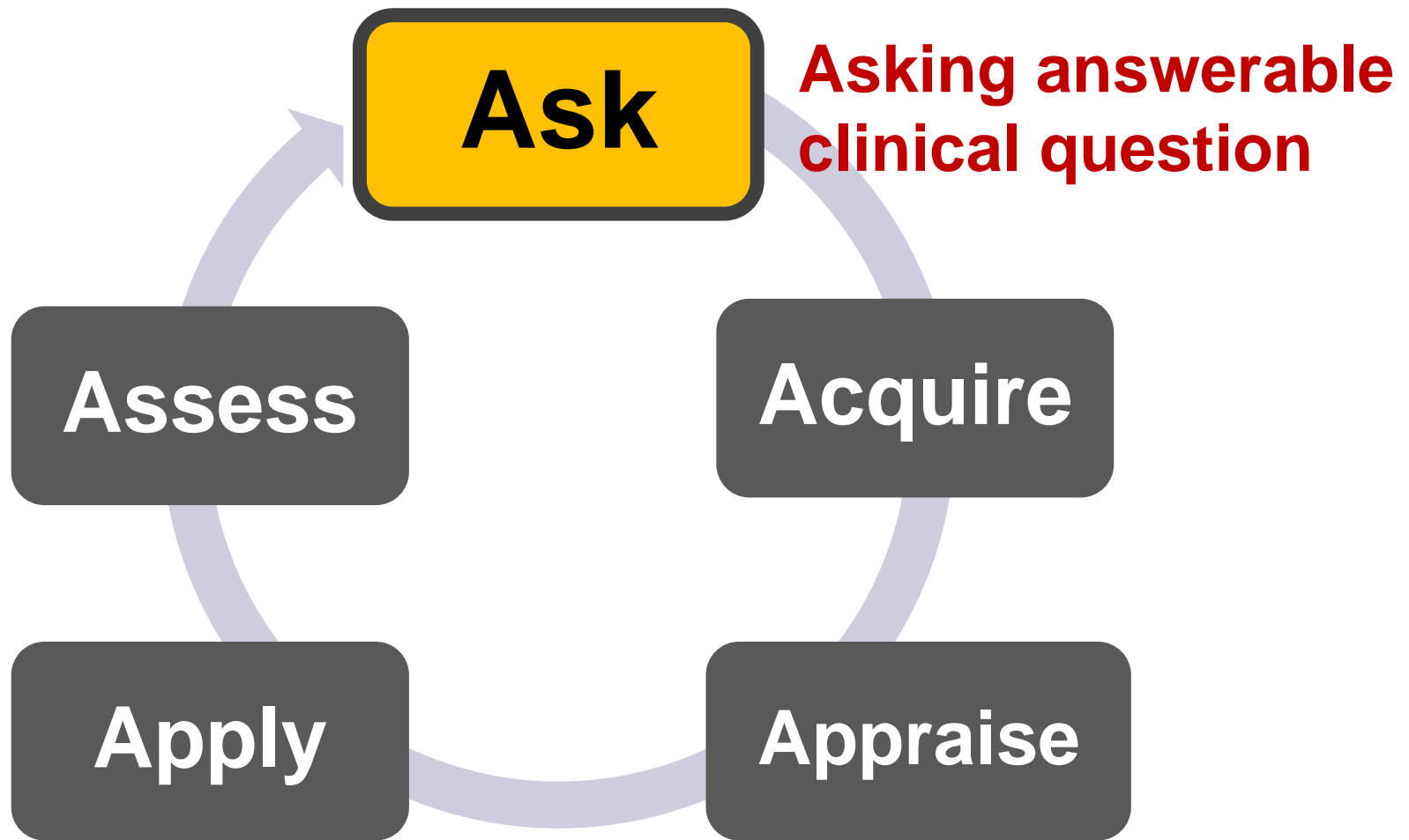




# Evidence-based medicine

神經外科

R 許子賢 R 鍾名軒



## 5-step Evidence-based medicine Process(5A)

# 提出問題1 Asking an answerable question

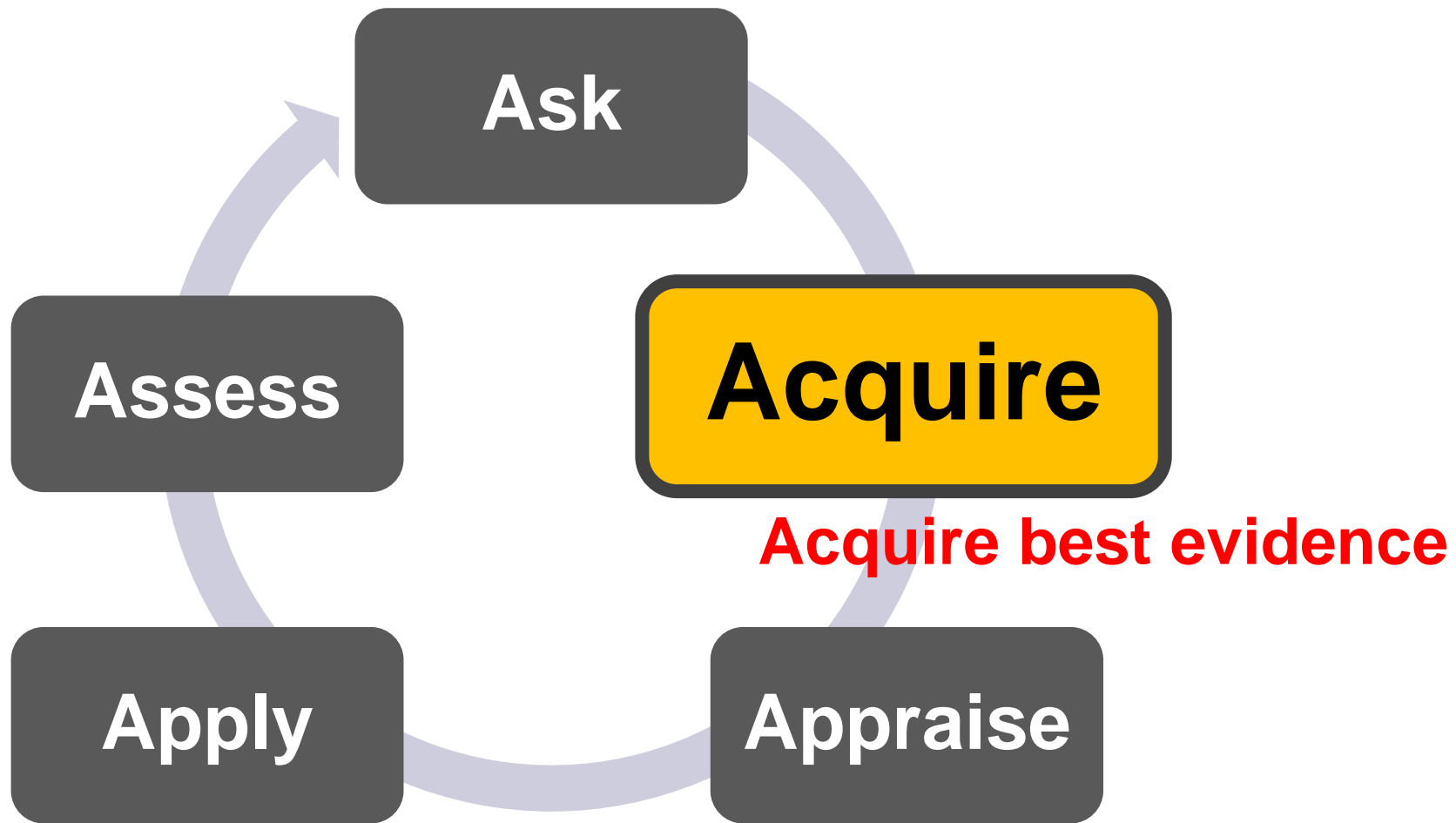
Nintedanib and prifenidone 相較於傳統治療在IPF的病人可否改善肺功能？



## 提出問題2 Asking an answerable question

運動對於IPF的病人可否改善肺功能？





# 5-step Evidence-based medicine Process(5A)

P

Middle-aged female  
IPF

Middle-aged female  
IPF

I

Nintedanib  
Pirfenidone

exercise

C

*N*-acetylcysteine

O

Pulmonary function decline  
Acute exacerbation  
Admission

Pulmonary function  
improvement

○ 傷害型問題



治療型問題



預後型問題



診斷型問題

# 尋找文獻 Acquired best evidence

以“PIO”搜尋，再依結果調整納入關鍵字和同義字

## Secondary database



## Primary database

Question type	Study design
Screen(篩檢)	RCT > cohort study > case series > mechanism-based reasoning(機轉)
Diagnosis(診斷)	Prospective, blinded cross-sectional study comparing with gold standard
Etiology(病因) / Harm(傷害)	<b>Cohort study &gt; Case control study &gt; Case series study</b>
Prognosis(預後)	Cohort study > case control study > case series study
Therapy(治療)	RCT > cohort study > case control > case series

Best type of study



P

Idiopathic pulmonary fibrosis









I

Nintedanib  
Pirfenidone

C

Pulmonary function decline  
Acute exacerbation  
Admission

O

資料庫	搜尋篇數	符合 PICO
	1556	
	622	
	0	
	99	
	275	
	0	
	0	
	0	

P

Idiopathic pulmonary fibrosis

I






Nintedanib  
Pirfenidone

C

*N*-acetylcysteine

O

Pulmonary function decline  
Acute exacerbation  
Admission

資料庫	搜尋 篇數	符合 PICO
	8	0
	9	4
	0	0
	1	0
	15	3
	0	0
	0	0
	0	0

# Secondary Database



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(((colchicine) OR N-acetylcysteine)) AND (((idiopathic pulmonor

