

How to Translate Research into Practice

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Disclosures

Grant support

Mpex Pharmaceuticals, Inc

Gilead Sciences, Inc

Bayer Healthcare AG

Novartis

Vertex Pharmaceuticals Inc

Inspire Pharmaceuticals Inc

Pharmaxis Limited

Boehringer Ingelheim Pharmaceuticals

Cystic Fibrosis Foundation

National Institutes of Health

Consultant

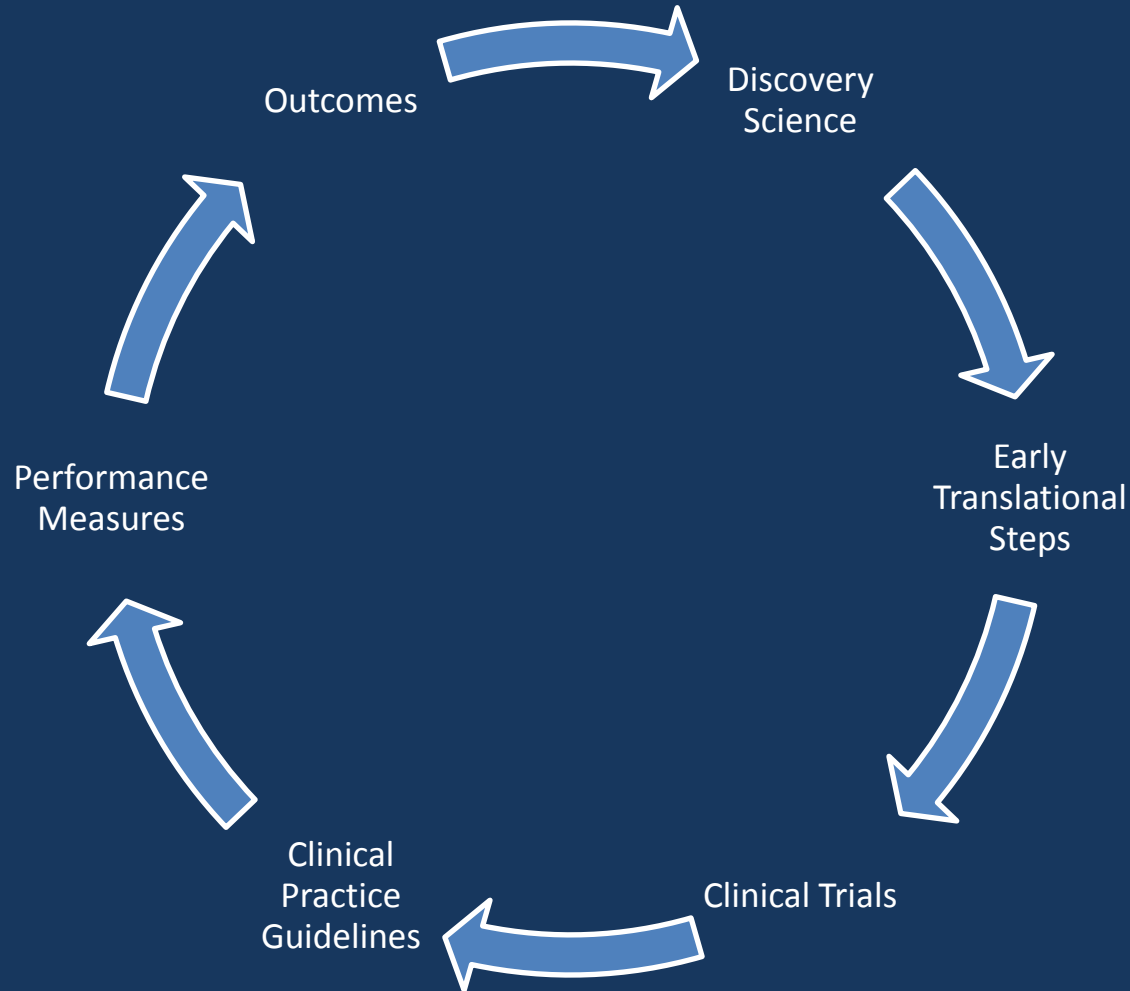
Gilead

Inspire

Speaker's Bureau

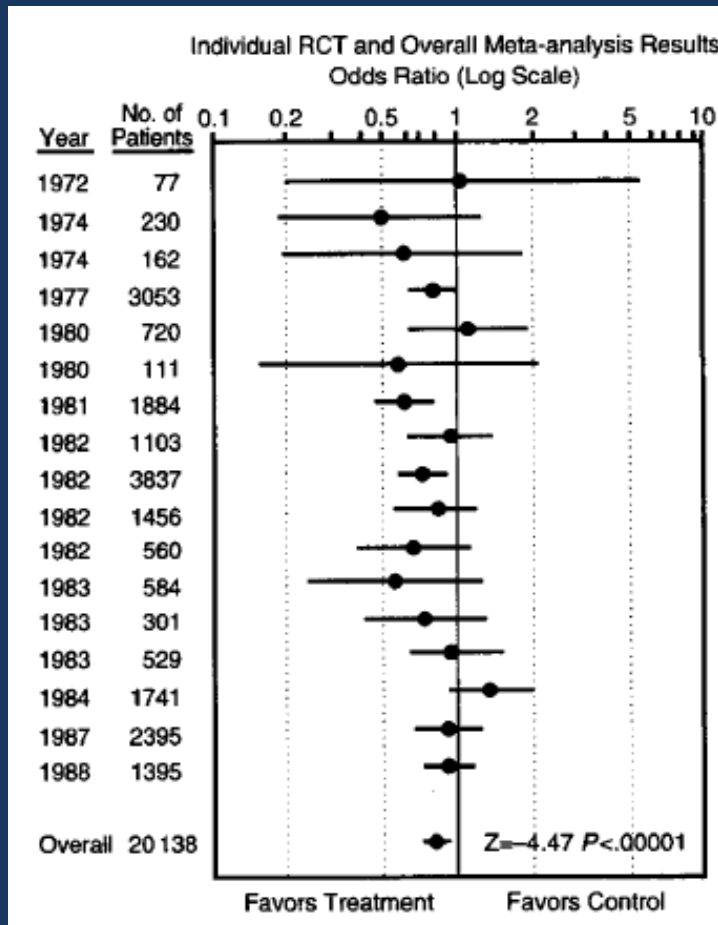
Astra-Zeneca

The Path from Bench to Bedside



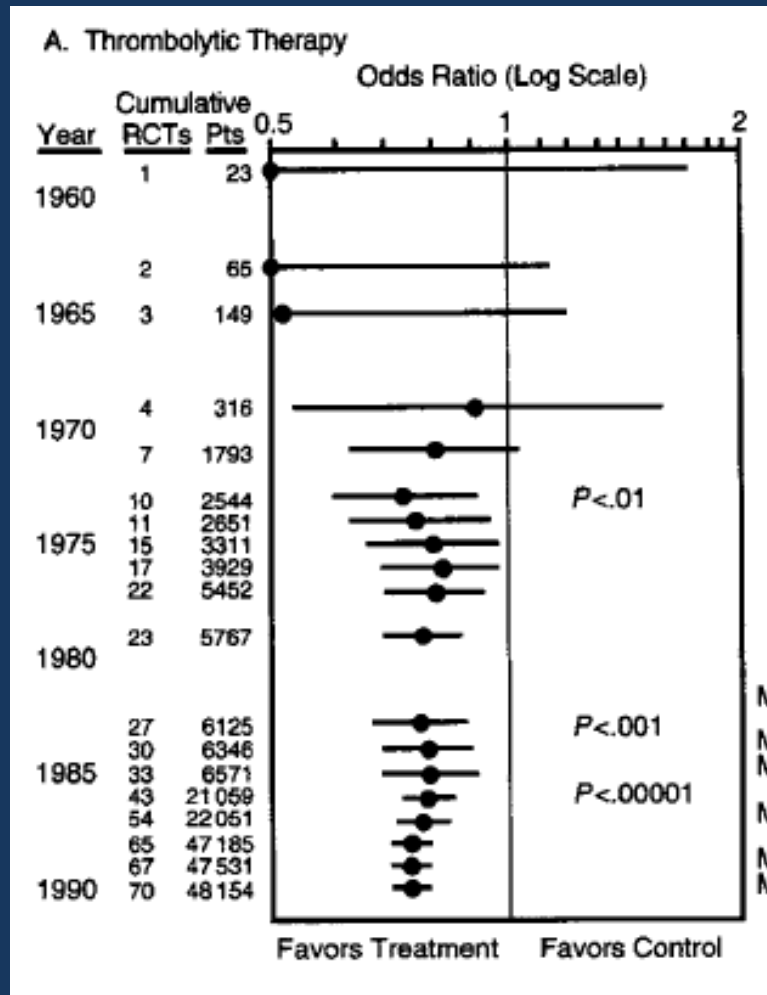
Why does it take so long for research findings to become routine practice?

