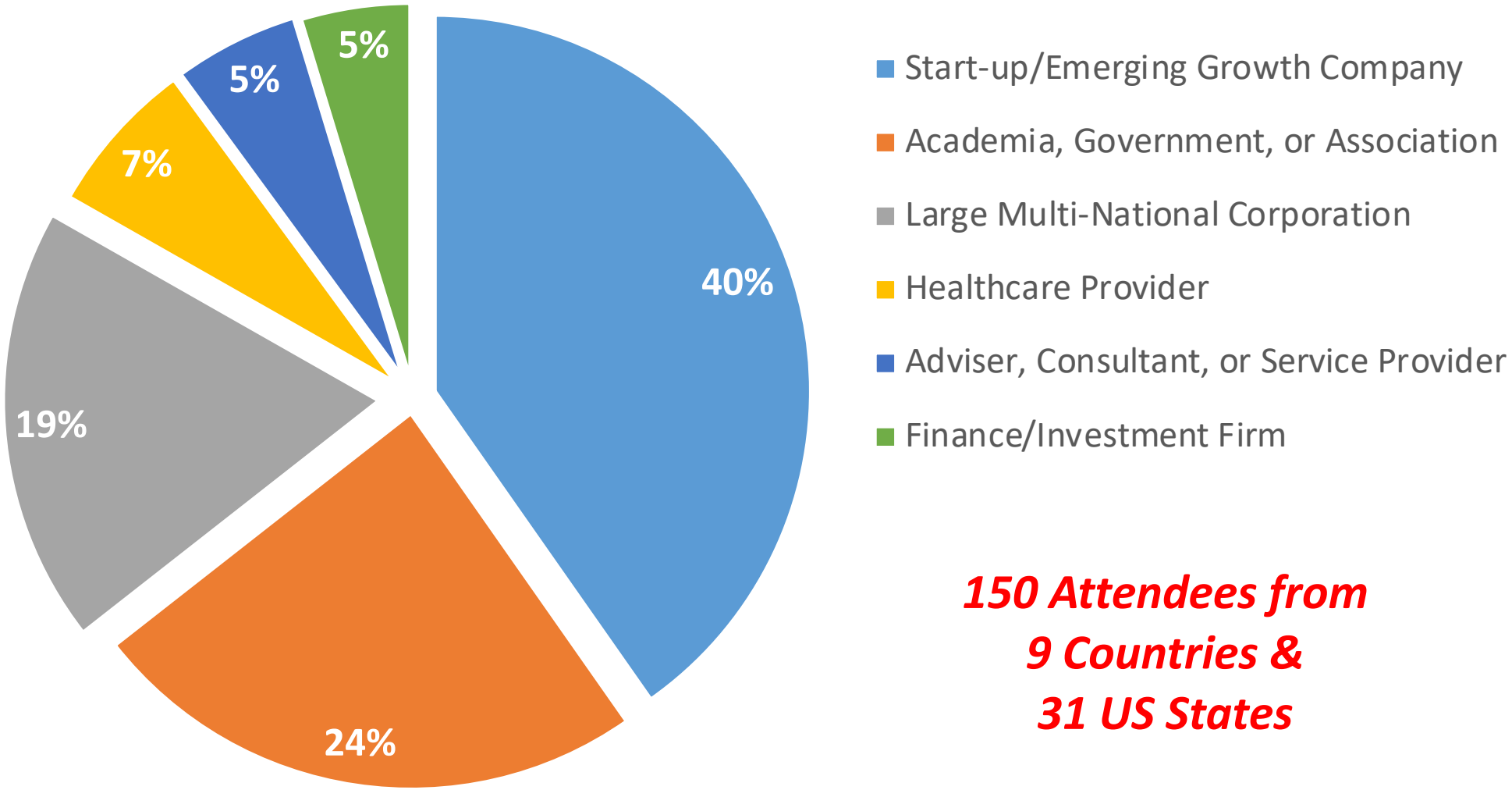
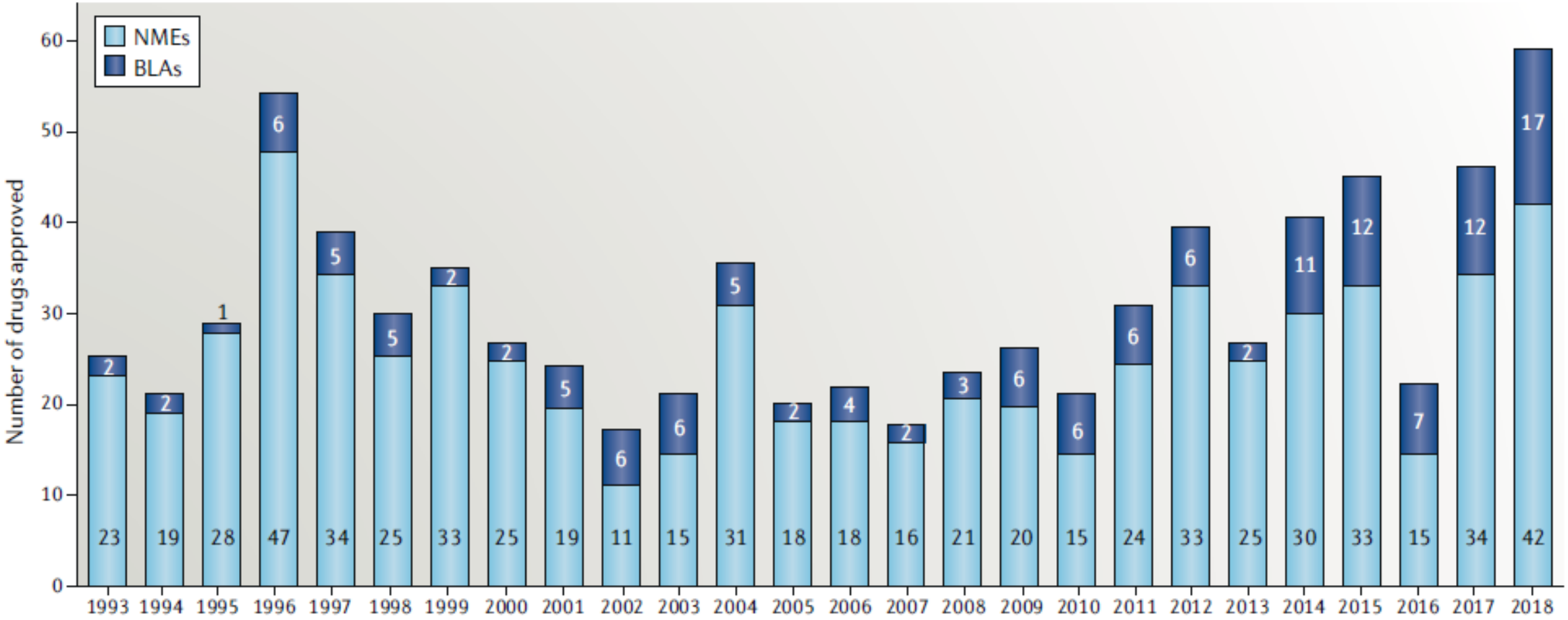
Celebrating our second year of innovation



150 Attendees from
9 Countries &
31 US States

2018 – A Bumper Approval Crop of 59 FDA Approvals



Novel FDA approvals since 1993. Annual numbers of new molecular entities and biologics license applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER). Approvals of products such as vaccines by the Center for Biologics Evaluation and Research are not included.

Source: Mullard A. 2018 FDA drug approvals. Nat Rev Drug Discov 2019;18 (2):85-9. Drugs@FDA

2018

U.S. Department of Health & Human Services | National Institutes of Health | NCATS

NIH National Center for Advancing Translational Sciences | GARD Genetic and Rare Diseases Information Center

1-888-205-2311

Diseases | Guides | News | About GARD | En Español

Search for Diseases, Organizations, News and More... GO

HOME > DISEASES > FIND DISEASES BY CATEGORY > LUNG DISEASES

Browse A-Z

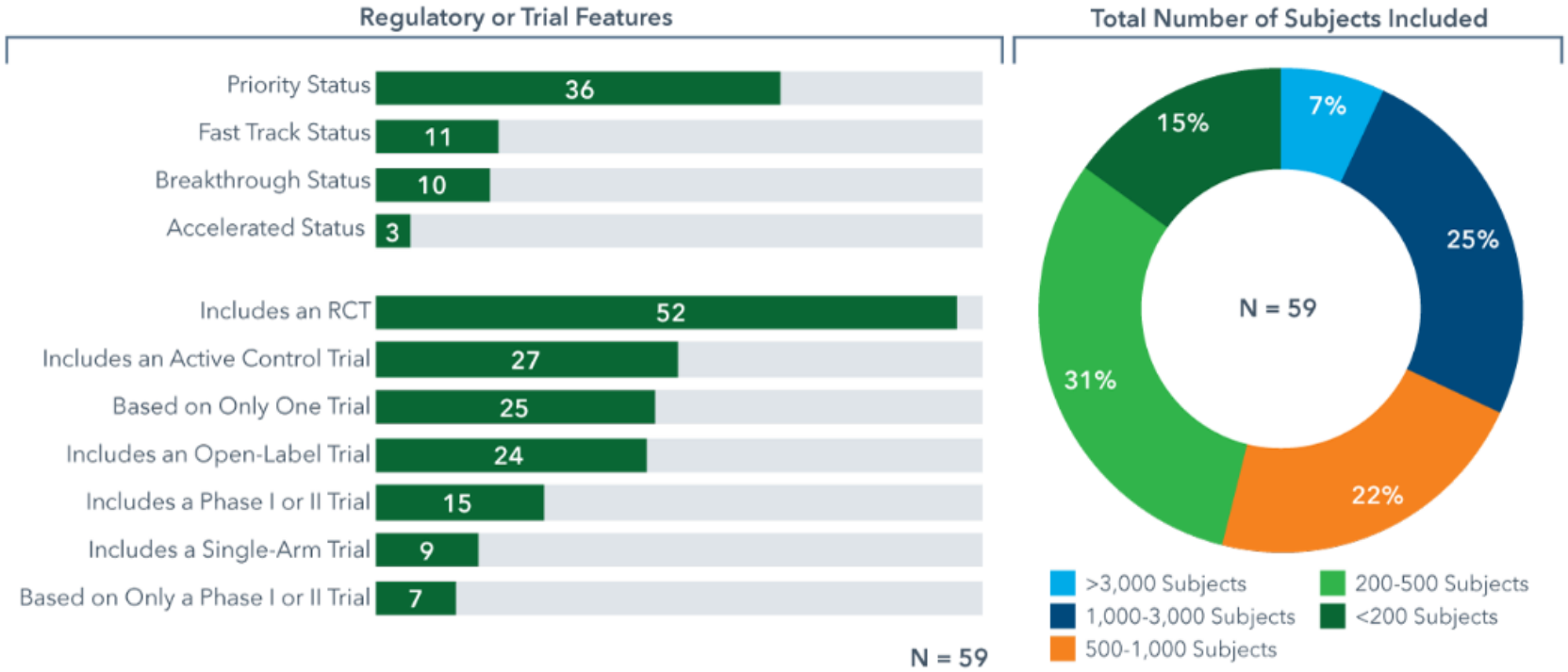
Find Diseases By Category

- Autoimmune / Autoinflammatory diseases
- Bacterial infections
- Behavioral and mental disorders
- Blood Diseases
- Chromosome Disorders
- Congenital and Genetic Diseases
- Connective tissue diseases
- Digestive Diseases
- Ear, Nose, and Throat Diseases
- Endocrine Diseases
- Environmental Diseases
- Eye diseases
- Female Reproductive Diseases
- Fungal infections
- Heart Diseases
- Hereditary Cancer Syndromes
- Immune System Diseases
- Kidney and Urinary Diseases