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Search Results for "(((colchicine) OR N-acetylcysteine)) AND (((idiopathic pulmonary fibrosis) AND ((Nintedanib) OR Pirfenidone))) AND pulmonary function"

[All](#) | [Adult](#) | [Pediatric](#) | [Patient](#) | [Graphics](#)

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Click on what you meant by or: [odds ratio](#), [operating room](#)

Click related term for pulmonary function: [pulmonary function tests](#), [predicted postoperative pulmonary function](#)

## Treatment of idiopathic pulmonary fibrosis

...medications, **nintedanib** and **pirfenidone**, appear to slow disease progression . In addition, **pirfenidone** may have a mortality benefit. For patients with mild or moderate IPF based on **pulmonary function** tests who ...

[Our approach](#)

[Summary and recommendations](#)

## Pathogenesis of idiopathic pulmonary fibrosis

... contributing to the pathogenesis of **pulmonary** fibrosis, two novel antifibrotic agents, **pirfenidone** and **nintedanib**,... aberrant fibroblast and epithelial cell **function** and abnormal epithelial-mesenchymal interactions with little or no inflammatory component .... mechanisms of disease pathogenesis in **idiopathic pulmonary fibrosis** (IPF) comes from work with animal models of **pulmonary** fibrosis (eg,...

[Idiopathic pulmonary fibrosis](#)

[Summary](#)

## Prognosis and monitoring of idiopathic pulmonary fibrosis

... every three to six months or more frequently, if clinically indicated. We monitor **pulmonary function** every three to six months, or more frequently if symptoms change.... **pulmonary function** tests (PFTs), respiratory hospitalizations, and "acute exacerbations" of **idiopathic pulmonary fibrosis** (AE-IPF) Symptoms of IPF,... **nintedanib** and **pirfenidone**) and the decreased use of harmful immunosuppressive agents (ie,...