β -blockers for prevention of death following MI



Why does it take so long for research findings to become routine practice?

Thrombolytic Therapy for Acute MI



How to Translate Research into Practice

- The experts need to stay up-to-date in interpreting results

Do evidence-based guidelines improve the quality of care?

- In principle, they should
 - If clinicians provide interventions which are known to improve clinical outcomes, then patients should benefit

The Science of Translating Research into Practice

- Advances in biomedical science are overshadowed by an estimated 200,000 deaths annually from healthcare-acquired infections, diagnostic or other medical errors, or mismanaged care
- Patients receive only about 50% of recommended evidence-based therapies*

The Quality of Health Care Delivered to Adults in the US

Table 3. Adherence to Quality Indicators, Overall and According to Type of Care and Function.

Variable	No. of Indicators	No. of Participants Eligible	Total No. of Times Indicator Eligibility Was Met	Percentage of Recommended Care Received (95% CI)*
Overall care	439	6712	98,649	54.9 (54.3–55.5)
Type of care				
Preventive	38	6711	55,268	54.9 (54.2–55.6)
Acute	153	2318	19,815	53.5 (52.0–55.0)
Chronic	248	3387	23,566	56.1 (55.0–57.3)
Function				
Screening	41	6711	39,486	52.2 (51.3–53.2)
Diagnosis	178	6217	29,679	55.7 (54.5–56.8)
Treatment	173	6707	23,019	57.5 (56.5–58.4)
Follow-up	47	2413	6,465	58.5 (56.6–60.4)

* CI denotes confidence interval.

Underuse
46.3%

Overuse
11.3%

The Quality of Health Care Delivered to Adults in the US

Condition	Percentage of Recommended Care Received
Diabetes	45.4%

β-blocker 45%

Reduced risk of death by 13% in first week
Reduced risk of death by 23% overall

Aspirin 61%

Reduced risk of death by 15%
Reduced risk of non-fatal MI by 30%
Reduced risk of stroke by 40%

How to Translate Research into Practice

- The experts need to stay up-to-date in interpreting results
- The clinicians need to implement clinically-proven therapies

Do evidence-based guidelines improve the quality of care?

- In principle, they should
 - If clinicians provide interventions which are known to improve clinical outcomes, then patients should benefit
- A guideline will have this affect, unless
 - It is based on unsound or inappropriate evidence
 - It is applied incorrectly
 - It is applied not at all

CF Clinical Practice Guidelines

- Diagnosis
 - CF diagnosis
 - Sweat testing
 - Newborn screening
 - CFTR metabolic syndrome
- Nutrition/GI
 - Nutrition in children and adults
 - Pancreatic enzyme replacement
 - CF-related diabetes
 - Bone health
 - Liver disease
 - Pediatric nutrition
- Respiratory
 - Chronic medications
 - Airway clearance
 - Pulmonary exacerbations
 - Pulmonary complications
 - ABPA
 - Lung transplantation
- Infection control
- Age-specific care
 - Infant care
 - CFTR metabolic syndrome
 - Adult care

Chronic Therapies for Maintenance of Lung Health

A Strong Recommendation for:	B Recommendation for:	D Recommendation against:
<ul style="list-style-type: none"> • Inhaled tobramycin <ul style="list-style-type: none"> • Mod-severe dz • Dornase alfa <ul style="list-style-type: none"> • Mod-severe dz 	<ul style="list-style-type: none"> • Inhaled tobramycin <ul style="list-style-type: none"> • Mild-asx dz • Dornase alfa <ul style="list-style-type: none"> • Mild-asx dz • Hypertonic saline • Macrolides • Ibuprofen • Inhaled β-agonists 	<ul style="list-style-type: none"> • Oral steroids <ul style="list-style-type: none"> • Age 6-18 • Inhaled steroids • Anti-Staph abx

Insufficient Evidence to make a recommendation:

- | | |
|--|--|
| <ul style="list-style-type: none"> • Other aerosolized antibiotics • N-acetyl cysteine • Cromolyn | <ul style="list-style-type: none"> • Inhaled anticholinergics • Leukotriene modifiers • Oral steroids (age>18) |
|--|--|

The Path from Bench to Bedside

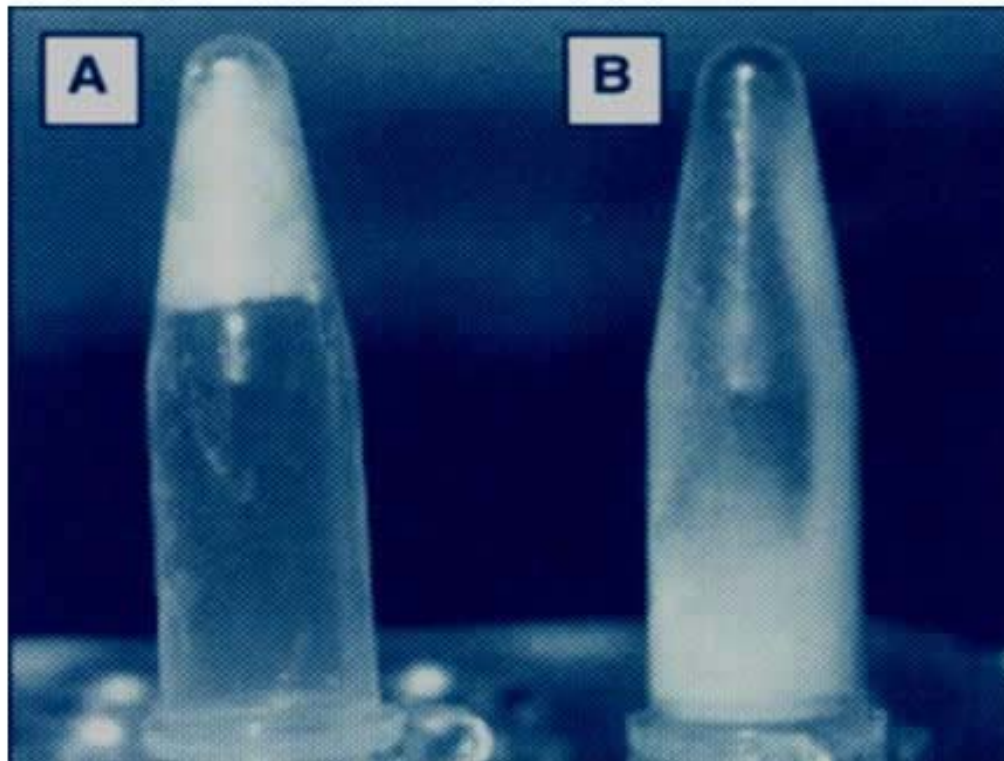
- Dornase alfa
- Tobramycin inhalation solution (TOBI)
- Azithromycin