Lung Diseases

Acropectorovertebral dysplasia F form
Acute interstitial pneumonia
Allergic bronchopulmonary aspergillosis
Alpha-1 antitrypsin deficiency
Alveolar capillary dysplasia
Arterial tortuosity syndrome
Asbestosis
Autoimmune pulmonary alveolar proteinosis
Beryllium disease
Birt-Hogg-Dube syndrome
Blau syndrome
Brain-lung-thyroid syndrome
Bronchiolitis obliterans
Bronchiolitis obliterans organizing pneumonia
Bronchogenic cyst
Bronchopulmonary dysplasia
Cantu syndrome
Catamenial pneumothorax
Children's interstitial lung disease
Chronic granulomatous disease
Chronic thromboembolic pulmonary hypertension
Classical-like Ehlers-Danlos syndrome
Coal worker's pneumoconiosis
Congenital diaphragmatic hernia
Congenital lobar emphysema
Congenital pulmonary alveolar proteinosis

A Trend Towards Faster FDA Reviews and Fewer Patients in Registrational Trials



- **>70% of new drugs approved in 2018 followed a regulatory process intended to accelerate their review**
- **Of the new drugs approved by FDA in 2018, 46% were based on in trials with <500 patients**

Source: IQVIA Institute, Mar 2019
Report: The Changing Landscape of Research and Development. IQVIA Institute for Human Data Science, April 2019

Source: IQVIA. "The Changing Landscape of Research and Development: Innovations, Drivers of Change, and Evolution of Clinical Trial Productivity." *IQVIA Institute for Human Data Science. April 2019, pg. 5 & 7.*

2018 – Scott Gottlieb, Modernizing the FDA's Office of New Drugs

FDA STATEMENT

Sharpless: 'There Will Be No Pause' On Existing FDA Initiatives

May 02, 2019

Speaking before a room full of lawyers representing FDA-regulated industries of all stripes, FDA Acting Commissioner Ned Sharpless reiterated that under his leadership the agency will stay the course on the wide range of initiatives that have been advanced under previous commissioners such as Scott Gottlieb, whose tenure marked new regulatory paradigm shifts in nearly every sector under agency oversight. "There will be no pause at the FDA," Sharpless said at the start of the Food and Drug Law Institute's...

disease, and perhaps slow its advance or lessen its insidious effects, more patients today can expect the ability to arrest the march of illness or achieve an outright cure.

Key Drug Approvals Relevant to PCCM

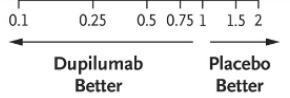
SANOFI

REGENERON

FDA Approved – October, 2018
3 clinical trials (2,888 subjects)

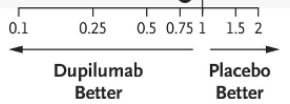
A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
FE_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)



B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)



Castro M et al. N Engl J Med 2018; 378:2486-2496

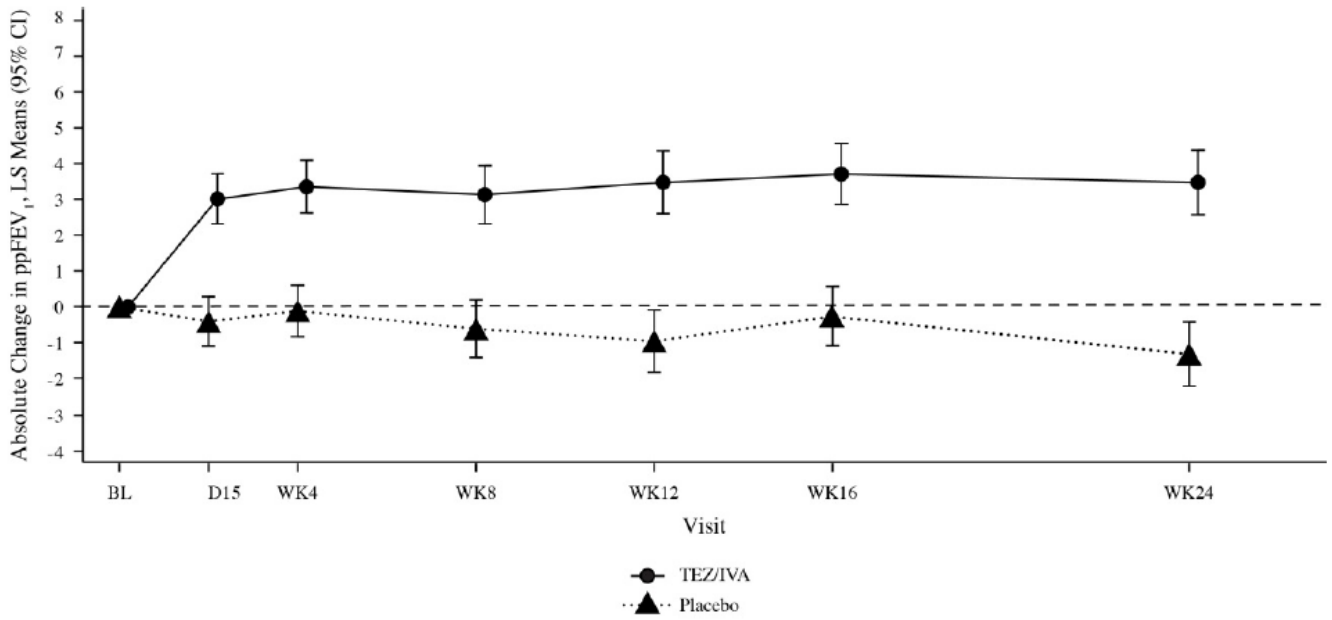
DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.
Limitation of Use: DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

VERTEX®

symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100 mg/150 mg and 150 mg tablets

FDA Approved – Cystic Fibrosis Review Type: Priority, Orphan, Breakthrough Therapy

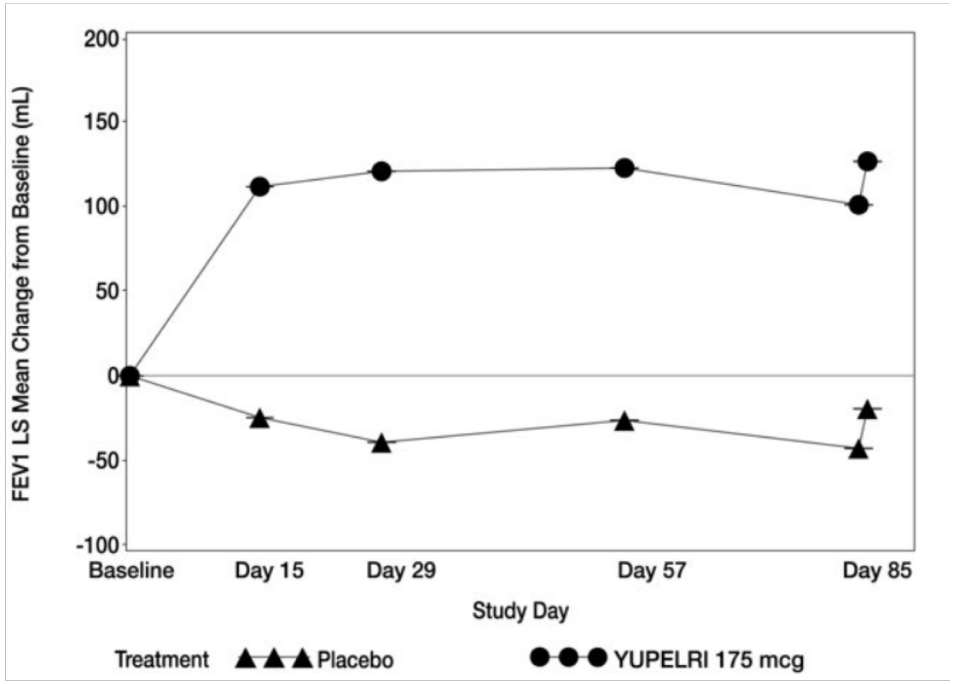
Figure 2: Absolute Change From Baseline in Percent Predicted FEV_1 at Each Visit in Trial 1



SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.