[Pulmonary function tests](#)

# Secondary Database

(((colchicine) OR N-acetylcysteine)) AND (((idiopathic pulmonary fibrosis) AND ((Nintedanib) OR Pirfenidone))) AND pulmonary function)

Search ?

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1-2 of 2 Page: 1

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**Idiopathic pulmonary fibrosis** >

Interstitial lung disease >

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  - All
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  - Protocol
- Other Reviews (0)
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- Economic Evaluations (0)
- Cochrane Groups (0)

All

Current Issue


**Cochrane Database of Systematic Reviews : Issue 5 of 12, May 2018**

Issue **updated daily** throughout month

There is **1** result from **10264** records for your search on '(((colchicine) OR N-acetylcysteine)) AND (((idiopathic pulmonary fibrosis) AND ((Nintedanib) OR Pirfenidone))) AND pulmonary function) in Title, Abstract, Keywords in Cochrane Reviews'

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-  **Non-steroid agents for idiopathic pulmonary fibrosis**  
Paolo Spagnolo , Cinzia Del Giovane , Fabrizio Luppi , Stefania Cerri , Sara Balduzzi , E. Haydn Walters , Roberto D'Amico and Luca Richeldi  
Online Publication Date: September 2010




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((colchicine) OR N-acetylcysteine)) AND ((pirfenidone))) AND pul

by quality ▾

1 Pirfenidone and nint

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# Trip

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PICO

ADVANCED PRO

RECENT PRO

(((colchicine) OR N-acetylcysteine)) AND (((idiopathic pulmor



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54 results for




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by quality ▾

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1. Pirfenidone and nintedanib modulate properties of fibroblasts and myofibroblasts in idiopathic pulmonary fibrosis.




Respiratory research 2016 Full Text: Link to full Text with Trip Pro PRO


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2. Efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with more preserved lung function




EvidenceUpdates 2016


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 Key Primary Research

3. Efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with more preserved lung function.

European Respiratory Journal 2016

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high or unclear est. of bias  Primary Research

4. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis.

NEJM 2015

Evidence type Clinical Area

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<input type="checkbox"/>	# ▲	Searches	Results	Type	Actions	Annotations
<input type="checkbox"/>	1	((colchicine or N-acetylcysteine) and (idiopathic pulmonary fibrosis and (Nintedanib or Pirfenidone) and pulmonary function)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	8	Advanced	<a href="#">Display Results</a> <a href="#">More</a> ▼	

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1. **Double-Blind Randomized Trial of Pirfenidone in Chinese Idiopathic Pulmonary Fibrosis Patients.**

Huang H; Dai HP; Kang J; Chen BY; Sun TY; Xu ZJ.

*Medicine.* 94(42):e1600, 2015 Oct.

[Clinical Trial, Phase II. Journal Article. Randomized Controlled Trial]

UI: 26496265

**Authors Full Name**

Huang, Hui; Dai, Hua Ping; Kang, Jian; Chen, Bao Yuan; Sun, Tie Ying; Xu, Zuo Jun.

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The screenshot shows the Embase search results page for search #7. The search results are displayed in a list format. The first result is highlighted with a yellow box. The search results are as follows:

- 1. Systematic Review and Network Meta-analysis of Idiopathic Pulmonary Fibrosis Treatments  
Fleetwood K., McCool R., Glanville J., Edwards S.C., Gsteiger S., Daigl M., Fisher M.  
*Journal of managed care & specialty pharmacy* 2017 23:3b Supplement (S5-S16)  
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- 2. Efficacy of antioxidant in idiopathic pulmonary fibrosis: A systematic review and meta-analysis  
Kandhare A.D., Mukherjee A., Ghosh P., Bodhankar S.L.  
*EXCLI Journal* 2016 15 (636-651) Cited by: 5  
Embase Abstract Index Terms View Full Text
- 3. Nintedanib cost-effectiveness in idiopathic pulmonary fibrosis  
Rinciog C., Watkins M., Chang S., Maier R.  
*Value in Health* 2016 19:7 (A553-)  
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- 4. Drug treatment of idiopathic pulmonary fibrosis systematic review and network meta-analysis  
Canestaro W.J., Forrester S.H., Raghu G., Ho L., Devine B.E.  
*Chest* 2016 149:3 (756-766) Cited by: 26  
Embase MEDLINE Abstract Index Terms View Full Text
- 5. Drug therapy for treatment of idiopathic pulmonary fibrosis: A systematic review and network meta-analysis  
Canestaro W.J., Forrester S., Ho L., Devine B.  
*Value in Health* 2015 18:3 (A170-)

未提及相關副作用比較

只比較N-acetylcysteine

文章內肺功能比較只針對nintedanib和pirfenidone 比較；未將N-acetylcysteine 納入文章時間較久



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(((colchicine) OR N-acetylcysteine)) AND (((idiopathic pulmonary fibrosis) AND ((Nintedanib

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## Search results

未提及相關副作用比較

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1. Fleetwood K, McCool R, Glanville J, Edwards SC, Gsteiger S, Daigl M, Fisher M. J Manag Care Spec Pharm. 2017 Mar;23(3-b Suppl):S5-S16. doi: 10.18553/jmcp.2017.23.3-b.s5. Review. PMID: 28287346 [Free Article](#)  
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[Pirfenidone, nintedanib and N-acetylcysteine for the treatment of Idiopathic pulmonary](#)

2. [fibrosis: A systematic review and meta-analysis.](#)  
Rogliani P, Calzetta L, Cavalli F, Matera MG, Cazzola M. Pulm Pharmacol Ther. 2016 Oct;40:95-103. doi: 10.1016/j.pupt.2016.07.009. Epub 2016 Jul 29. Review. PMID: 27481628  
[Similar articles](#)