History of Development of Dornase Alfa

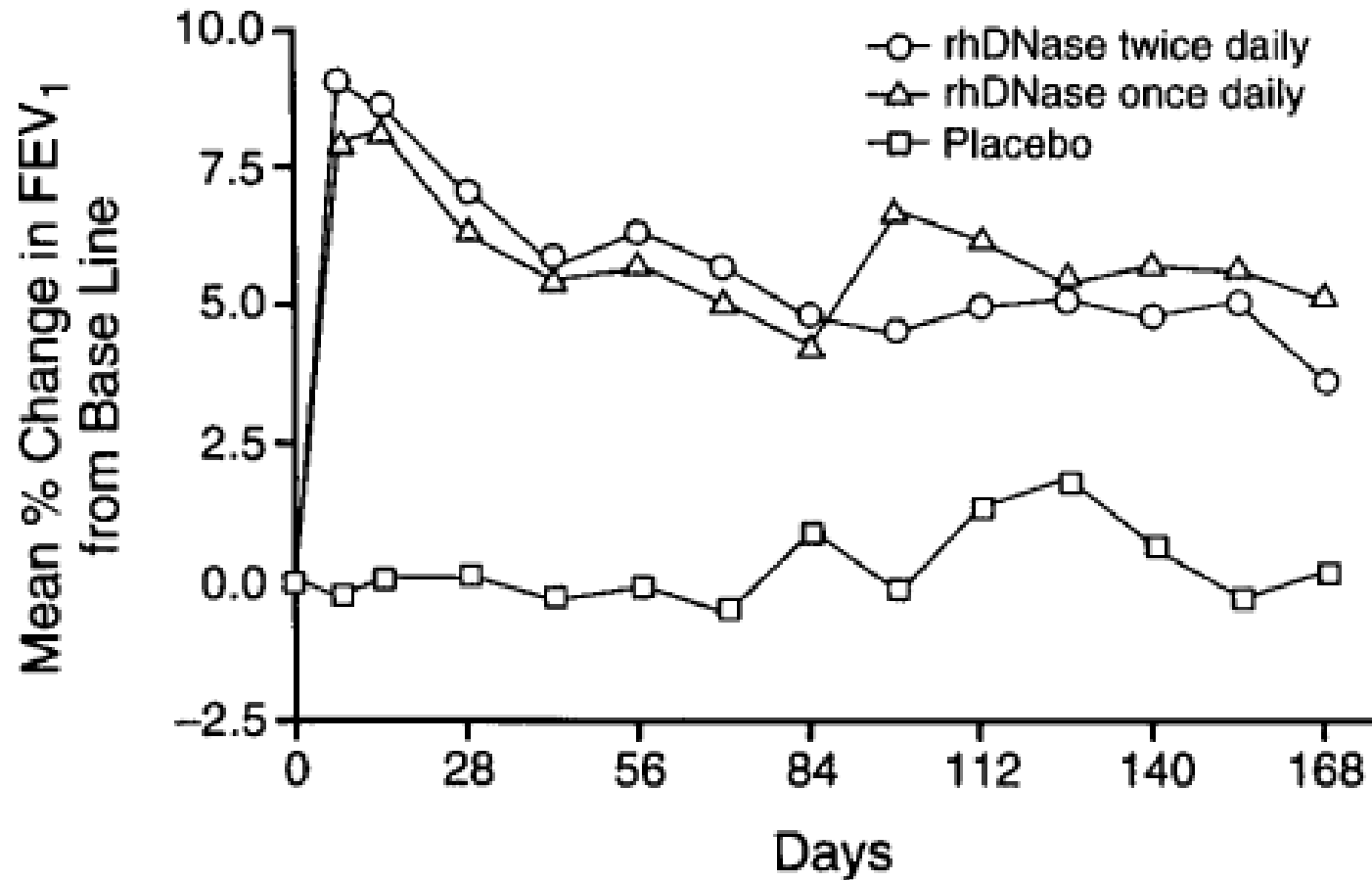
- CF sputum contains large amounts of DNA (Chernick & Guilo 1959; Potter et al 1960)
 - Source is from degenerating PMNs
 - Contributes to high sputum viscoelasticity
- Sputum viscoelasticity can be reduced by bovine pancreatic dornase (Armstrong et al 1950; Elmes et al 1953; Salomon et al 1954; Spier et al 1961)