Theravance Biopharma

FDA Approved – COPD
Mechanisms: Long-acting muscarinic receptor antagonist
Review Type: Standard



YUPELRI (revefenacin) inhalation solution is an anticholinergic indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)

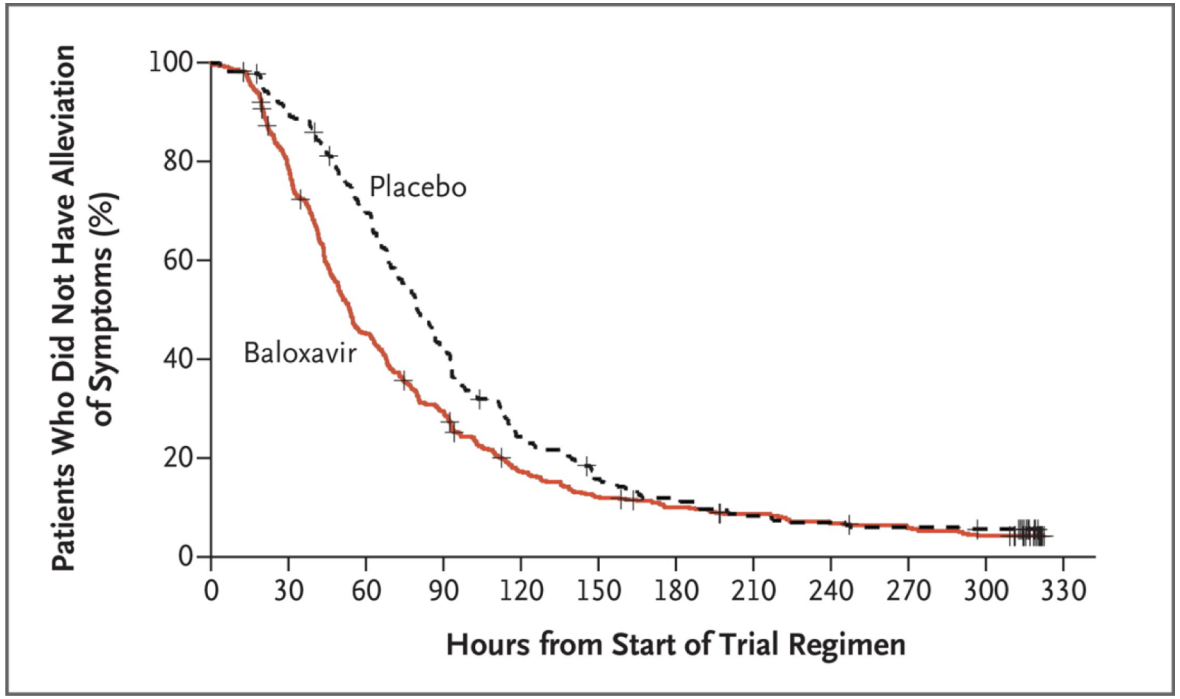
SHIONOGI

Roche

xofluza™

(baloxavir marboxil) tablets 20mg 40mg

FDA Approved – Acute uncomplicated influenza Review Type: Priority



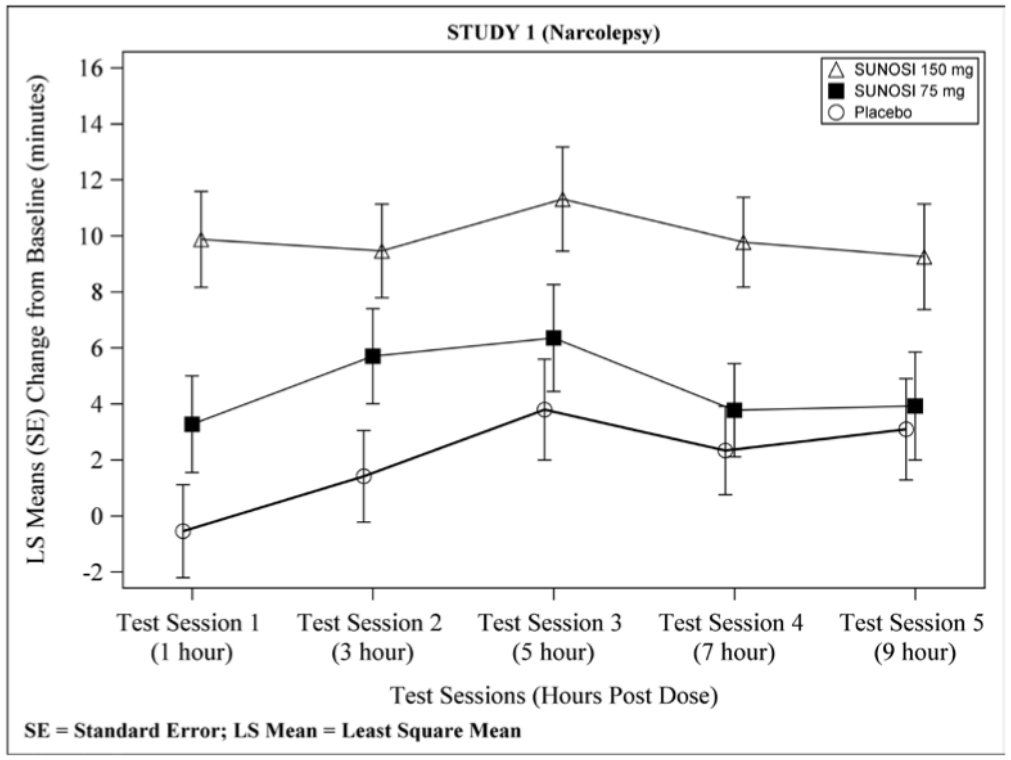
Hayden FG et al. N Engl J Med 2018;379:913-923

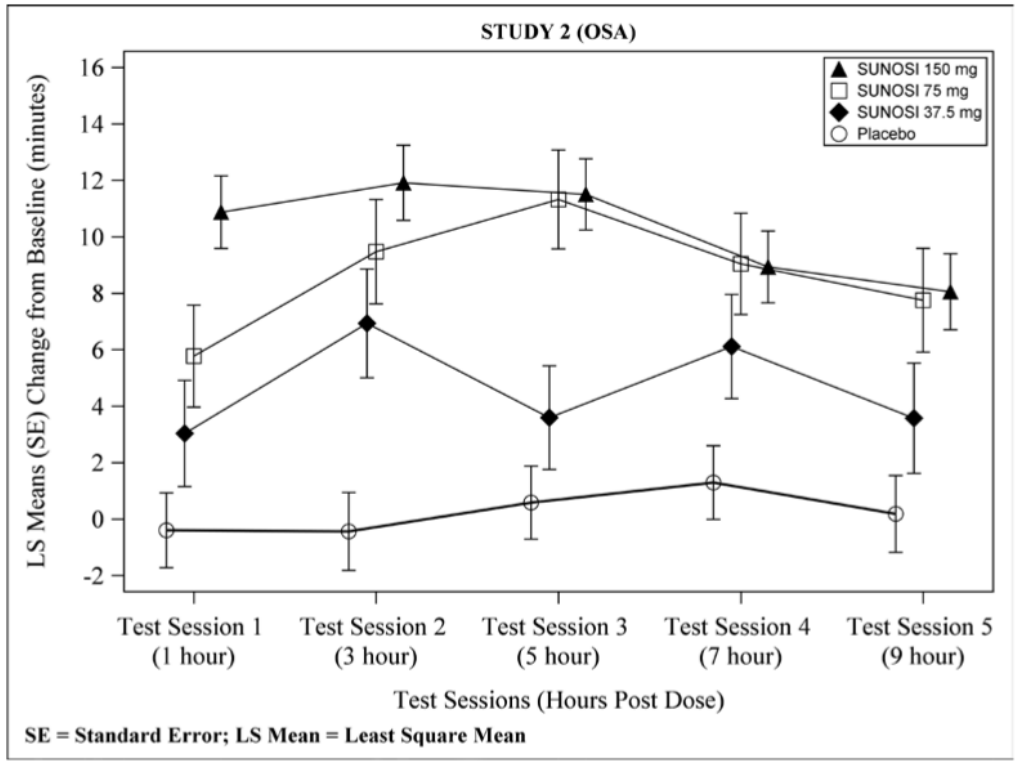
XOFLUZATM is a polymerase acidic(PA)endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.

Jazz Pharmaceuticals

Sunosi™

FDA Approved – March 20, 2019
Review Type: Orphan





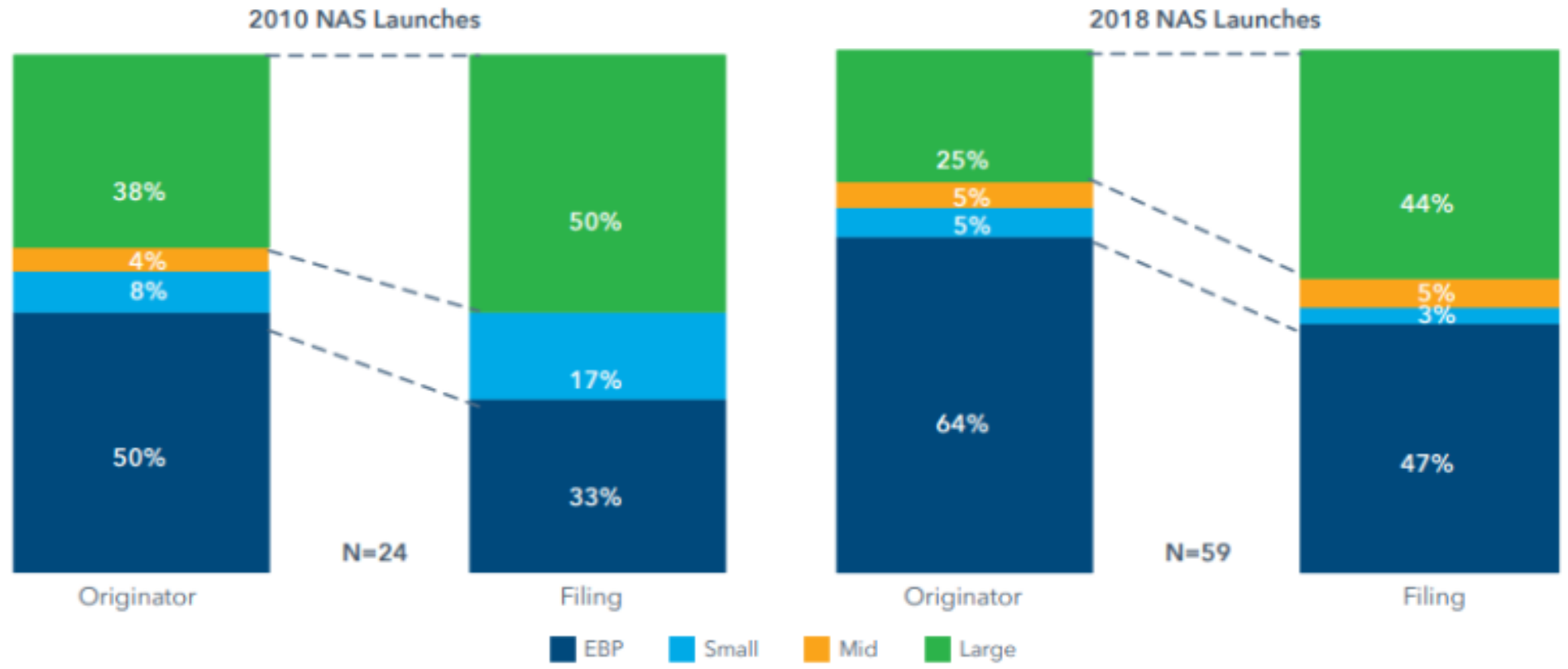
SUNOSI is a dopamine and norepinephrine reuptake inhibitor (DNRI) indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA)