[New treatments in idiopathic pulmonary fibrosis.](#)

3. Strâmbu I. Pneumologia. 2016 Jun;67(6):457-462. doi: 10.1016/j.pneum.2016.05.009. Epub 2016 Jun 1. Review. PMID: 29542881  
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文章內肺功能比較只針對nintedanib和 pirfenidone 比較；未將N-acetylcysteine 納入

[Drug Treatment of Idiopathic Pulmonary Fibrosis: Systematic Review and Network Meta-Analysis.](#)

4. Canestaro WJ, Forrester SH, Raghu G, Ho L, Devine BE.

[All \(29\)](#)

[Clinical Trial \(2\)](#)

[Diagnosis/Broad \(13\)](#)

[Etiology/Broad \(14\)](#)

[Prognosis/Broad \(12\)](#)

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(("colchicine"[MeSH Terms]

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1. Fleetwood K, McCool R, Glanville J, Edwards SC, Gsteiger S, Daigl M, Fisher M.  
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Rogliani P, Calzetta L, Cavalli F, Matera MG, Cazzola M.  
Pulm Pharmacol Ther. 2016 Oct;40:95-103. doi: 10.1016/j.pupt.2016.07.009. Epub 2016 Jul 29. Review.  
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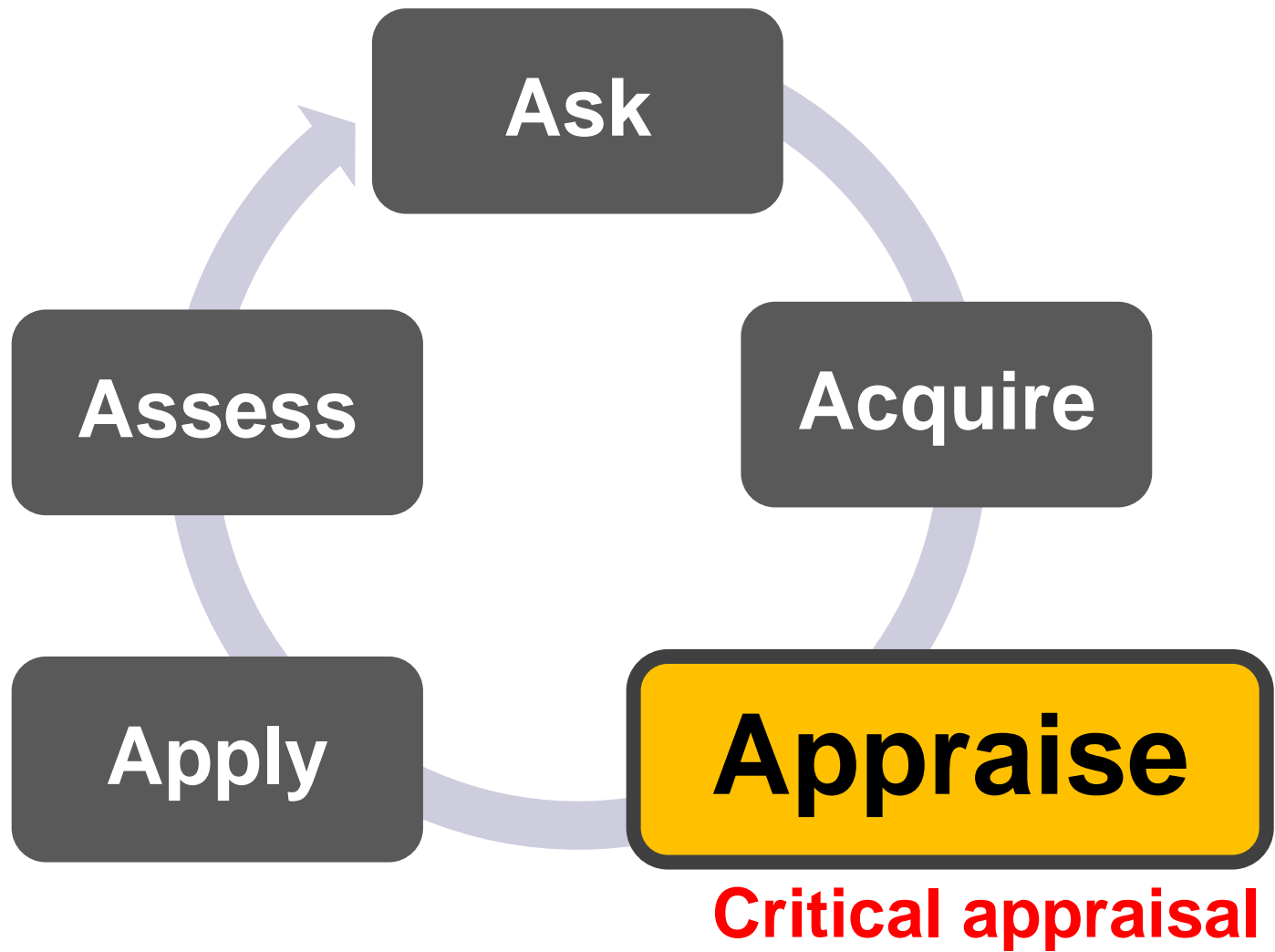
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# 5-step Evidence-based medicine Process(5A)

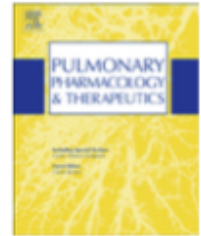


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## Pulmonary Pharmacology & Therapeutics

journal homepage: [www.elsevier.com/locate/ypupt](http://www.elsevier.com/locate/ypupt)



### Pirfenidone, nintedanib and *N*-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis



Paola Rogliani <sup>a, b</sup>, Luigino Calzetta <sup>a, \*</sup>, Francesco Cavalli <sup>b</sup>, Maria Gabriella Matera <sup>c</sup>,  
Mario Cazzola <sup>a, b</sup>