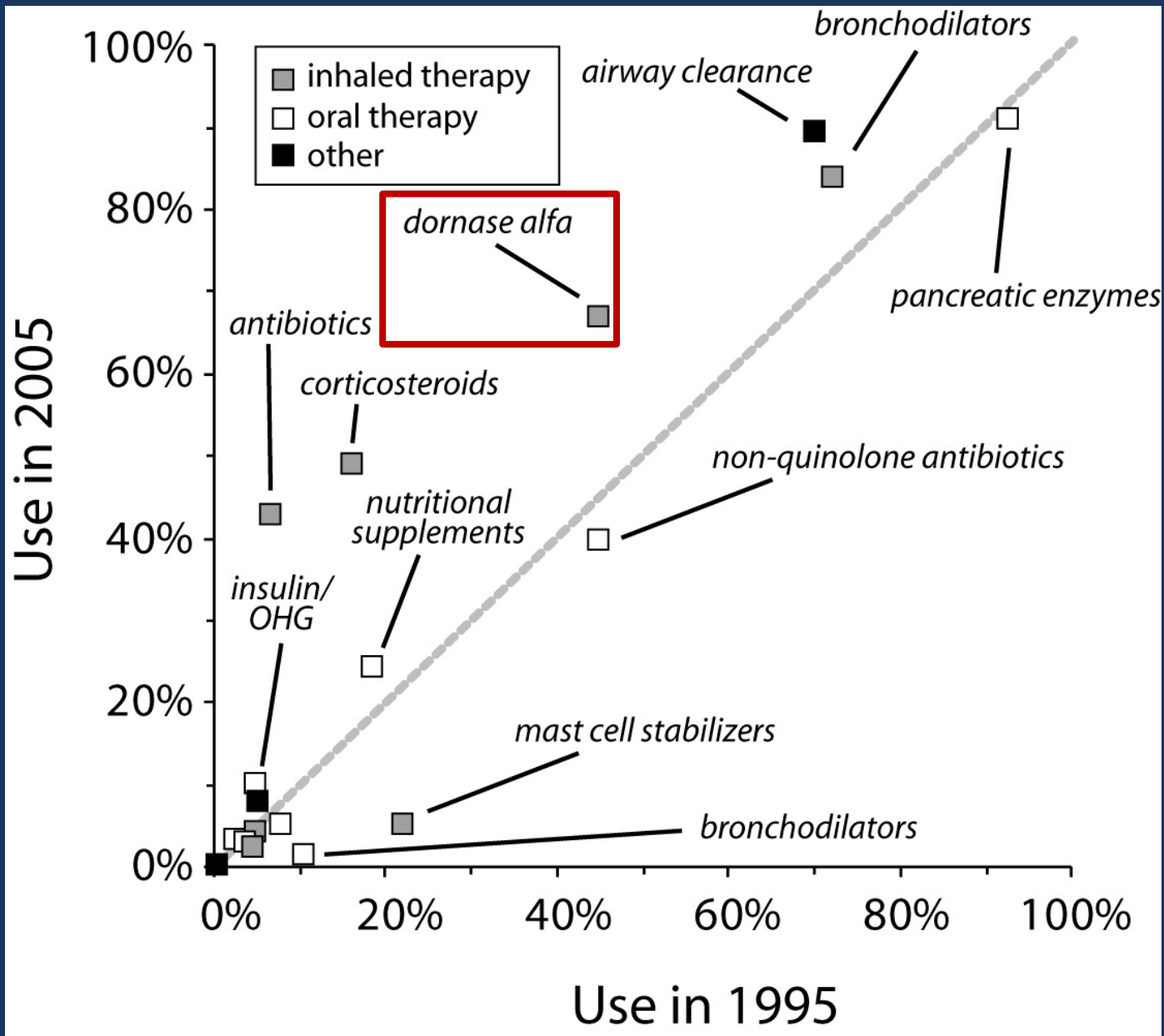
History of Development of Dornase Alfa

Effect of dornase alfa on sputum
in vitro

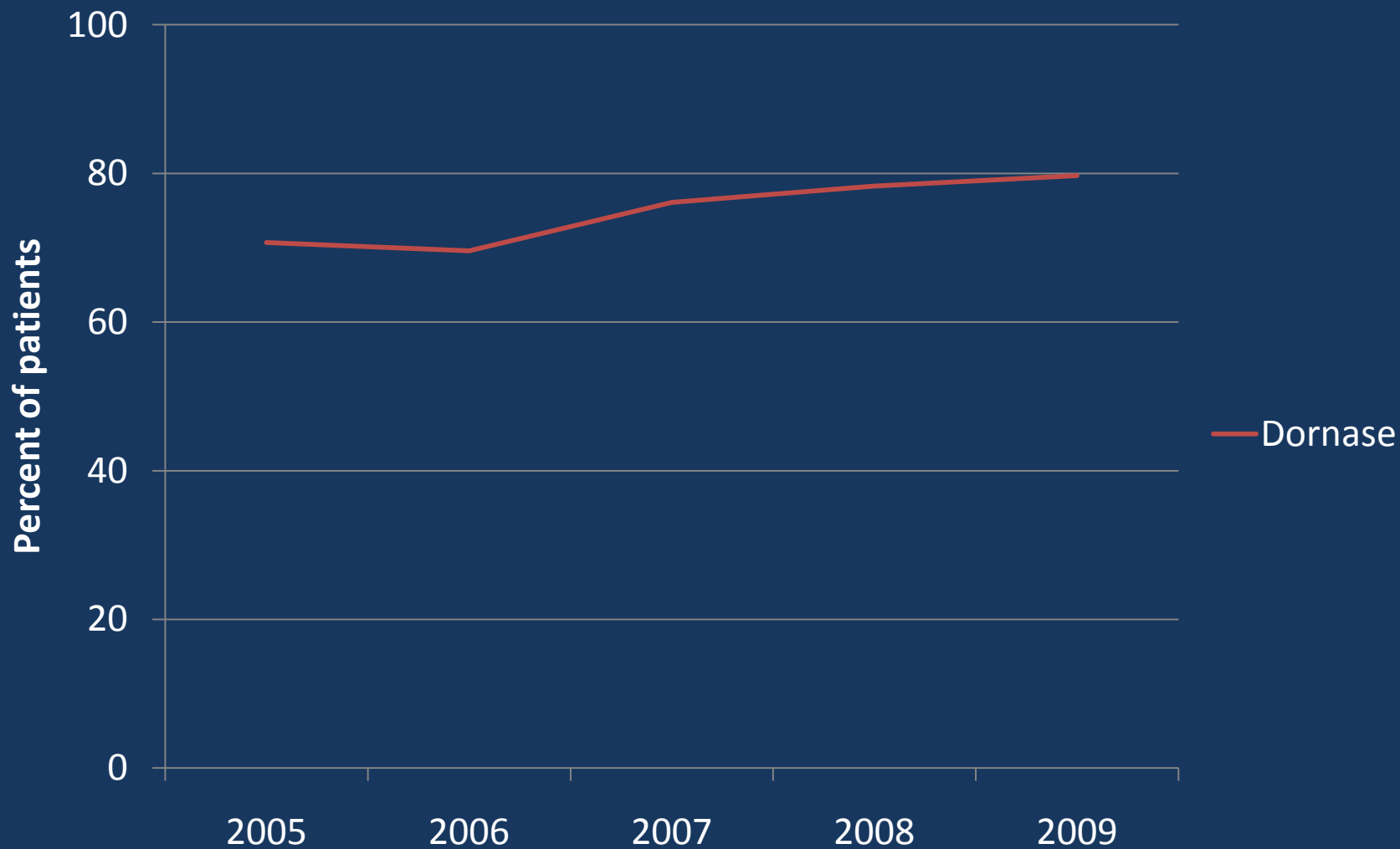


Effect of Aerosolized Dornase Alfa in CF





Usage of Chronic Medications Included in Pulmonary Guidelines



The Path from Bedside to Bench to Bedside

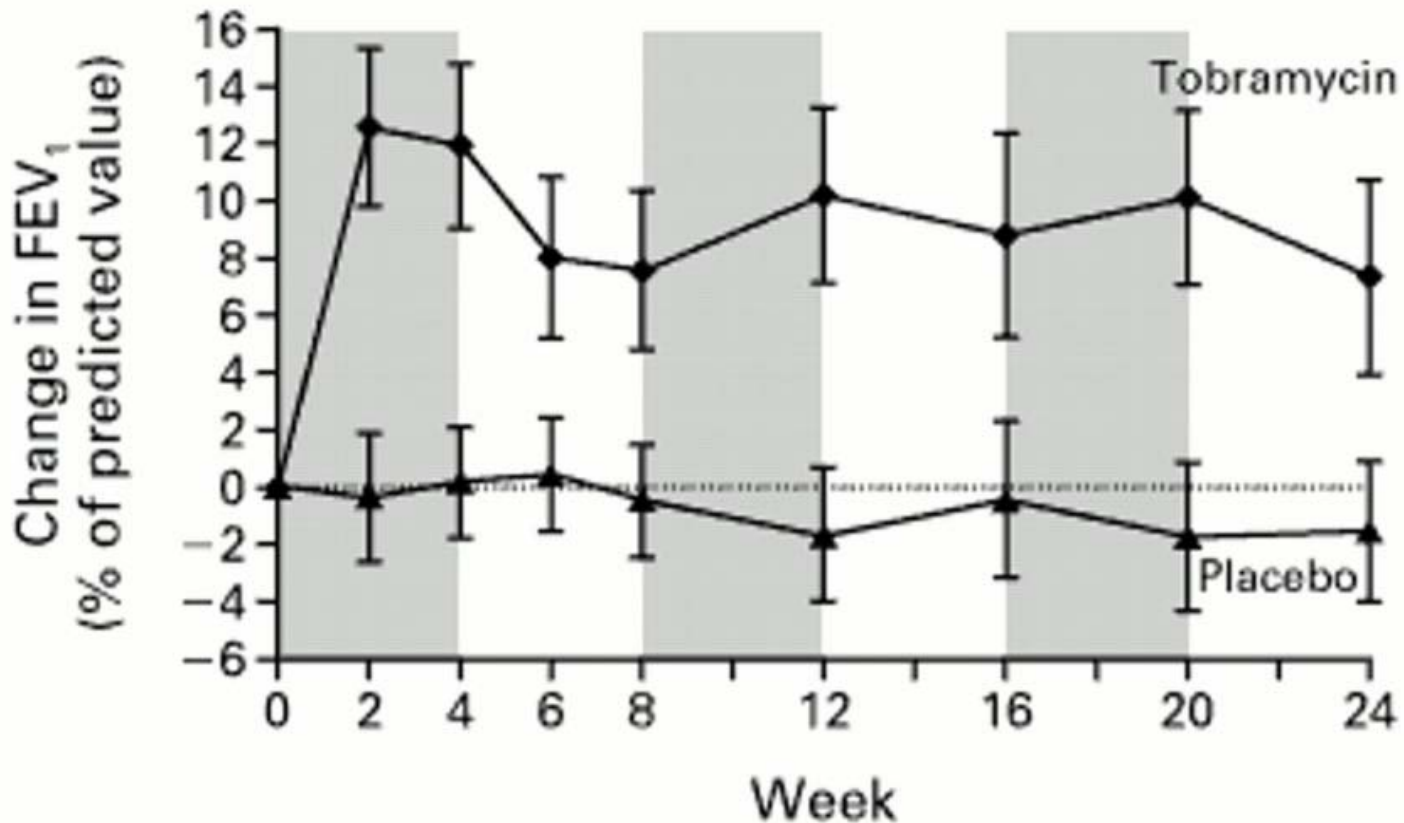
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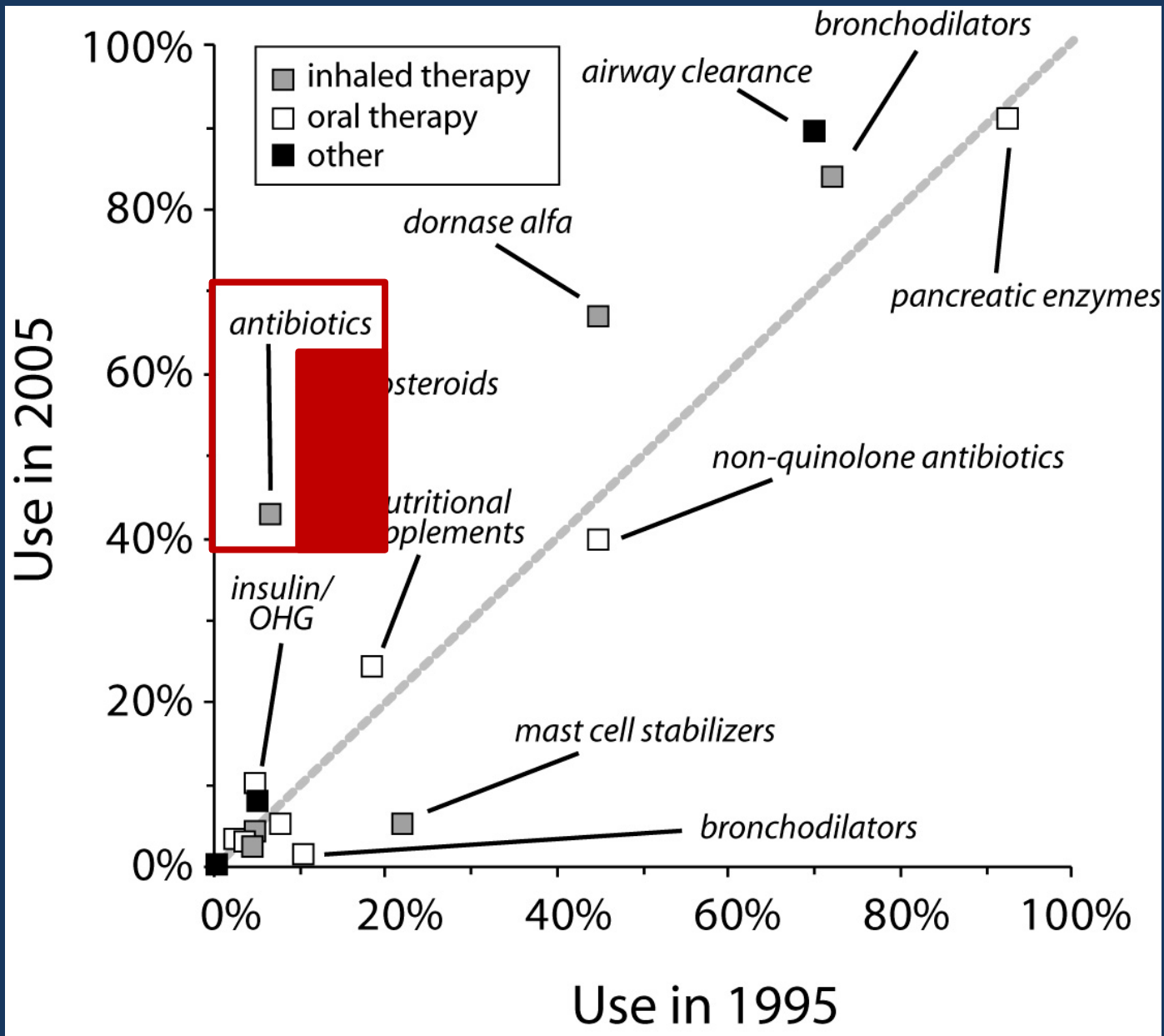
Aerosolized Antibiotics in CF