Othe

Dr	ew Type
Sodiu cyclos	ard
Plazo	y
Tecov	y, Orphan
Tafen	y, Orphan, hrough
Erava	y
Lorlat	y, Orphan, hrough, rated

Emerging biopharma companies patented almost two-thirds of new drugs in 2018, while large pharma patented one-quarter

Exhibit 5: Originator Companies and Companies Filing FDA Regulatory Submission by Company Segment



Source: IQVIA MIDAS restricted MAT Q4 2017; FDA websites; Clarivate Analytics Cortellis

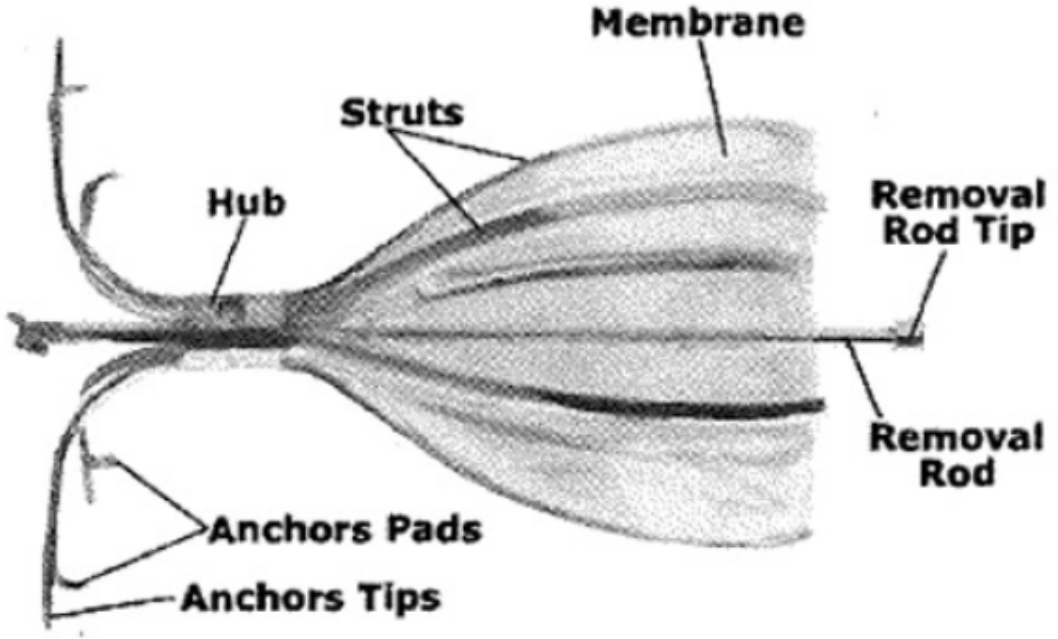
NAS = New active substances, EBP = Emerging biopharma *Credit: "The Changing Landscape of Research and Development," IQVIA Institute for Human Data Science*

Key Device Approvals Relevant to PCCM

FDA Approved – Emphysema

OLYMPUS

Spiration
Valve System



FDA Approved – Emphysema

zephyr® valve

Image of Device in Lung Airway

pulmonX®

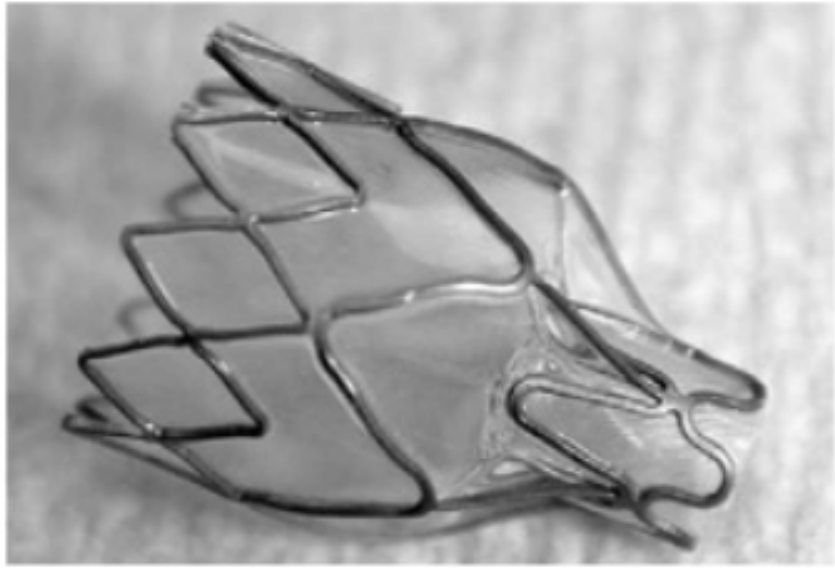


Image of the Device

FDA Approved – Improving Lung Transplant

TransMedics

OCS™ Lung

XVIVO Perfusion System (XPS™) with STEEN Solution™ Perfusate - P180014

XVIVO PERFUSION

Opportunities & Challenges: New Respiratory Therapeutic Modalities On the Horizon

Precision medicine in COPD: where are we and where do we need to go?

Venkataramana K. Sidhaye[1,2], Kristine Nishida[1] and Fernando J. Martinez

Number 8 in the Series "Personalised medicine in respiratory diseases"
Edited by Renaud Louis and Nicolas Roche

Artificial Intelligence

Interventional

Design of IPF Clinical Trials in the Era of Approved Therapies

Robert J. Kaner*[1,2], Ednan K Bajwa[3], Moustapha El-Amine[4], Eduard Gorina[5], Renu Gupta[6], Howard M. Lazarus[7], Tracy R. Luckhardt[8], Majd Mouded[9], Kaity Posada[10], Luca Richeldi[11], John Stauffer[12], Ahmet Tutuncu[13], Fernando J. Martinez[1,*]

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Cecilia Gonzalo
Partner

OBERLAND CAPITAL

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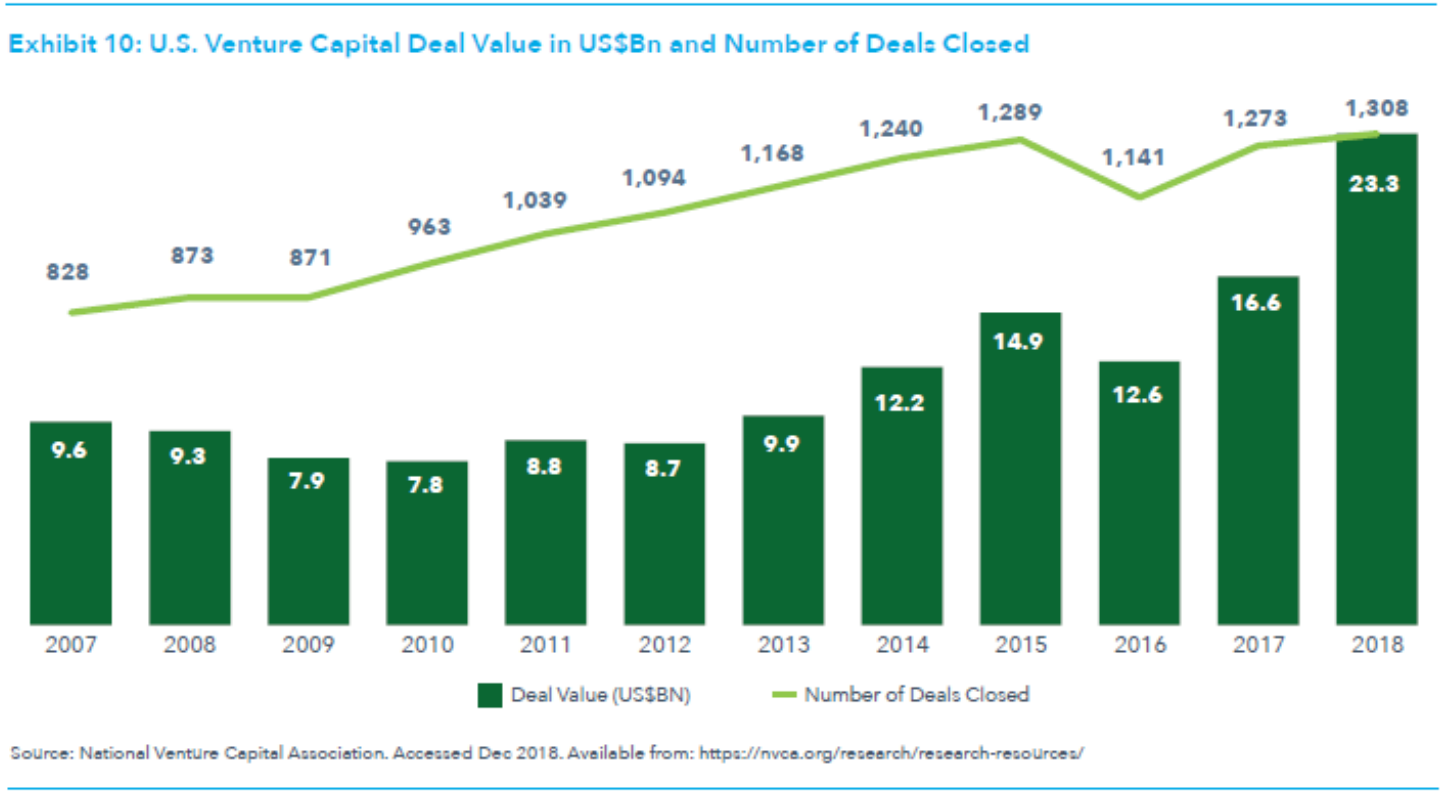
NVCA Data Shows Continued Growth in Venture Capital Investment in the Life Sciences Sector

