Evidence-based medicine

神經外科
R 許子賢 R 鍾名軒

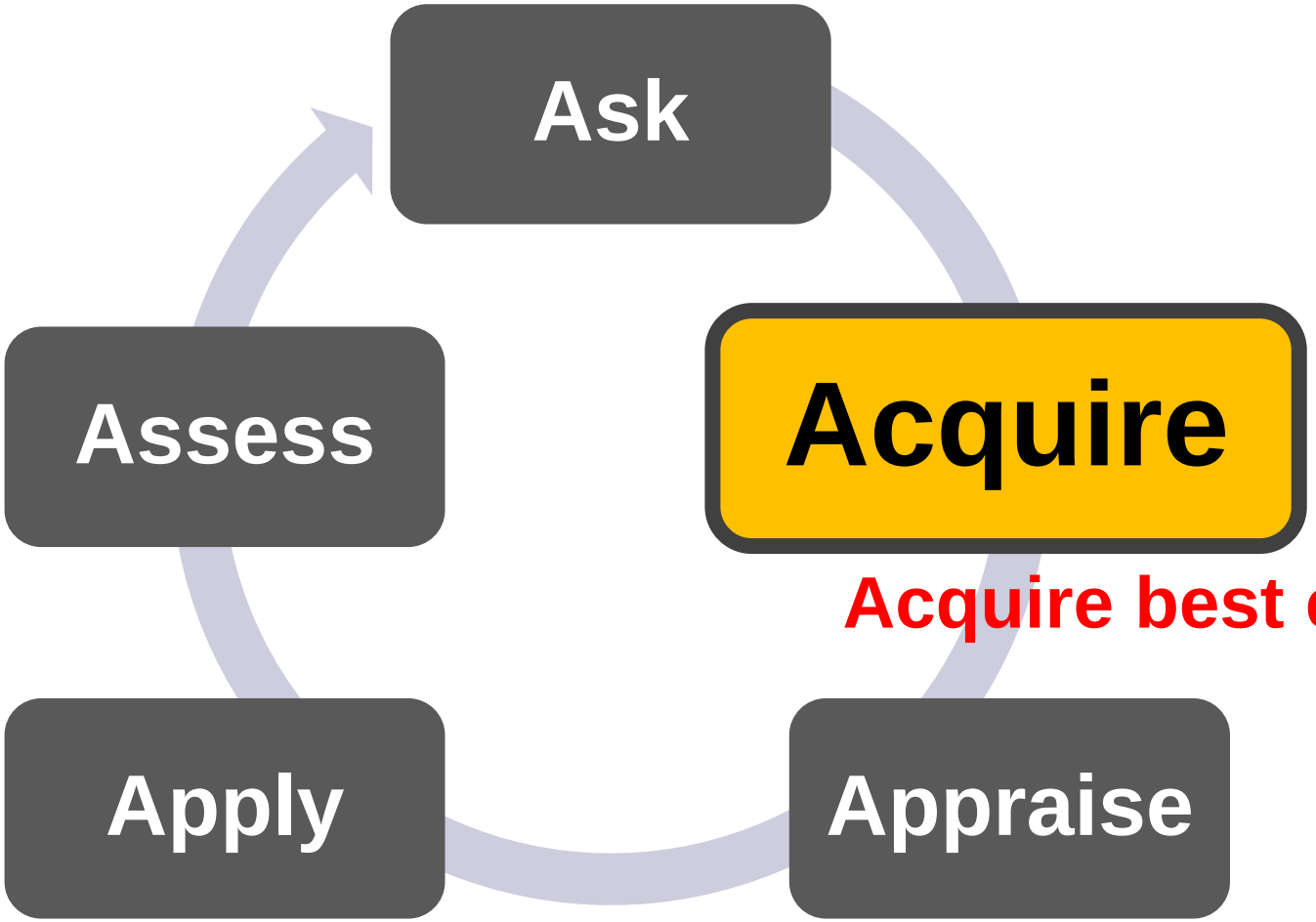
5-step Evidence-based medicine Process(5A)

提出問題1Asking 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2Asking 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)	**Cohort study > Case control study > Case series study**
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

O Pulmonary function decline
Acute exacerbation
Admission

資料庫	搜尋篇數	符合PICO
Ovid®	1556	
Embase®	622	
The Cochrane Library	0	
Trip	99	
PubMed www.pubmed.gov	275	
airiti Library 華藝線上圖書館	0	
UpToDate	0	
DynaMed Powered by EBSCOhost	0	