Study	Year	N	Design	Drug
Hodson et al ¹	1981	20	XO	Gentamicin 80 mg bid
Kun et al ²	1984	29	XO	Gentamicin 20 mg bid
Jensen et al ³	1987	40	DB parallel	Colistin 1 MU bid
Steinkamp et al ⁴	1989	14	Open-label	Tobramycin 80 mg bid
MacLuskey et al ⁵	1989	27	Open-label	Tobramycin 80 mg bid
Smith et al ⁶	1989	22	Open-label	Tobramycin 600 mg tid
Ramsey et al ⁷	1993	71	DB XO	Tobramycin 600 mg tid
Ramsey et al ⁸	1999	520	RCT	Tobramycin 300 mg bid

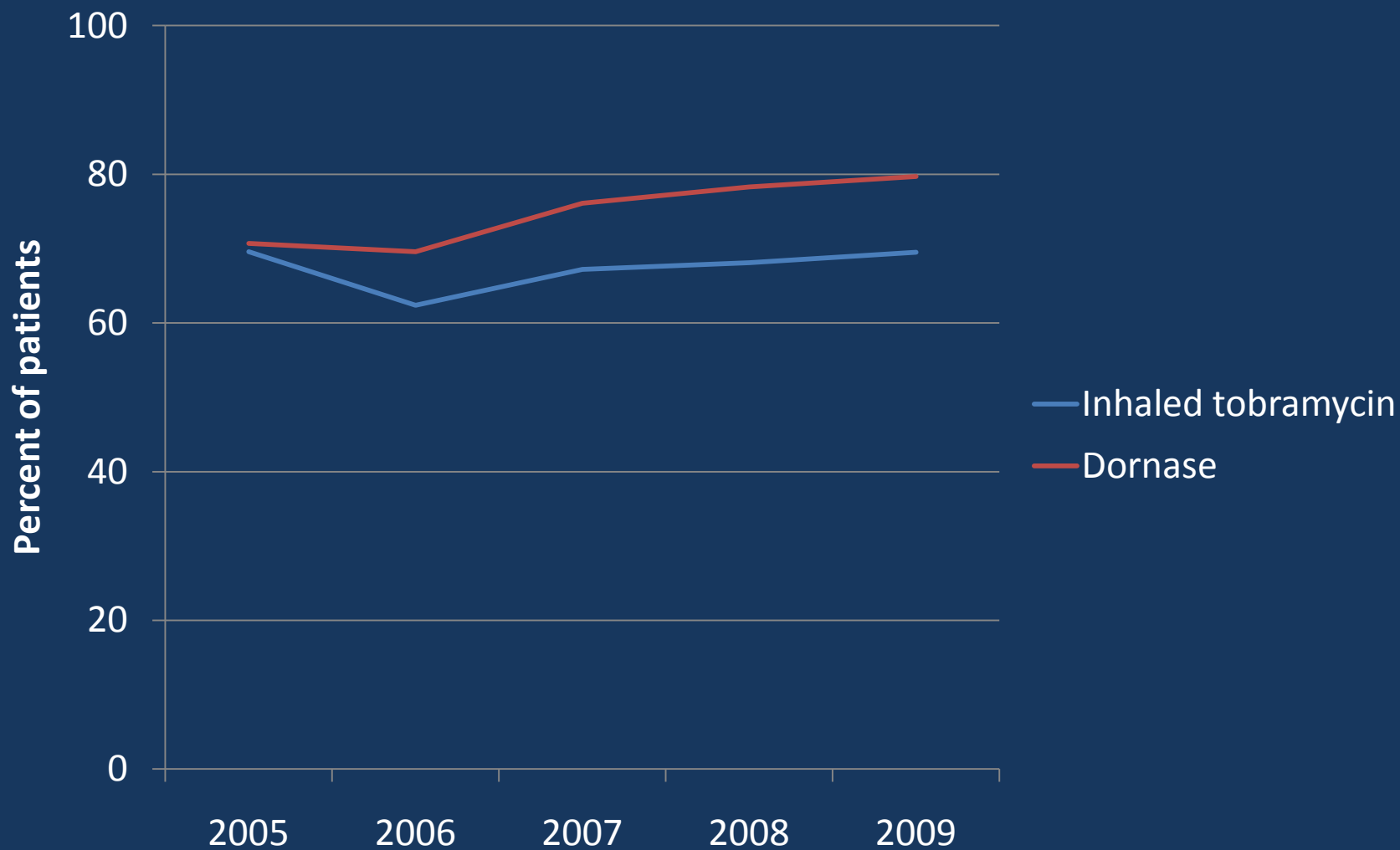
¹Lancet 1981, 2: 1137-1139; ²Aust Paediatr J 1984, 20: 43-45; ³J Antimicrob Chemother 1987, 19: 831-838; ⁴Pediatr Pulmonol 1989, 6: 91-98; ⁵Pediatr Pulmonol 1989, 7: 42-48; ⁶Pediatr Pulmonol 1989, 7: 265-271; ⁷NEJM 1993, 328: 1740-1746; ⁸NEJM 1999: 340: 23-30

Aerosolized Antibiotics in CF





Usage of Chronic Medications Included in Pulmonary Guidelines



The Path from Bedside to Trial to Bedside

- Dornase alfa
- Tobramycin inhalation solution (TOBI)
- Azithromycin

Diffuse panbronchiolitis and cystic fibrosis: East meets West

- Clinical observation of similarities between the two diagnoses
 - Chronic *P aeruginosa* infection of the lungs
- Specific comments on benefit of macrolides for DPB

“Maybe it is time for scientists and clinicians working on cystic fibrosis and diffuse panbronchiolitis to come together to exchange results and ideas to the benefit of both groups of patients.”

Macrolides for *Pseudomonas*?