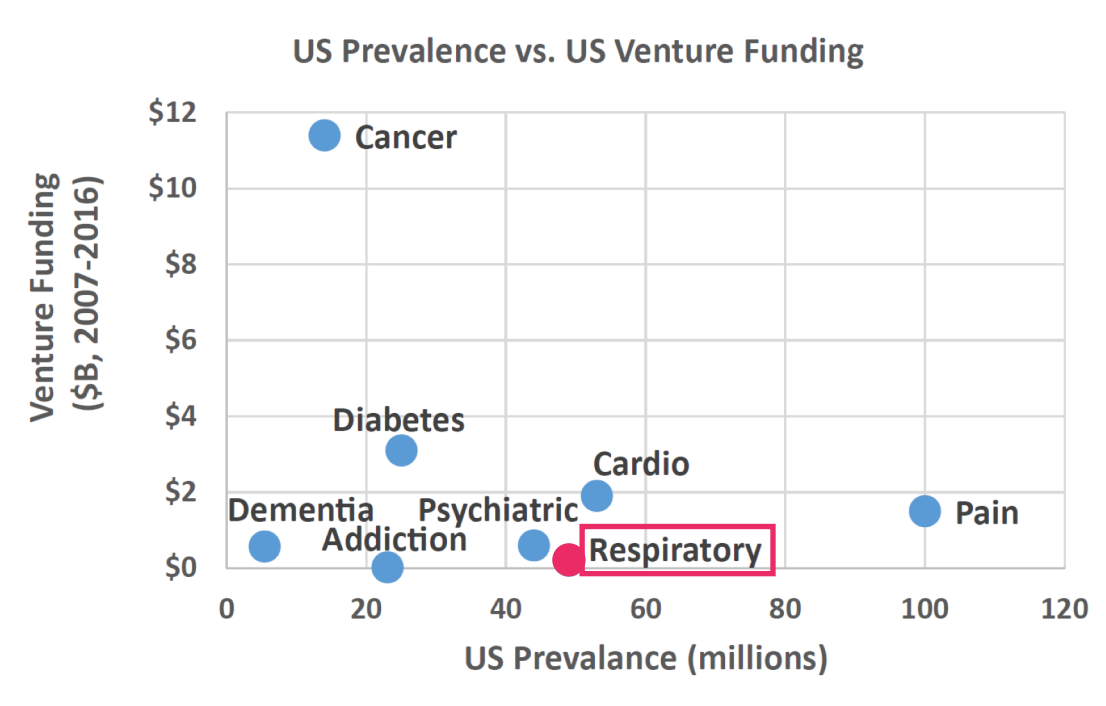


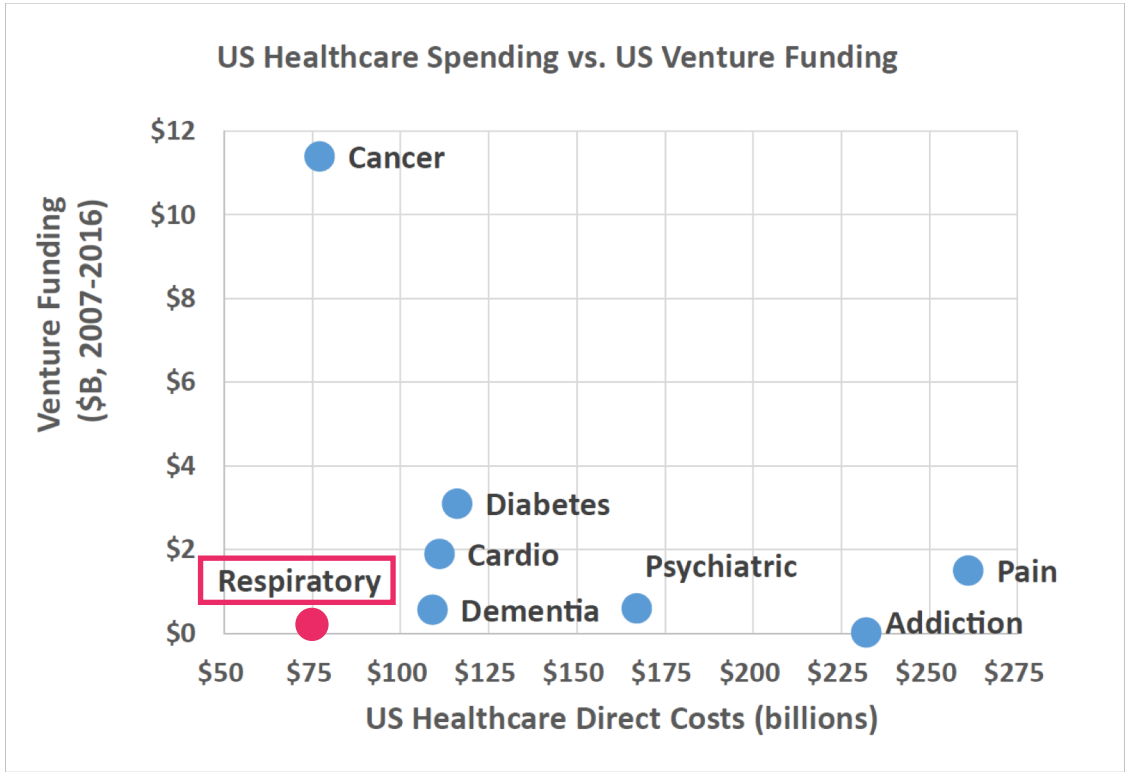
- >$23.3B invested in 2018
- >1,300 deals closed
- 2.5x dollars invested in 2018 versus 10 years ago

Source: IQVIA. "The Changing Landscape of Research and Development: Innovations, Drivers of Change, and Evolution of Clinical Trial Productivity." *IQVIA Institute for Human Data Science. April 2019, pg. 16.*

So How is the Respiratory Therapeutic Area Faring Relative to Others From a VCPE Investment Standpoint?

Respiratory Disease Presents a Significant Burden, Yet Garners Disproportionately Low VC Investment and Healthcare Spending





Source: Thomas, David and Chad Wessel. "Volume II: Pain and Addiction Therapeutics." *BIO Analysis,* Biotechnology Innovation Organization, May 2018, pg. 2.

US Mortality from Chronic Respiratory Diseases Continues to Increase

Mortality rates in the U.S. by category of deaths

CAUSE OF DEATH	EST. DEATHS PER 100K 1980	TREND	2014
Cardiovascular diseases	507.4		252.7
Cancers	240.2		192.0
Neurological diseases	80.3		95.4
Diabetes, blood and endocrine diseases	46.2		55.9
Chronic respiratory diseases	40.8		52.9
Diarrhea and common infectious diseases	38.5		30.0
Self-harm and interpersonal violence	25.2		19.6
Unintentional injuries	23.8		19.1
Cirrhosis and other chronic liver diseases	19.9		16.8
Digestive diseases	19.9		14.2
Transport injuries	25.2		13.8
Mental and substance use disorders	4.6		13.4
Other non-infectious diseases	9.7		5.8
Neonatal disorders	9.2		3.3
Musculoskeletal disorders	2.8		2.9
HIV/AIDS and tuberculosis	1.5		2.7
Other infectious diseases	1.9		1.4
Nutritional deficiencies	1.7		1.2
Maternal disorders	0.3	—	0.3
Forces of nature, war and legal intervention	0.3	—	0.1
Neglected tropical diseases and malaria	0.1	—	0.1

Trends not shown for causes of death with <1 death per 100,000 people

FiveThirtyEight SOURCE: INSTITUTE FOR HEALTH METRICS AND EVALUATION

Est. Deaths Per 100,000 People

Cardiovascular diseases
507.4 in 1980 → 252.7 in 2014

Cancers
240.2 in 1980 → 192.0 2014

Neurological diseases
80.3 in 1980 → 95.4 in 2014

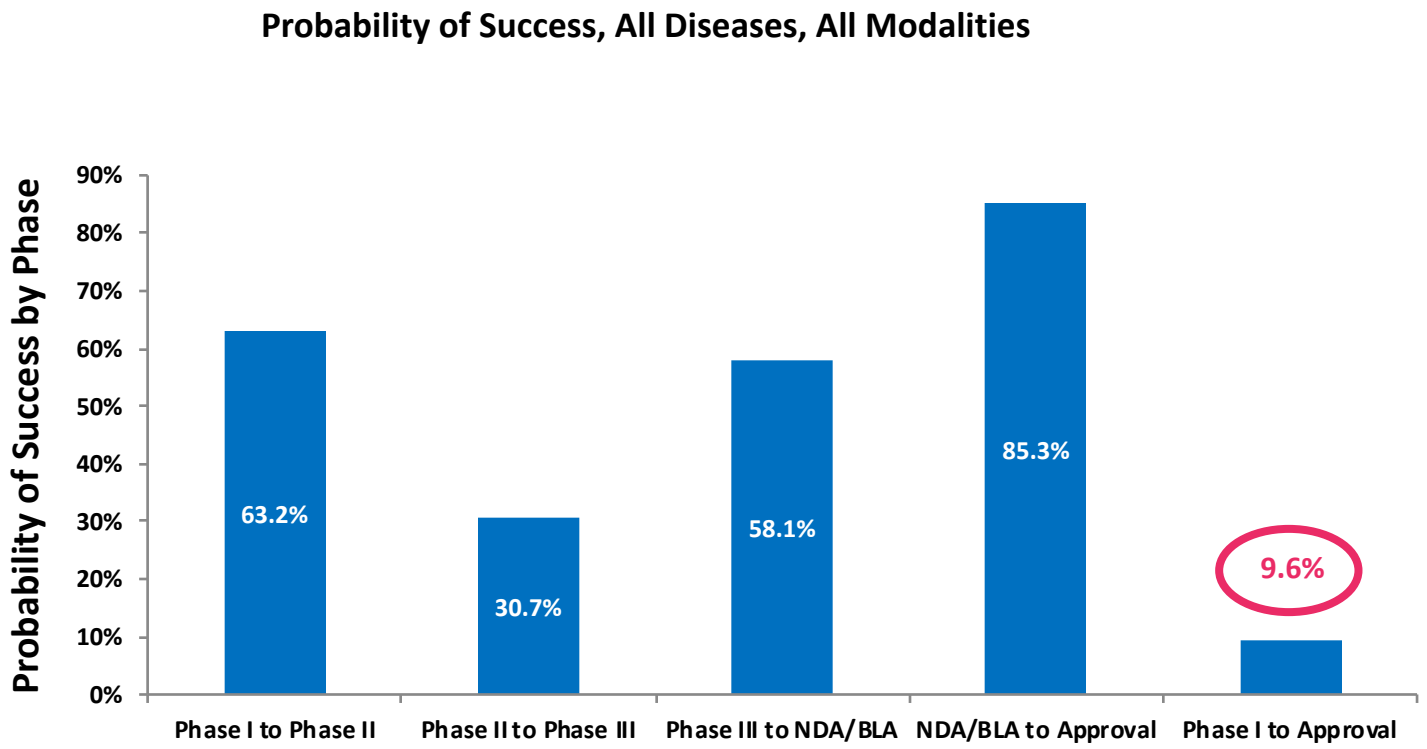
Diabetes, blood & endocrine diseases
46.2 in 1980 → 55.9 in 2014