<sup>a</sup> University of Rome Tor Vergata, Department of Systems Medicine, Unit of Respiratory Clinical Pharmacology, Rome, Italy

<sup>b</sup> University of Rome Tor Vergata, Department of Systems Medicine, Chair of Respiratory Medicine, Rome, Italy

<sup>c</sup> Second University of Naples, Department of Experimental Medicine, Unit of Pharmacology, Naples, Italy

### 這篇文獻「納入理由」

✓ 最符合臨床問題

✓ 發表年份較新

✓ 最佳的研究設計

✓ 有全文可供評讀

# Critical Appraisal

## CASP Checklists (click to download)



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[CASP Clinical Prediction Rule Checklist](#)

## 1. Did the review address a clearly focused question?

In view of the lack of head-to-head RCTs of treatment interventions, considering the confounding findings resulting from a plethora of reviews and meta-analysis on IPF therapy [5–11], and also the recent positive evidences on combination therapy including NAC [12], we have carried out a treatment comparison by systematic review and synthesis of the available clinical variables to evaluate the effectiveness and safety of pirfenidone, nintedanib and NAC for IPF treatment vs. placebo, with unbiased analyses that incorporated exclusively the data from high quality RCTs lasting at least 6 months.



## 2. Did the authors look for the right type of papers?

### 2.2. Study selection

We included RCTs reported in English, lasting at least 6 months and concerning the influence of treatment with pirfenidone, nintedanib and NAC administered in patients suffering from IPF diagnosed by high-resolution computed tomography (HRCT) or biopsy [1,15]. All RCTs regarding IPF patients receiving oral administration of pirfenidone or nintedanib or oral/inhalant administration of NAC were included in the analysis.



### 3. Do you think all the important, relevant studies were included?

#### 2.2. Study selection

We included RCTs reported in English, lasting at least 6 months and concerning the influence of treatment with pirfenidone, nintedanib and NAC administered in patients suffering from IPF diagnosed by high-resolution computed tomography (HRCT) or biopsy [1,15]. All RCTs regarding IPF patients receiving oral administration of pirfenidone or nintedanib or oral/inhalant administration of NAC were included in the analysis.

Yes

Can't tell

No



## 4. Did the review's authors do enough to assess quality of the included studies?

### 2.3. Data extraction and quality assessment

Two reviewers independently checked the relevant RCTs found from literature and databases, and any difference in opinion about eligibility was resolved by consensus.

Data from included studies were extracted and checked for study characteristics and duration, doses of medications, disease characteristics, age, gender, smoking habits, smoking history, sex, forced vital capacity (FVC), carbon monoxide diffusing capacity (DLCO), 6 min walking distance (6MWD), time since diagnosis (years), weight, and Jadad score.

The Jadad score was used to assess the quality of the papers [16], and a score <3 was used as cut-off for subgroup analysis.

The risk of publication bias was assessed by applying the funnel plot and Egger's test [17–19]. Evidence of asymmetry from Egger's test was considered to be significant for  $P < 0.1$  [19].



Yes



Can't tell



No

## 5. If the results of the review have been combined, was it reasonable to do so?

Due to high heterogeneity :  $I^2 > 50\%$

The analysis was performed via a binary random-effects model [20–23]. Values have been expressed as mean difference (MD), standardized MD (SMD), or risk difference (RD) and 95% confidence interval (CI) for the impact of pirfenidone, nintedanib and NAC on the examined variables.

The rank of effectiveness between the currently approved drugs for IPF treatment was performed by analyzing the delta of change from baseline in FVC summary estimates of nintedanib vs. pirfenidone.

The OpenMetaAnalyst and GraphPad Prism (CA, USA) software were used to carry out this meta-analysis. The statistical significance was assessed for  $P < 0.05$  [24,25], significant ( $P < 0.05$ ) moderate to high levels of heterogeneity were considered for  $I^2 > 50\%$  [26], and the optimal information size (OIS) was assessed as previously reported [27].



Yes

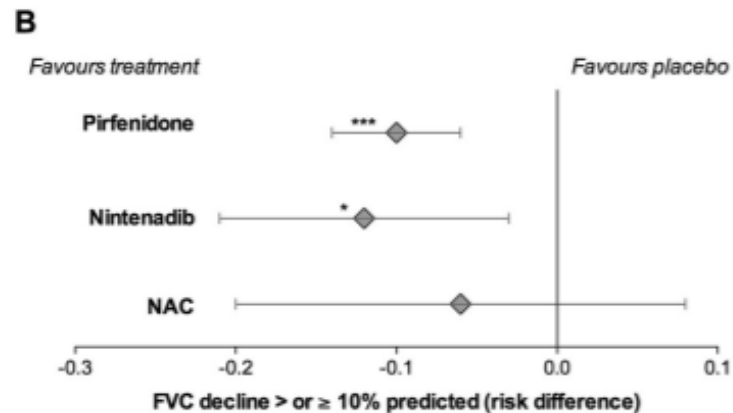
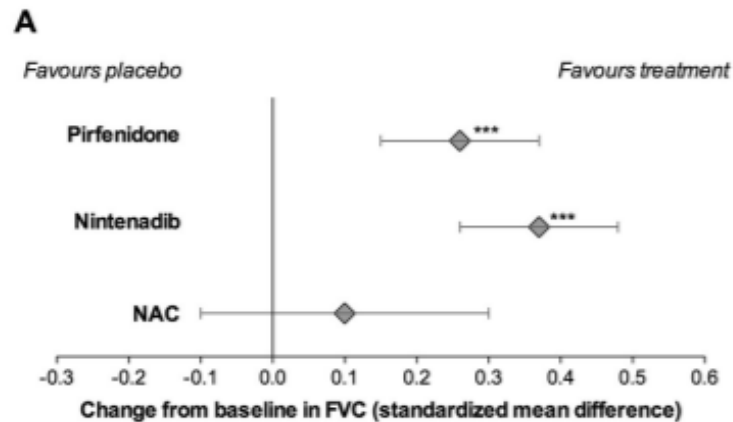