- MIC for erythromycin: 125-512 mg/L
- Erythromycin concentrations
 - peak serum (250 mg dose): 1.0-1.5 mg/L
 - mean sputum (1 g IV q 12 h): 2.6 mg/L

Macrolides in CF

Study	Year	N	Design	Outcome
Jaffe et al ¹	1998	7	Open-label	↑ FEV ₁ 2%
Anstead et al ²	1999	20	Open-label	↑ FEV ₁ 21%
Pirzada et al ³	1999	36	Retro	↑ FEV ₁ 5.9%
Anstead et al ⁴	2000	14	Open-label	↑ FEV ₁ 5.8%
Hallberg et al ⁵	2000	25	Open-label	↑ FEV ₁ 3%
Anstead et al ⁶	2001	17	RCT	Fewer Pex
Ordonez et al ⁷	2001	10	XO	No change
Wolter et al ⁸	2002	60	RCT	↑ FEV ₁ 3.6%
Equi et al ⁹	2002	41	RCT	↑ FEV ₁ 5.4%
Saiman et al ¹⁰	2003	185	RCT	↑ FEV ₁ 6.2%

¹Lancet 1998, 351: 420 (letter); ²Pediatr Pulmonol 1999, Suppl 19: S283 (abstract); ³Pediatr Pulmonol 1999, Suppl 19: S263 (abstract); ⁴Pediatr Pulmonol 2000, Suppl 20: S244 (abstract); ⁵13th Intl CF Congress 2000: 336 (abstract); ⁶ATS Conference 2001: 515 (abstract); ⁷Pediatr Pulmonol 2001, 32: 29-37; ⁸Thorax 2002, 57: 212-216; ⁹Lancet 2002, 360:978-984; ¹⁰JAMA 2003, 290: 1749-1756

Cystic Fibrosis in the 20th Century

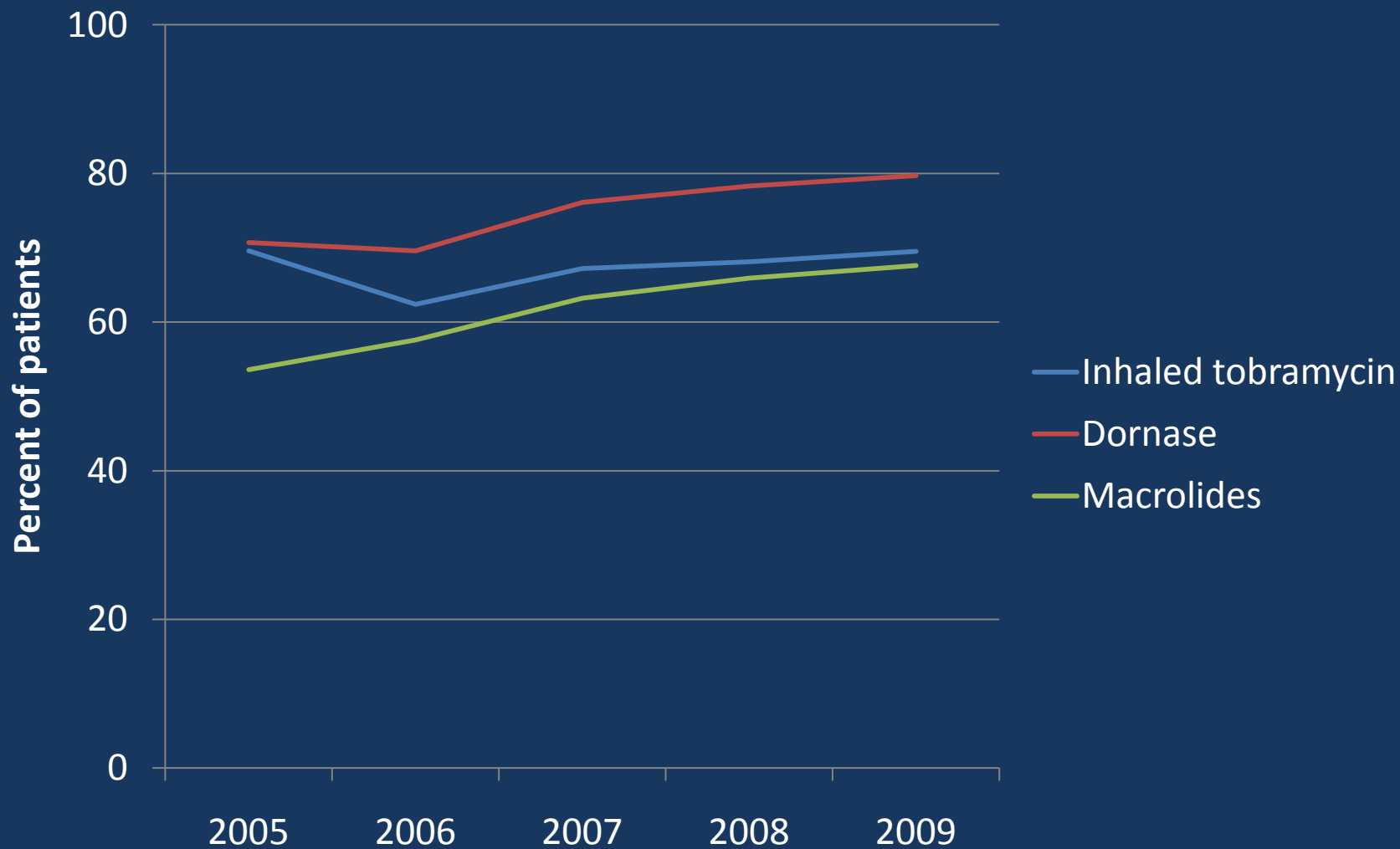
People, Events, and Progress

Carl F. Doershuk, MD, Editor

Harry Shwachman said,
“When patients have bacteria
that are resistant to all antibiotics,
prescribe erythromycin, leave them
on it for a long time, and
they will do much better.”

Warren J. Warwick, MD

Usage of Chronic Medications Included in Pulmonary Guidelines



Do CF Guidelines Work?

More Circumstantial Evidence

- West et al – chronic macrolides
 - Decreased hospitalization rate in patients on macrolides over 2 years
 - Incidence rate ratio (IRR) 0.85, $p=0.043$
- Sawicki et al – chronic medications
 - Reduced mortality in subsequent years
 - TIS: IRR 0.85 (95% CI 0.76-0.94), $p=0.003$
 - Dornase: IRR 0.86 (95% CI 0.76-0.97), $p<0.05$
- Vandyke et al – inhaled tobramycin
 - Slower rate of decline of FEV_1
 - Accounting for treatment-by-condition confounder

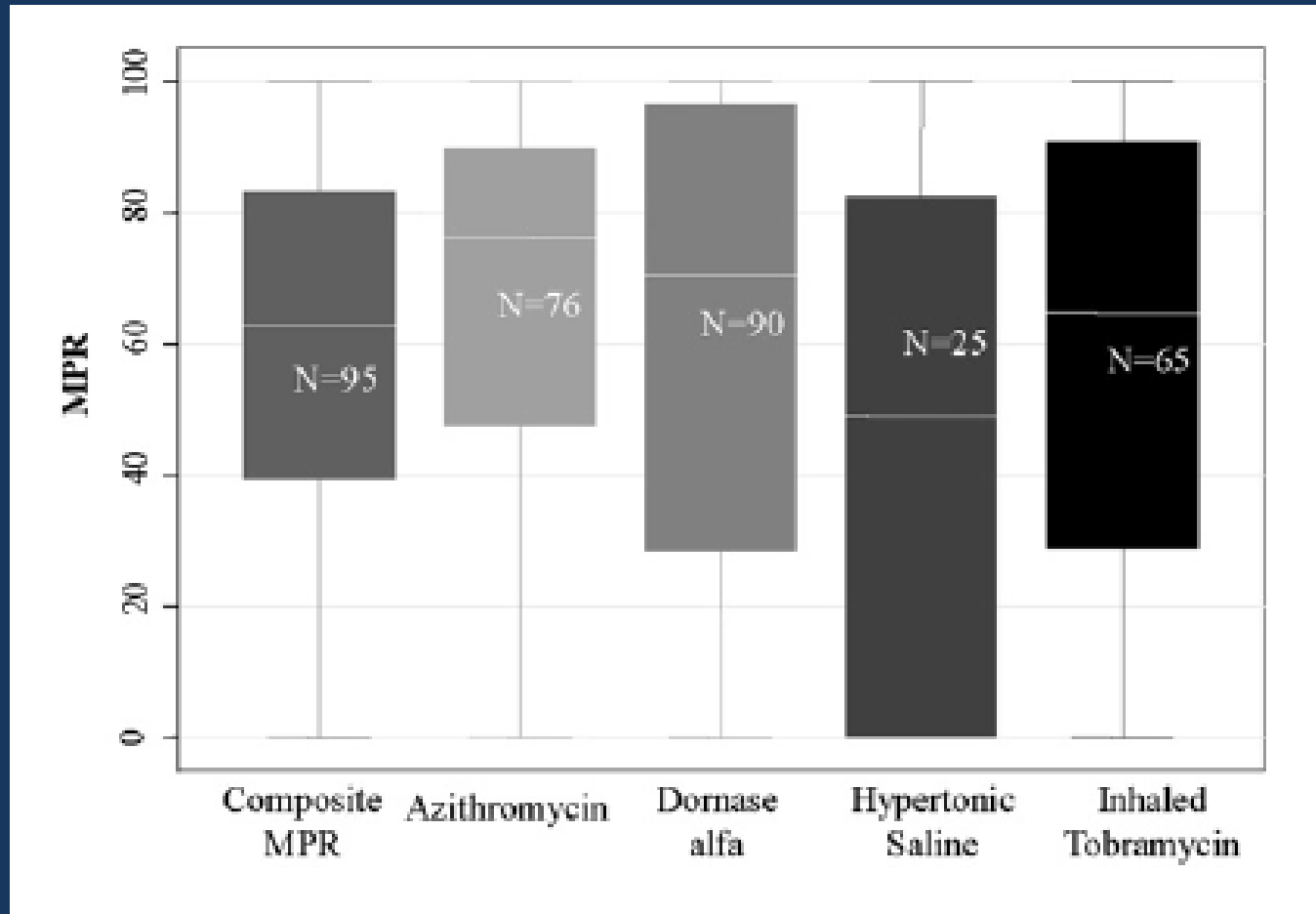
What makes the difference between guidelines that are effective and those that are not?