Chronic respiratory diseases
40.8 in 1980 → 52.9 in 2014

Mental and substance use disorders
4.6 in 1980 → 13.4 in 2014

Source: FiveThirtyEight; Institute for Health Metrics and Evaluation

Drug Development Overall Probability of Success By Stage

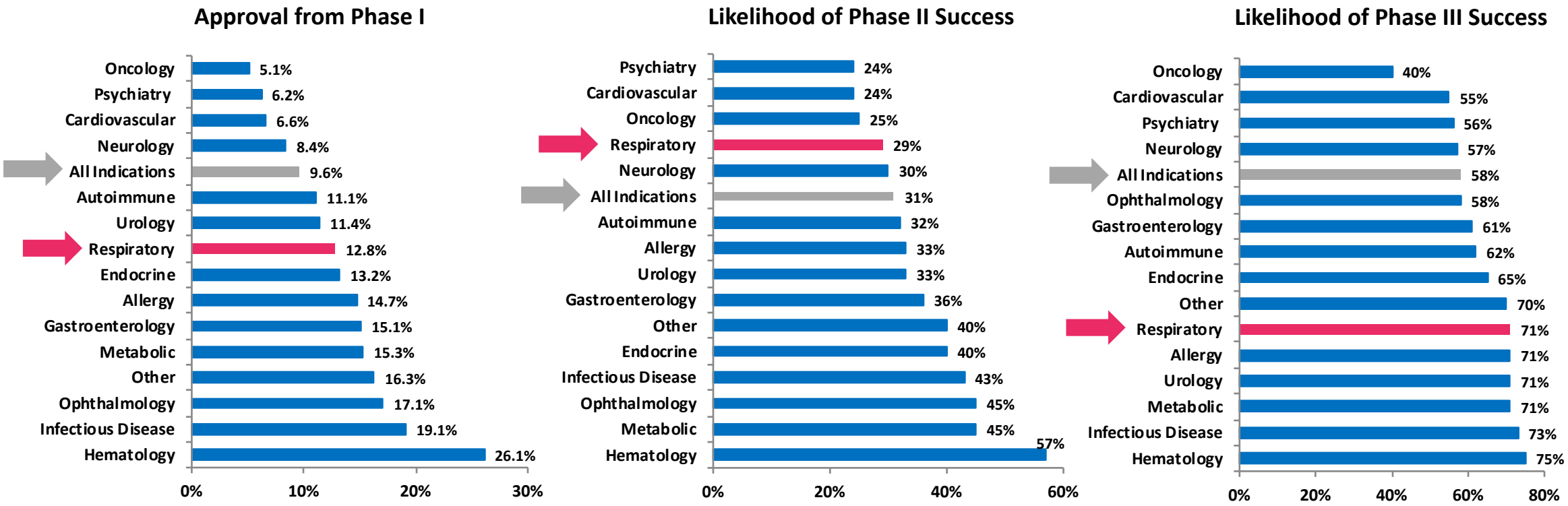


- …But how does *respiratory* drug development POS compare to the averages?

Source: Biotechnology Innovation Organization, Biomedtracker, Amplion. *Clinical Development Success Rates 2006-2015.*
Data based on 9,985 clinical and regulatory phase transitions from 7,455 development programs across 1,103 companies.

NDA = New Drug Application; BLA = Biologics License Application.

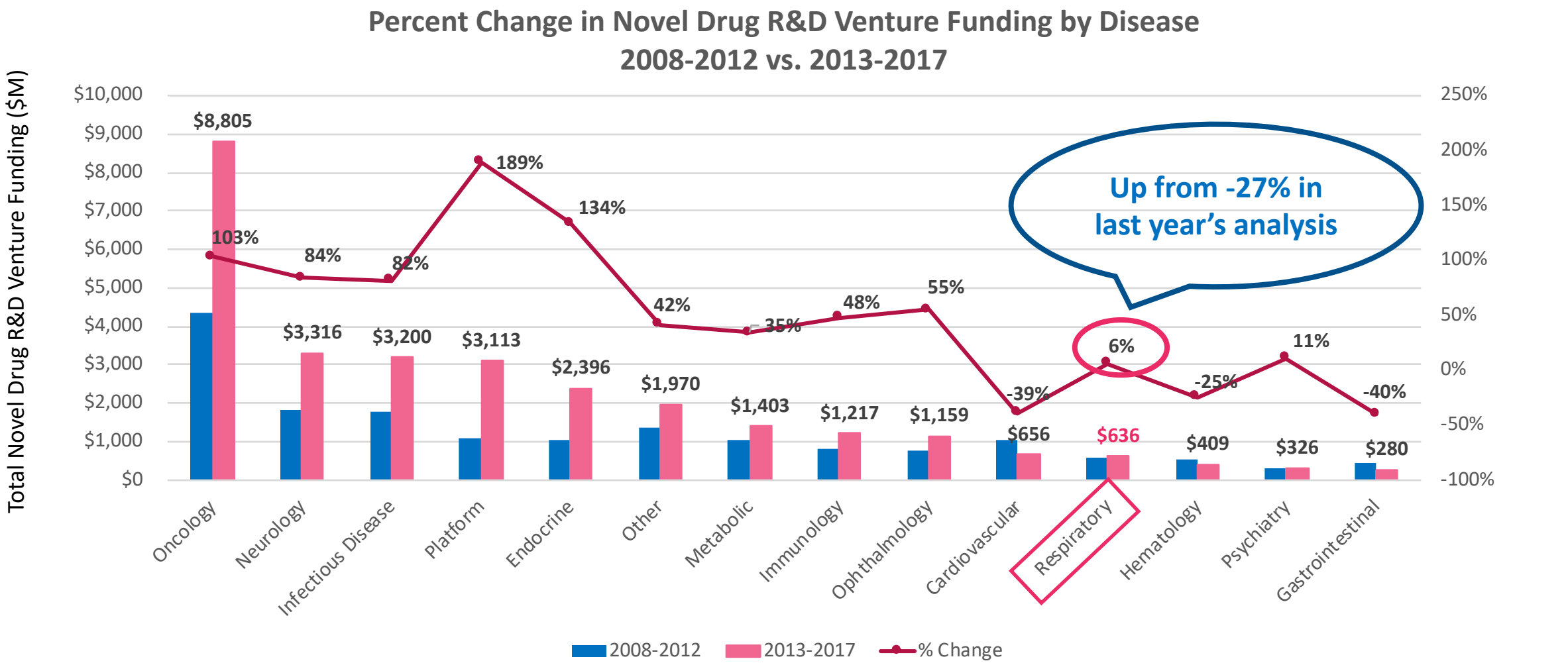
Respiratory Likelihood of Clinical Success vs. Other Therapeutic Areas is Relatively In-line…



Source: Biotechnology Innovation Organization, Biomedtracker, Amplion. *Clinical Development Success Rates 2006-2015.*
Data based on 9,985 clinical and regulatory phase transitions from 7,455 development programs across 1,103 companies.

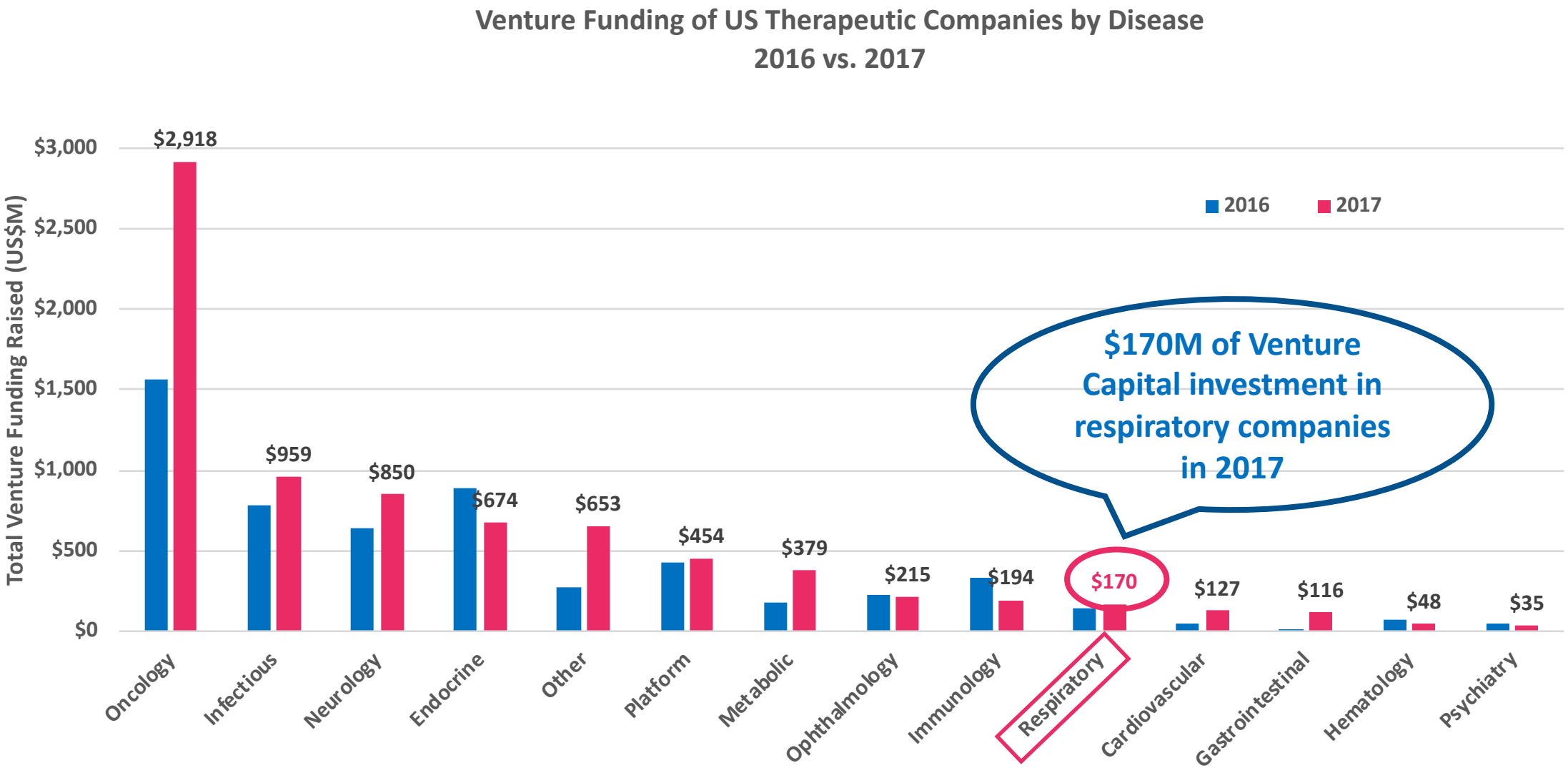
NDA = New Drug Application; BLA = Biologics License Application.