Can't tell



No

## 6. What are the overall result of the review ?



FVC decline

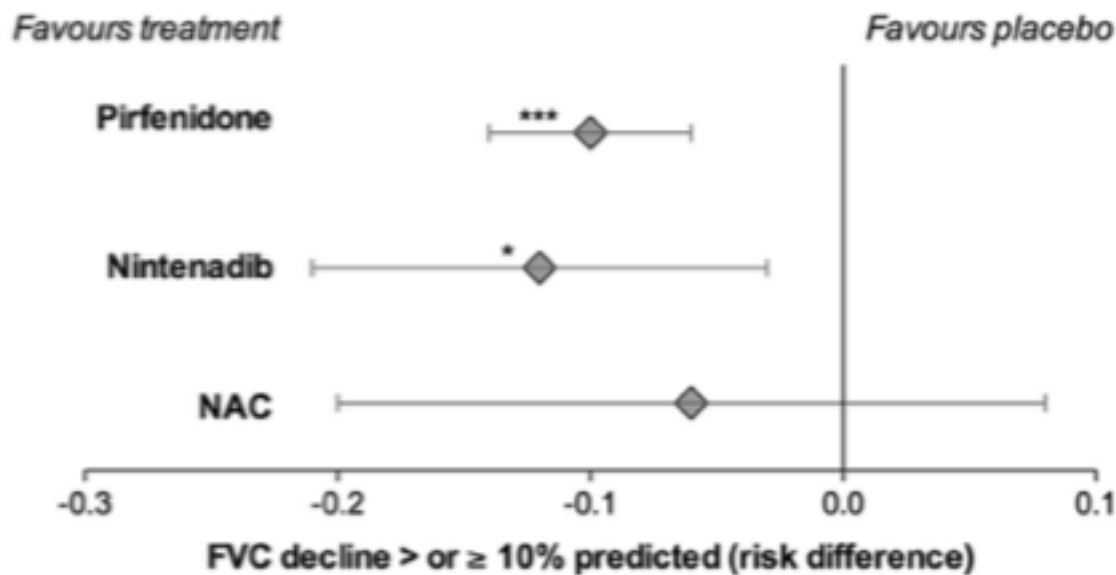
pirfenidone -0.10, 95%CI -0.14 ~- 0.06, P<0.001

nintedanib -0.12, 95%CI -0.21 ~- 0.03, P<0.05

NAC -0.06, 95%CI -0.20~-0.08, P>0.05,

## 7. How precise are the results?

**B**



FVC decline

pirfenidone -0.10, 95%CI -0.14 ~- 0.06, P<0.001

nintedanib -0.12, 95%CI -0.21 ~- 0.03, P<0.05

NAC -0.06, 95%CI -0.20~-0.08, P>0.05,

# 8. Can the results be applied to the local population?



**Table 1**  
Patient demographics, baseline and study characteristics.

Study and year	ClinicalTrials.gov Identifier	Study characteristics	Duration of study (weeks)	Number of analyzed patients	Drugs (doses)	Administration regimen	Patients characteristics	Age (years)	Male (%)	Current smokers (%)	Time since diagnosis (yr)	FVC or VC (% or L)	6MWD (metres)	DL <sub>CO</sub> (% or mmol/min/kPa)	Jadad score
Azuma et al., 2005 [34]	NA	A multicentre, double-blind, placebo-controlled, randomized clinical trial	39	107	Pirfenidone (1800 mg/die; 200 mg)	3 tablets t.i.d. (oral)	PaO <sub>2</sub> ≥ 70 mmHg at rest; SpO <sub>2</sub> of 90% or less during exertion while breathing air	64.0	86.0	10.0	<1yr 28.0%	81.6%	NA	57.6%	4
Taniguchi et al., 2010 [42]	NA	A multicentre, double-blind, placebo-controlled, randomized clinical trial	52	267	Pirfenidone (1800 mg/die; 200 mg); (1200 mg/die; 200 mg)	3 tablets t.i.d.(oral); 2 tablets t.i.d. (oral)	Oxygen desaturation of ≥5% difference between resting SpO <sub>2</sub> and the lowest SpO <sub>2</sub> during a 6MET; the lowest SpO <sub>2</sub> during the 6MET of ≥85% while breathing air	64.7	82.1	9.2	<1yr 35.6%	2.4 L	NA	52.9%	4
Noble et al., 2011 (CAPACITY 04) [37]	NCT00287716	A multicentre, double-blind, placebo-controlled, randomized clinical trial	72	435	Pirfenidone (2403 mg/die; 267 mg); (1197 mg/die; 133 mg)	3 tablets t.i.d.(oral); 3 tablets t.i.d. (oral)	FVC of 50% until 90%; Dlco of 35% until 90%; 6MWD of at least 150 m	66.9	71.5	4.2	<1yr 49.4%	75.5%	4	46.8%	4
Noble et al., 2011 (CAPACITY 06) [37]	NCT00287729	A multicentre, double-blind, placebo-controlled, randomized clinical trial	72	344	Pirfenidone (2403 mg/die; 267 mg)	3 tablets t.i.d.(oral)	FVC of 50% until 90%; Dlco of 35% until 90%; 6MWD of at least 150 m	66.8	72.0	0.0	<1yr 58.0%	74.9%	378.0	47.8%	4
King et al., 2014 (ASCEND) [44]	NCT01366209	A multicentre, double-blind, placebo-controlled, randomized clinical trial	52	555	Pirfenidone (2403 mg/die; 267 mg)	3 tablets t.i.d. (oral)	FVC of 50% until 90%; Dlco of 30% until 90%; FEV <sub>1</sub> /FVC of 0.80 or more; 6MWD of 150 m or more	68.4	79.9	NA	1.7	67.8%	415.0	43.7%	4
Richeldi et al., 2011 (TOMORROW) [40]	NCT00514683	A multicentre, double-blind, placebo-controlled, randomized clinical trial	52	428	Nintedanib (300 mg/die; 150 mg); (200 mg/die; 100 mg); (100 mg/die; 50 mg); (50 mg/die; 50 mg)	1 tablet b.i.d. (oral); 1 tablet b.i.d.(oral); 1 tablet b.i.d. (oral); 1 tablet q.d. (oral)	FVC of ≥50%; Dlco of 30% until 79%	65.2	75.0	NA	1.2	2.8 L	NA	3.8 mmol/L min/kPa	4
Richeldi et al., 2014 (INPULSIS-1) [41]	NCT01335464	A multicentre, double-blind, placebo-controlled, randomized clinical trial	52	513	Nintedanib (300 mg/die; 150 mg)	1 tablet b.i.d. (oral)	FVC of ≥50%; Dlco of 30% until 79%	66.9	81.2	6.8	1.7	2.8 L	NA	47.8%	4
Richeldi et al., 2014	NCT01335477	A multicentre,	52	548	Nintedanib (300	1 tablet b.i.d.	FVC of ≥50%; Dlco	66.4	77.8	2.4	1.6	2.7 L	NA	47.0%	4