- The benefits of implementation are large
 - For patients, the change will improve outcomes
 - For clinicians, care will be quicker or easier
 - For healthcare systems, cost savings will follow and outcomes improve
 - An authoritative professional body will support the guideline's use
 - There will be time to consult the guidelines

Adherence with TIS and Health Care Utilization

- Analysis of healthcare claims data
- Measurement of adherence based on refills of TIS
 - Low utilization ≤ 2 cycles (n=570)
 - High utilization ≥ 4 cycles (n=54)
- Patients hospitalized
 - Low: 42.9%
 - High 25.9%
 - AOR relative to low use = 0.40; 95% CI 0.19-0.84

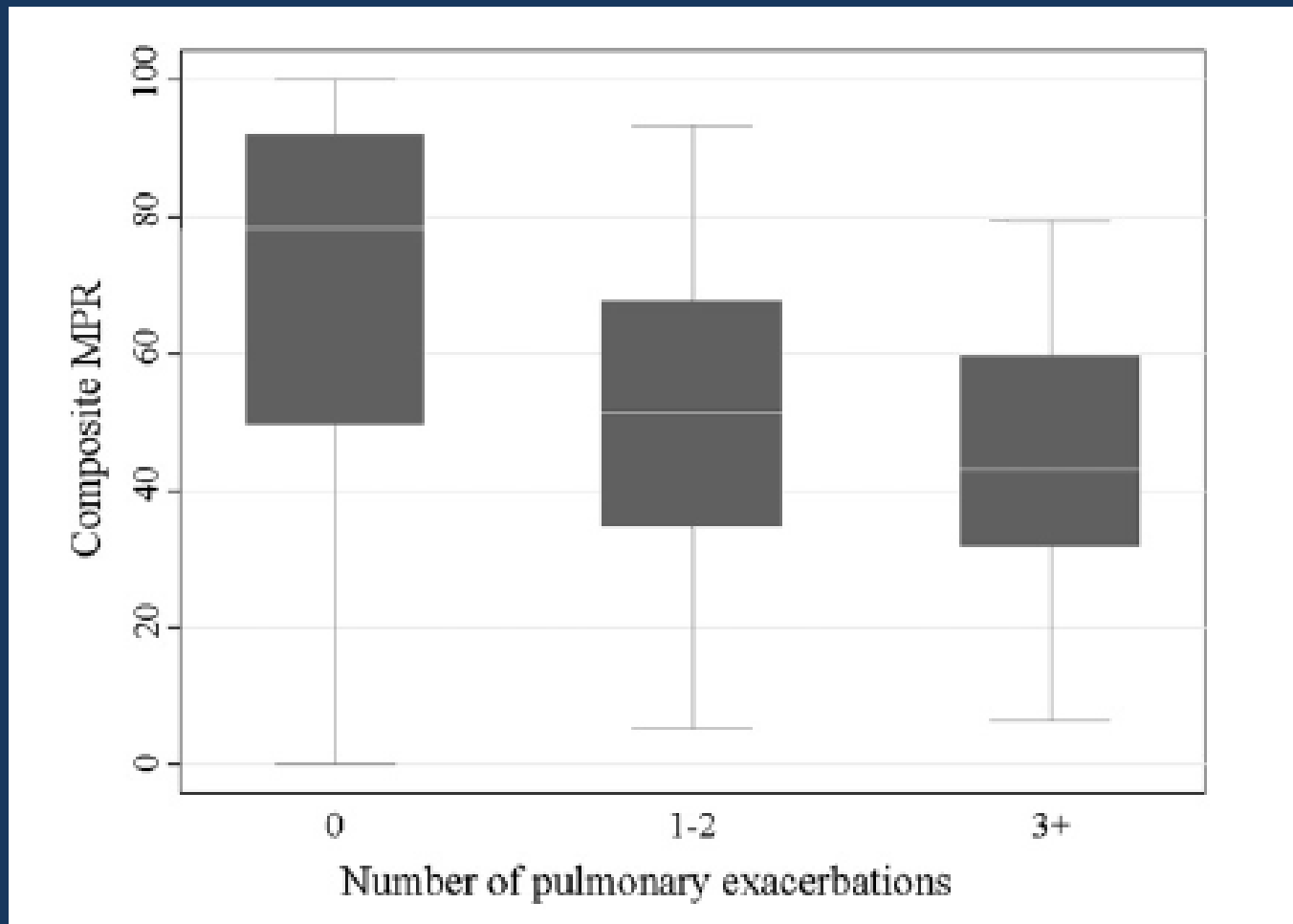
Association Between Medication Adherence and Lung Health in People with CF



MPR = medication possession ratio (days medication received/days medication prescribed)

Association Between Medication Adherence and Lung Health in People with CF

Composite MPR predicted pulmonary exacerbations, Incidence rate ratio 2.34, $p=0.05$



How to Translate Research into Practice

- The experts need to stay up-to-date in interpreting results
- The clinicians need to implement clinically-proven therapies
- The patients need to use clinically –proven therapies

Conclusions: Do Guidelines Work?

- Guidelines probably do work
- Guideline development
 - Should follow strict methodologies to ensure sound recommendations based on the evidence
 - Should summarize the evidence concisely into several key interventions described in an unambiguous manner
 - Should include consideration of implementation and investigate local barriers preventing evidence-based practice

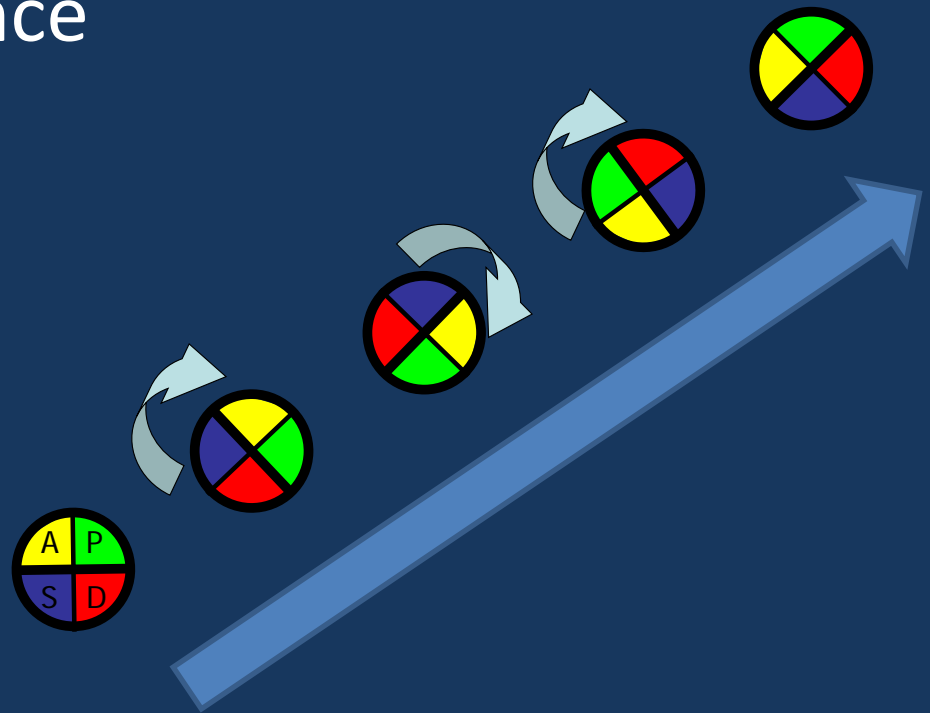
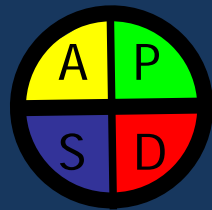
Conclusions: Do Guidelines Work?