…Yet VC Funding in Novel Respiratory Ventures Continues to Be Low Relative to Other TAs



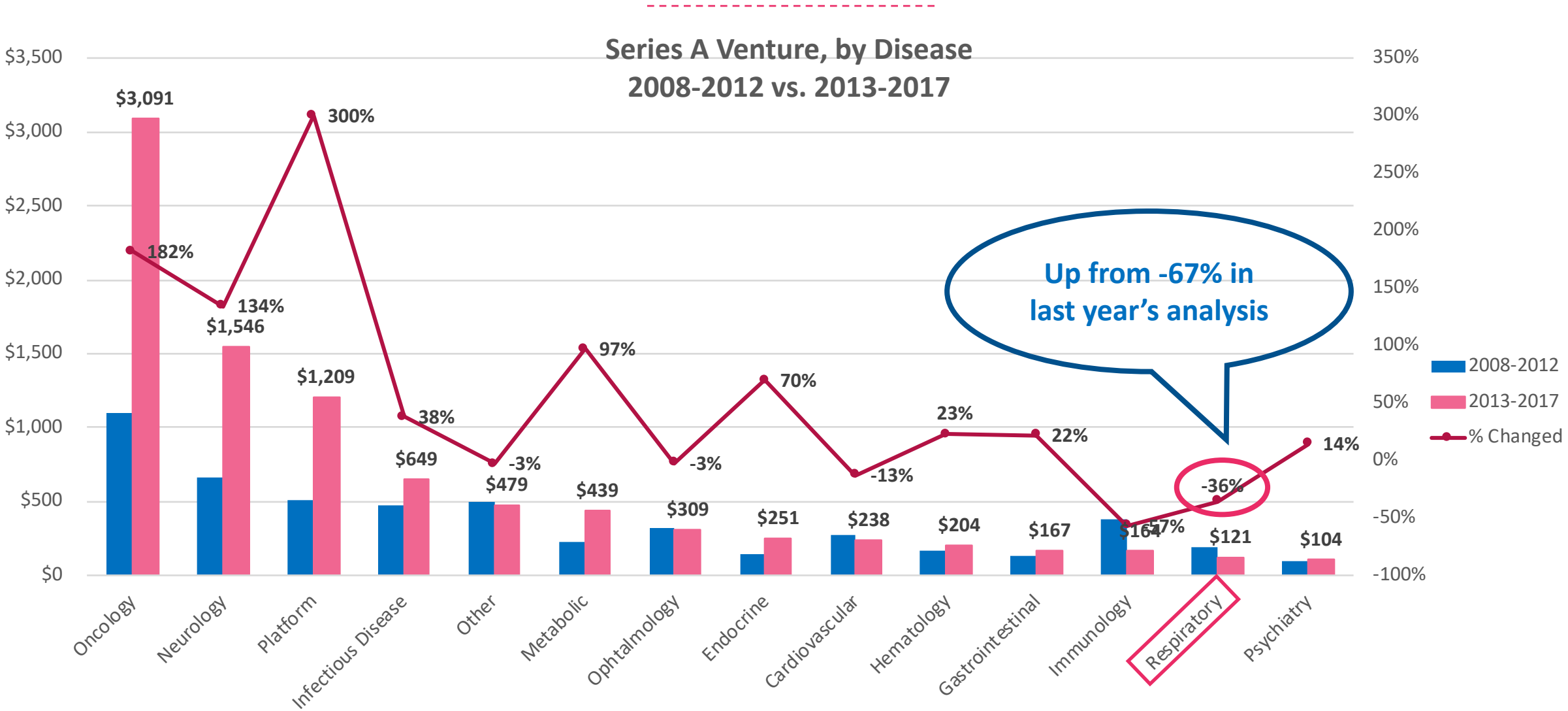
Source: Thomas, David and Chad Wessel. "Emerging Therapeutic Company Investment and Deal Trends." *BIO Industry Analysis,* Biotechnology Innovation Organization, May 2018, pg. 10.

Respiratory VC Investment Continues to be Less Popular vs. Other TAs (e.g. Oncology, etc.)…



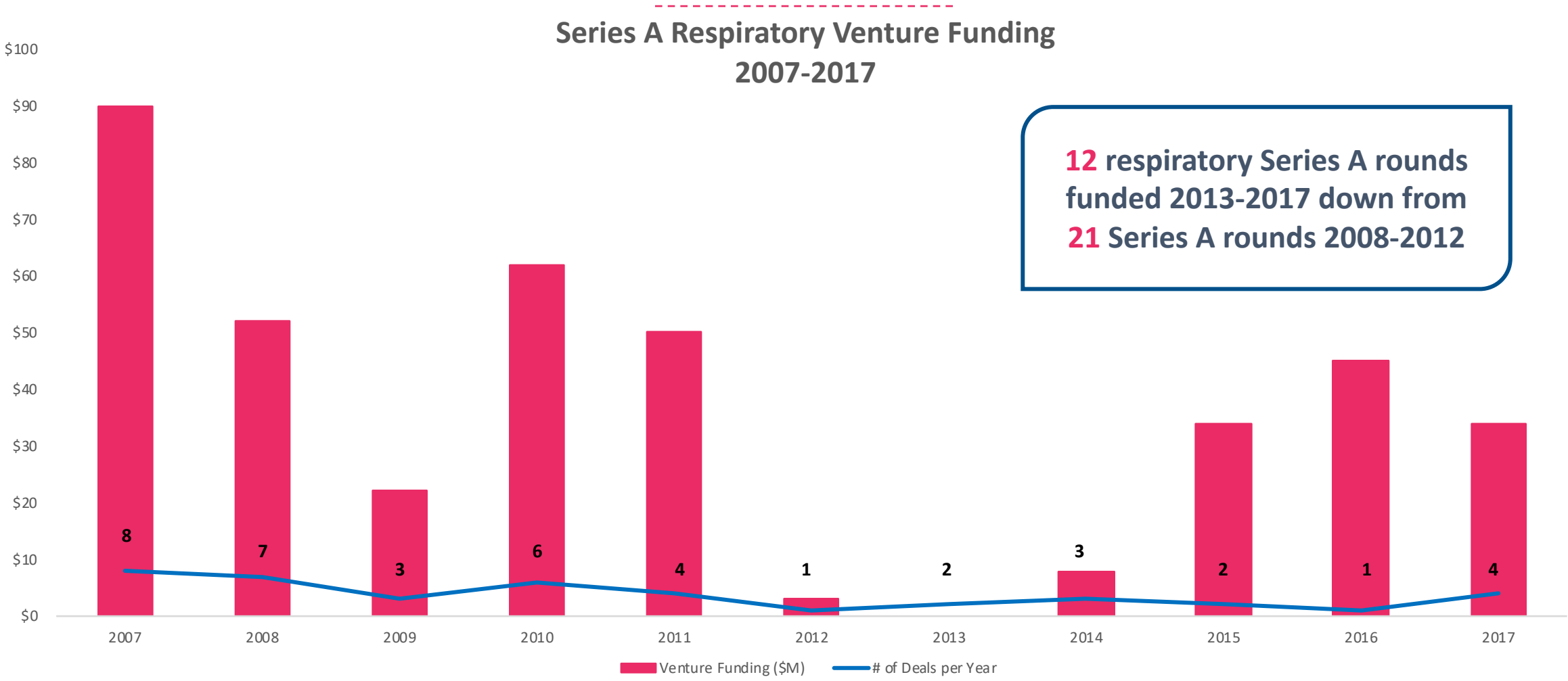
Source: Thomas, David and Chad Wessel. "Emerging Therapeutic Company Investment and Deal Trends." *BIO Industry Analysis,* Biotechnology Innovation Organization, May 2018, pg. 8.