## 9. Were all important outcomes considered?

### 3.3. Safety profile of pirfenidone, nintedanib and NAC

**Adverse events** were reported in 12 RCTs (treated n = 2,261, placebo n = 1604).

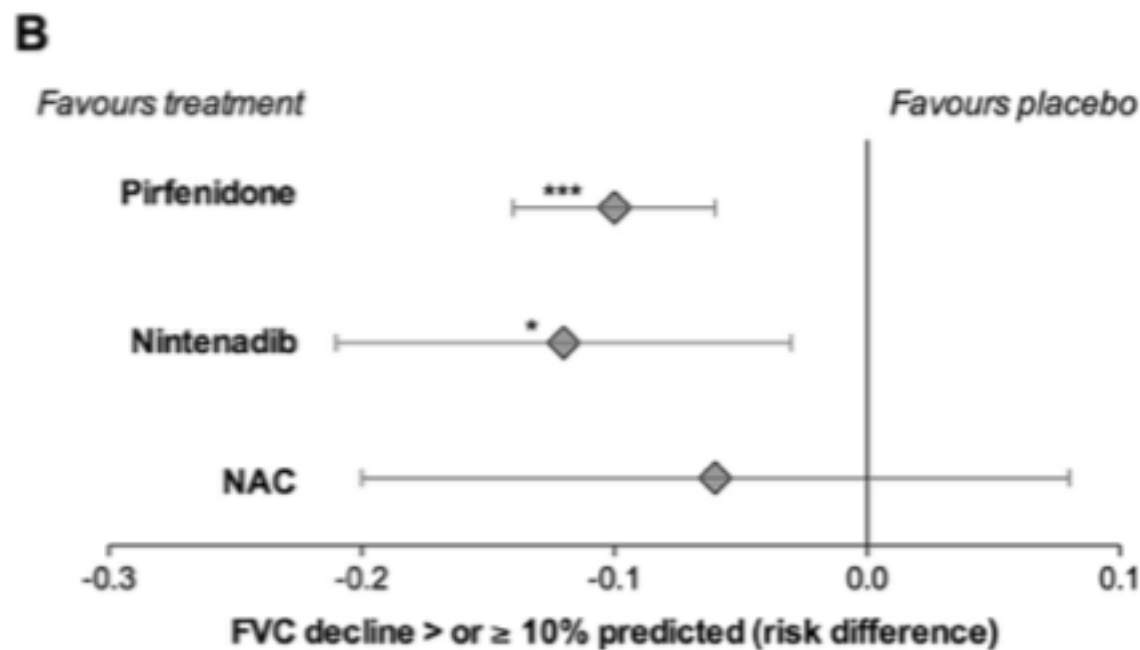
Pirfenidone and nintedanib did not increase the RD of serious **adverse events** (pirfenidone 0.00, 95%CI -0.02–0.02,  $I^2$  0%; nintedanib -0.02, 95%CI -0.06–0.03,  $I^2$  0%; both  $P > 0.05$  vs. control), while NAC slightly, although not significantly, enhanced the RD of serious **adverse events** (0.12, 95%CI -0.05–0.29,  $I^2$  80%;  $P > 0.05$  vs. control; Fig. 2A). Nintedanib, but neither pirfenidone nor NAC, significantly ( $P < 0.05$ ) protected against both the overall and respiratory-specific risk of death (pirfenidone -0.01, 95%CI -0.02–0.00,  $I^2$  24%; nintedanib -0.03, 95%CI -0.06 to -0.001,  $I^2$  28%; NAC 0.03, 95%CI -0.02–0.08,  $I^2$  18%), compared with placebo (Fig. 2B and C). The inclusion into the meta-analysis of the study with a Jadad score  $< 3$  did not change the safety profile of NAC.

Further details are reported in the supplemental file (Figs. S6–S8).