- Implement the guidelines to ensure that all patients receive the therapy
 - Engage (help clinicians recognize the local impact of non-compliance with evidence-based practice)
 - Educate (assure that clinicians agree with evidence and understand the actions needed to comply with the evidence)
 - Execute (e.g. checklist to standardize care)
 - Evaluate (performance should be measured)

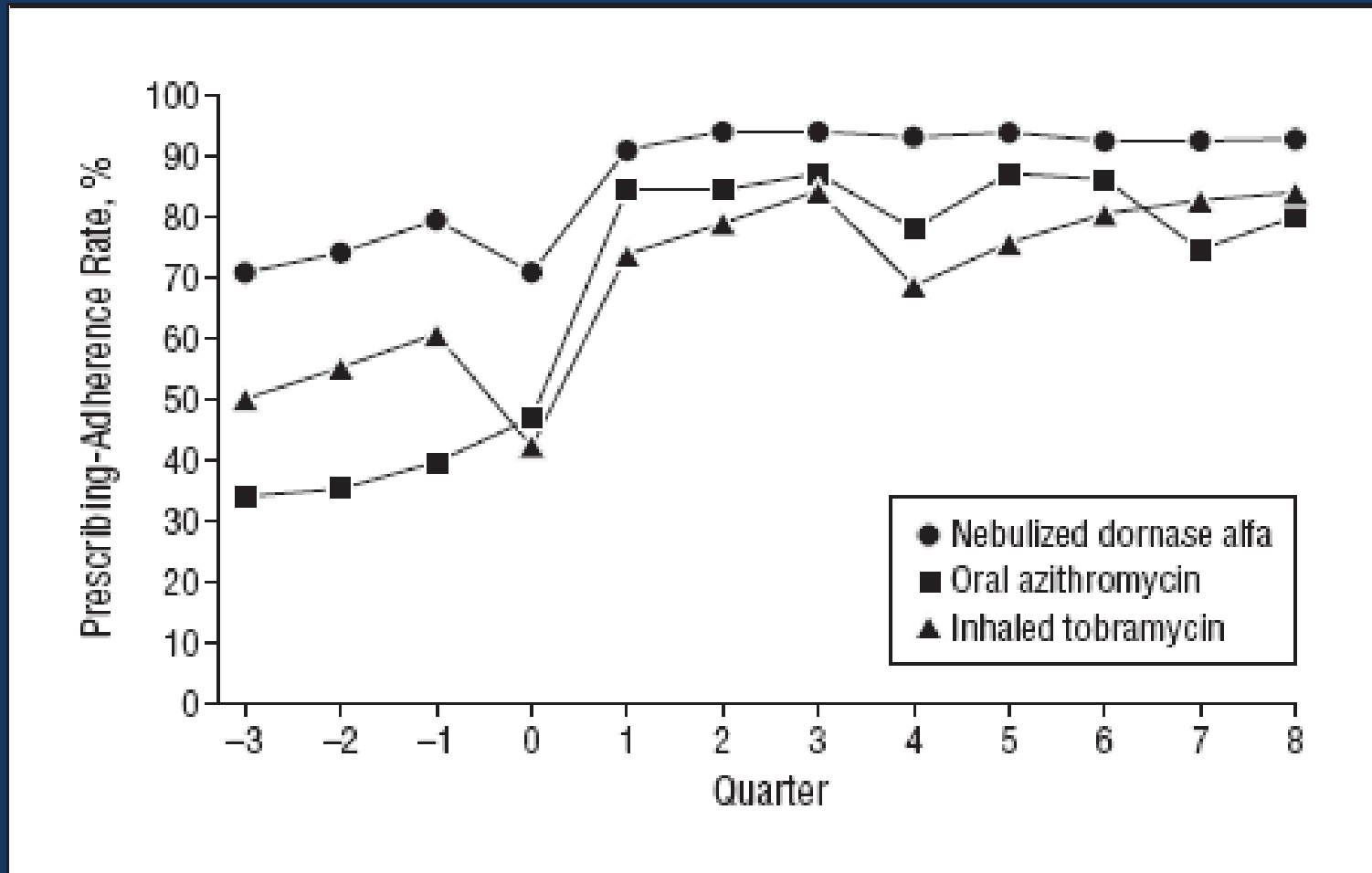
Accelerating Improvement in CF Care

- Measure performance
 - Processes of care
 - Outcomes of care

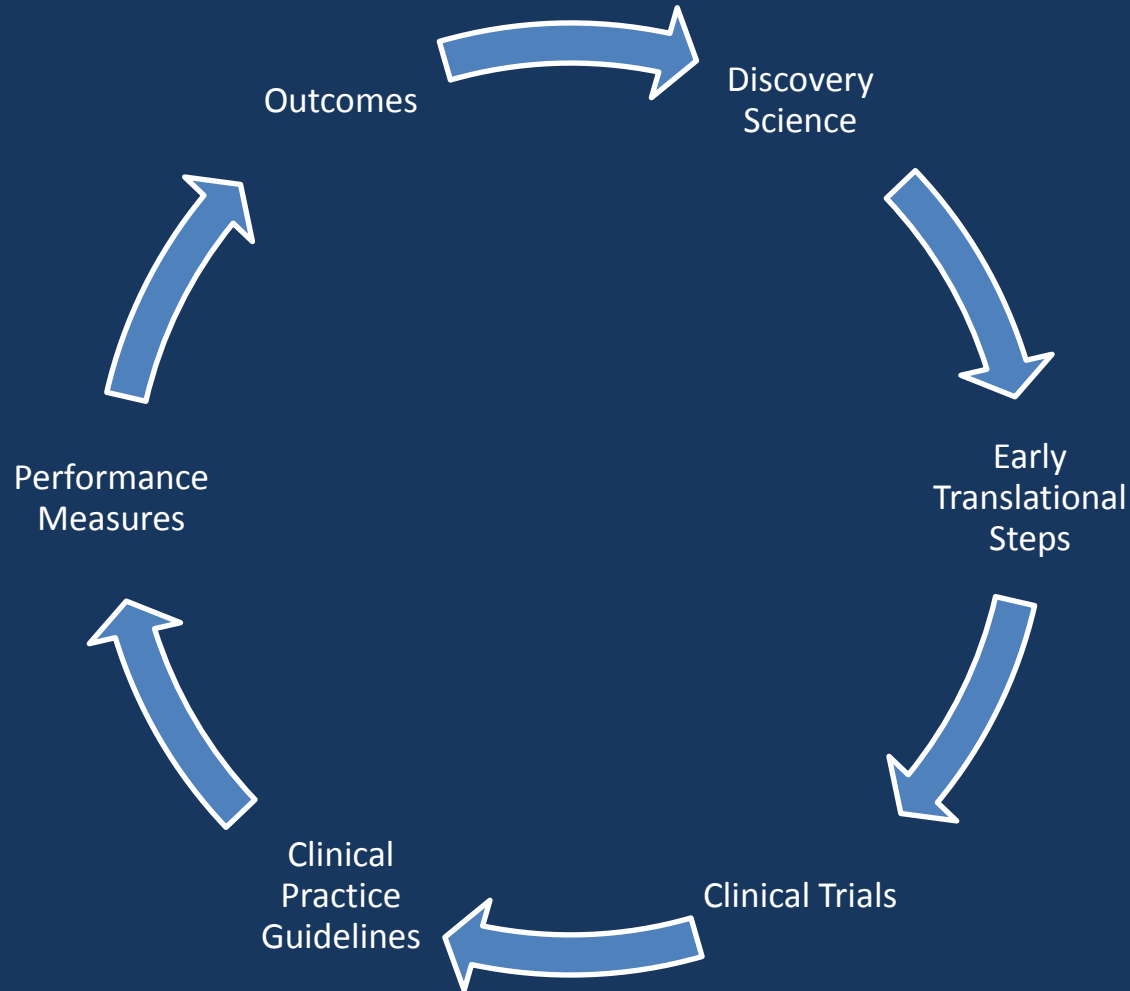
Plan
Do
Study
Act



Improving Evidence-Based Care in Cystic Fibrosis Through Quality Improvement



The Path from Bench to Bedside



Conclusions: Do Guidelines Work?

- Guidelines probably do work
 - But like birth control, only if you use it