…Including Series A Rounds, Reflecting New Company Formations…



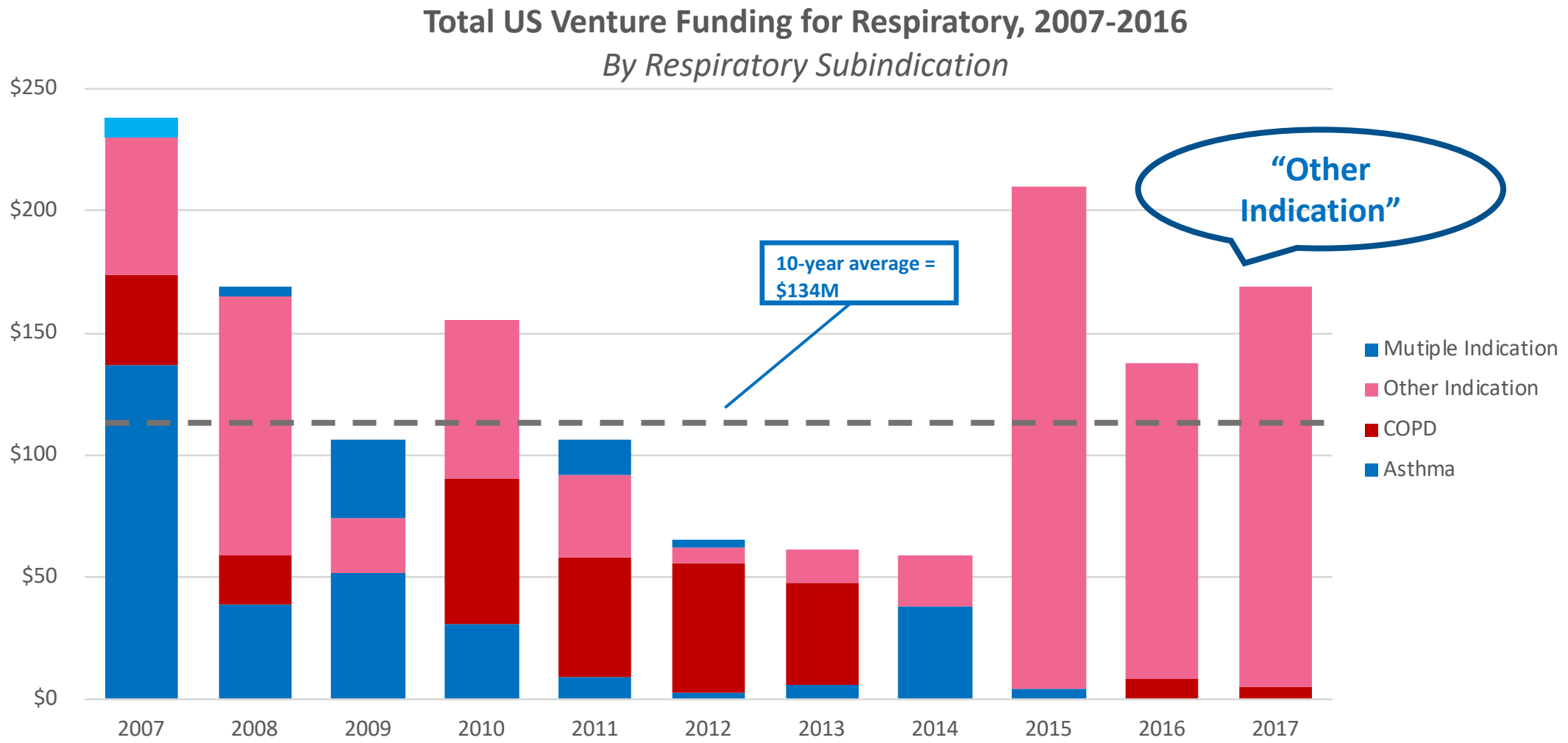
Source: Thomas, David and Chad Wessel. "Emerging Therapeutic Company Investment and Deal Trends." *BIO Industry Analysis,* Biotechnology Innovation Organization, May 2018, pg. 14.

Only Four Series A Rounds in 2017; Single-Digit #'s in Last 10 Years



Source: Thomas, David and Chad Wessel. "Emerging Therapeutic Company Investment and Deal Trends." *BIO Industry Analysis,* Biotechnology Innovation Organization, May 2018, pg. 14.

When They do Invest, Where are VC Investors Deploying Capital Within the Respiratory Space?



Source: Thomas, David and Chad Wessel. "Emerging Therapeutic Company Investment and Deal Trends." *BIO Industry Analysis,* Biotechnology Innovation Organization, May 2018, pg. 34.

Respiratory Sector Investment Considerations

Challenges

- Large and costly clinical trials
- High clinical and regulatory hurdles
- Drug-device combinations require specific technical expertise
- Significant CMC investment
- Largely primary care commercialization

Opportunities

- **Significant unmet need, dearth of curative therapies (generally symptomatic treatments)**
- **High prevalence and debilitating disease burden**
  - **251M COPD patients WW in 2016; COPD was 4th leading cause of death among adults WW in 2015 at 3.17M[(i)]; expected to become 3rd leading cause of death by 2030[(ii)]**
  - **235M Asthma patients WW in 2016[(iii)]**
  - **IPF median survival rate 2-3 years[(iv)]**
- **Demographic trend tailwinds**
- **Multi-billion dollar market ($30B+ WW) [(v)]**
- **Barriers to entry (difficult to genericize)**
- **Longevity of product lifecycle**
- **Specialty patient segments (e.g., CF, IPF, PAH, etc.)**
  - **Orphan drug designation potential**

Sources:
(i) WHO, *Disease and burden mortality estimates*, WHO regions.
(ii) WHO, *Projections of mortality and causes of death, 2015 and 2030,* WHO Regions.
(iii) WHO, Asthma, 13 August 2017.
(iv) ATS, *Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis.*
(v) Cowen Equity Research, March 2018.

A Call to Action!

- New funding models
  - E.g., AstraZeneca raising equity stake in Circassia, April 2018
- New partnership models
  - E.g., Avillion & Pearl / AstraZeneca co-development agreement, March 2018
  - E.g., Auris Health / J&J Ethicon bronchoscope ablation development deal, May 2018 → led to M&A for $3.4B in cash upfront and up to $2.35M in earnouts in April 2019
- Innovative clinical trial and regulatory strategies to reduce costs and increase POS
  - Better surrogate endpoints, biomarkers, etc.
- Other?

Selected Respiratory M&A Transactions Over Last 10 Years

Pharmaceutical & Medical Device Companies

US$M

Date Announced	Target	Acquiror	Indication	Stage	Transaction Size (US$M) Upfront	Milestones	Total
2/13/2019	Auris Health	J&J	Robotic surgery	Commercial	$ 3,400	$ 2,350	$ 5,750
1/7/2019	Propeller Health	ResMed	Digital therapeutics	Commercial	$ 225	$ -	$ 225
4/27/2017	Mast Therapeutics	Savara	aPAP / CF	Reverse merger	$ 165	$ -	$ 165
12/15/2016	Takeda Respiratory Business	AstraZeneca	COPD	Commercial	$ 575	$ -	$ 575
6/9/2016	Afferent Pharmaceuticals	Merk	Chronic Cough & IPF	Phase 2b	$ 500	$ 750	$ 1,250
4/15/2016	Ikaria	Mallinckrodt	Neonatal critical care	Commercial	$ 2,300	$ -	$ 2,300
3/16/2016	Vectura	SkyePharma	Asthma, other	Commercial	$ 621	$ -	$ 621
1/11/2016	Inova Labs	ResMed	COPD Devices	Commercial	$ 110	$ -	$ 110
10/5/2015	Quinsair (levofloxacin inh.sol'n)	Raptor Pharmaceuticals	Pulmonary Infections in CF	Approved EU	$ 34	$ 350	$ 384
5/31/2015	Aerocrine	Circassia	Asthma	Commercial	$ 213	$ -	$ 213
5/31/2015	Prosonix	Circassia	Asthma/COPD	EU Regulatory Review	$ 107	$ 46	$ 153
2/5/2015	Activis Respiratory Branded Assets	AstraZeneca	COPD	Commercial	$ 600	$ 100	$ 700
7/30/2014	Almiral Respiratory Franchise	AstraZeneca	Asthma/COPD	Commercial & Pipeline	$ 875	$ 1,200	$ 2,075
8/30/2013	Action Pharmaceuticals	MEDA	Asthma	Approved	$ 135	$ 65	$ 200
8/24/2013	InterMune	Roche	IPF	Commercial EU; NDA Filed US	$ 8,003	$ -	$ 8,003
6/10/2013	Pearl Therapeutics	AstraZeneca	COPD	Phase 3	$ 560	$ 590	$ 1,150
9/20/2012	Asthmatx	Boston Scientific	Asthma	Commercial	$ 194	$ 250	$ 444
8/30/2012	Elevation Pharma	Sunovion	COPD	Phase 2b	$ 100	$ 330	$ 430
11/9/2011	Pfizer Respiratory Delivery Platform	Mylan	COPD/Asthma	Various	$ 18	$ 327	$ 344
4/14/2011	mPex Pharmaceuticals	Apitalis	Cystic Fibrosis	Phase 3	$ 18	$ 195	$ 213
10/21/2008	Nektar Pulmonary Division	Novartis	COPD/Asthma/CF	Various	$ 115	$ -	$ 115
6/17/2008	Actimis	Boehringer Ingelheim	Asthma	Phase 1	N.A.	N.A.	$ 515
12/10/2007	Adams Respiratory Therapeutics	Reckitt Benckiser	OTC Cough and Cold	Commercial	$ 2,159	$ -	$ 2,159

Mean	**$ 956**	**$ 298**	**$ 1,221**
Median	**$ 219**	**$ 55**	**$ 444**
Max	**$ 8,003**	**$ 2,350**	**$ 8,003**
Min	**$ 18**	**$ -**	**$ 110**

Source: Pitchbook, news releases.

Selected Respiratory M&A Transactions Over Last 10 Years

Pharmaceutical & Medical Device Companies

Roche / InterMune — $8,003M IPF ✓

J&J / Auris — 2019 ✓ — $5,750M Robotic surgery

Mallinckrodt / Ikaria — ✓ — $2,300M Neonatal critical care

Reckitt Benckiser / Adams Respiratory Therapeutics — ✓ — $2,159M OTC

AstraZeneca / Almirall — $2,075M Asthma & COPD

Merck / Afferent Pharmaceuticals — ✓ — $1,250M Chronic cough

AstraZeneca / Pearl — ✓ — $1,150M COPD

AstraZeneca / Actavis — $700M COPD

Vectura / Skyepharma — ✓ — $621M Asthma

AstraZeneca / Takeda — $575M COPD

Boehringer Ingelheim / actimis pharmaceuticals — ✓ — $515M Asthma

ResMed / Propeller — ✓ — 2019 — $225M COPD Mgmt

Source: Pitchbook, news releases, amount includes upfront and potential earnouts.

✓ = VC Backed

Patients First!