The most frequent **adverse events** detected in the arms treated with different doses of pirfenidone, nintedanib and NAC and in placebo groups are reported in Table S3. The most common ( $\geq 1/10$ ) **adverse events** associated with the administration of approved dose of pirfenidone were rash (30.34%), nausea (25.68%), cough (19.42%), dizziness (17.98%), headache (16.05%), anorexia (13.00%), dyspepsia (12.68%), dyspnoea (11.08%) and insomnia (10.43%), whereas those associated with the approved dose of nintedanib were diarrhoea (60.86%), nausea (24.34%), cough (12.86%), nasopharyngitis (12.86%), vomiting (11.62%) and decrease appetite (11.07%). However, overall 40% of very common ( $\geq 1/10$ ) and 87% of common ( $\geq 1/100$  to  $< 1/10$ ) **adverse events** were also observed with similar frequency in the placebo arms.

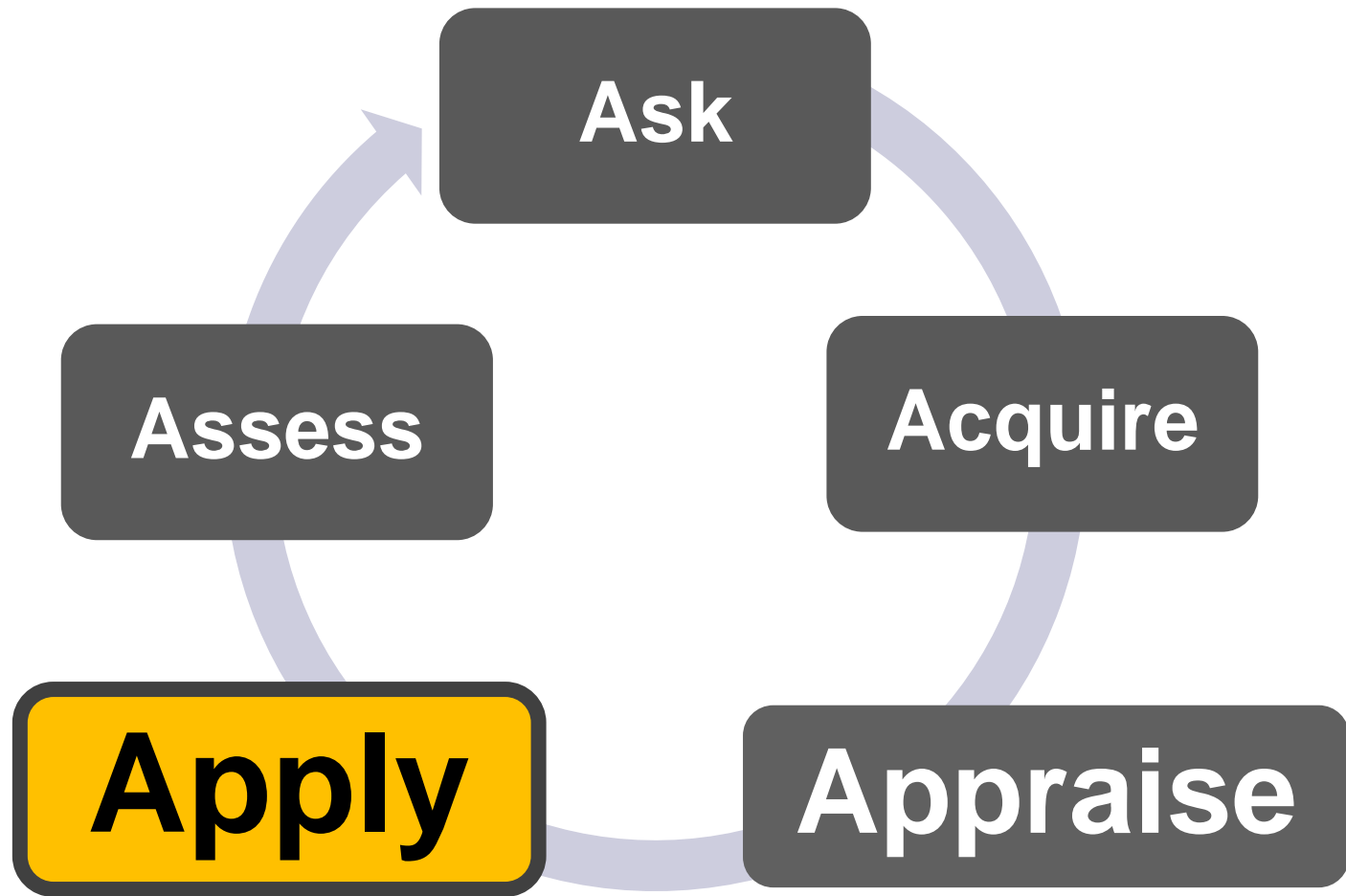


## 10. Are the benefits worth the harms and costs?



FVC decline

pirfenidone	-0.10, 95%CI -0.14 ~- 0.06, P<0.001	NNT: 1.1 (139元/tab) : 417-1251元
nintedanib	-0.12, 95%CI -0.21 ~- 0.03, P<0.05	NNT:1.13 (876元/tab): 1752元
NAC	-0.06, 95%CI -0.20~-0.08, P>0.05,	NNT: 1.06 (6元/tab): 6-18元



**5-step Evidence-based  
medicine Process(5A)**



根據文獻搜查結果，使用新型藥物相對於傳統藥物治療更能減緩肺功能惡化，較少次數的急性發作，較少因呼吸問題造成的死亡，但是在台灣健保規範下須提出申請，自費價錢也較為昂貴。

**Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence**

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
<b>How common is the problem?</b>	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
<b>Is this diagnostic or monitoring test accurate?</b> (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
<b>What will happen if we do not add a therapy?</b> (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
<b>Does this intervention help?</b> (Treatment Benefits)	Systematic review of randomized trials or <i>n</i> -of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
<b>What are the COMMON harms?</b> (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, <i>n</i> -of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
<b>What are the RARE harms?</b> (Treatment Harms)	Systematic review of randomized trials or <i>n</i> -of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
<b>Is this (early detection) test worthwhile?</b> (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning



**Thanks for your Listening !**