P Idiopathic pulmonary fibrosis

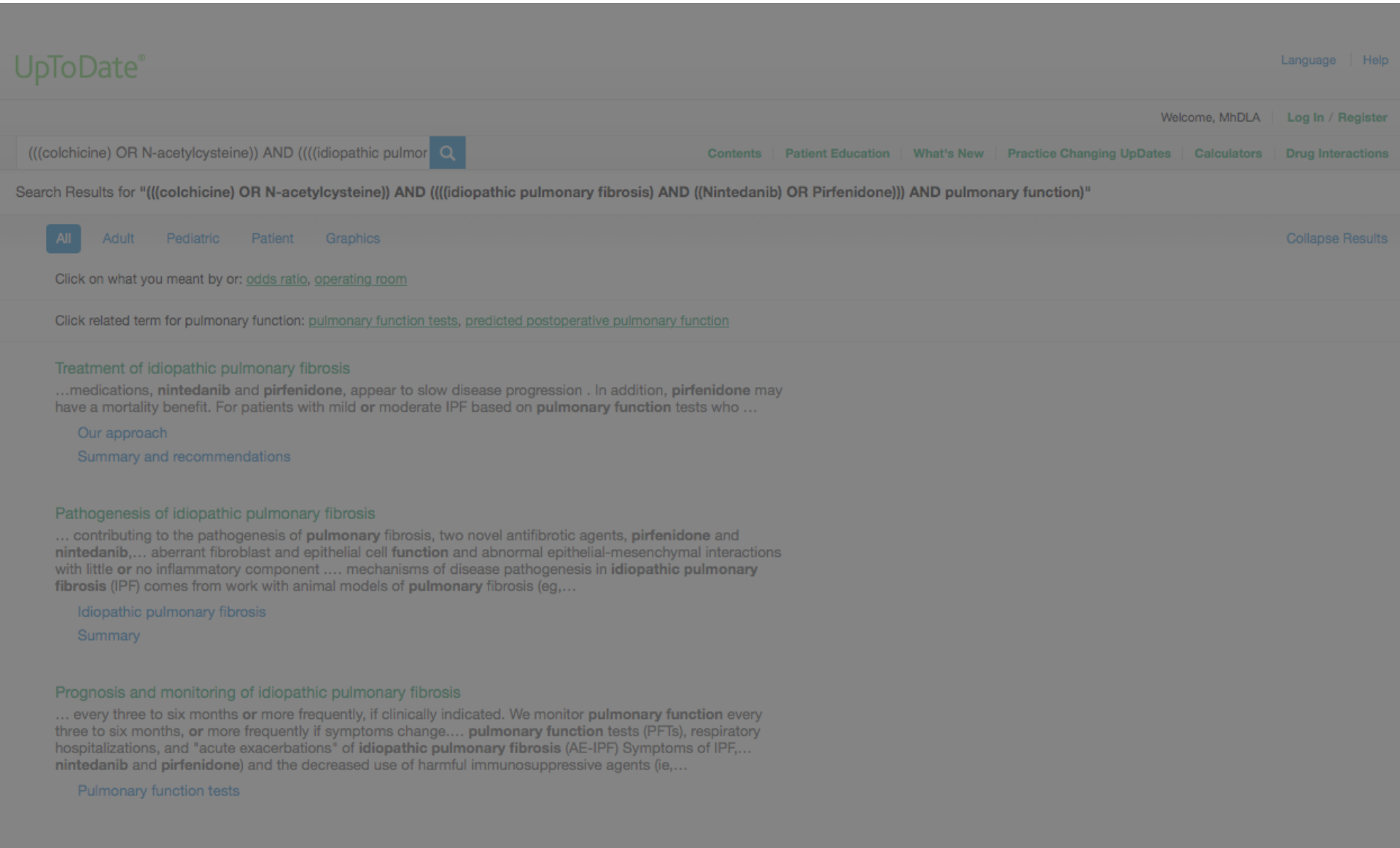
I Nintedanib
Pirfenidone

C *N*-acetylcysteine

O Pulmonary function decline
Acute exacerbation
Admission

資料庫	搜尋篇數	符合PICO
Ovid®	8	0
Embase®	9	4
The Cochrane Library	0	0
Trip	1	0
PubMed www.pubmed.gov	15	3
airiti Library 華藝線上圖書館	0	0
UpToDate	0	0
DynaMed Powered by EBSCOhost	0	0

Secondary Database



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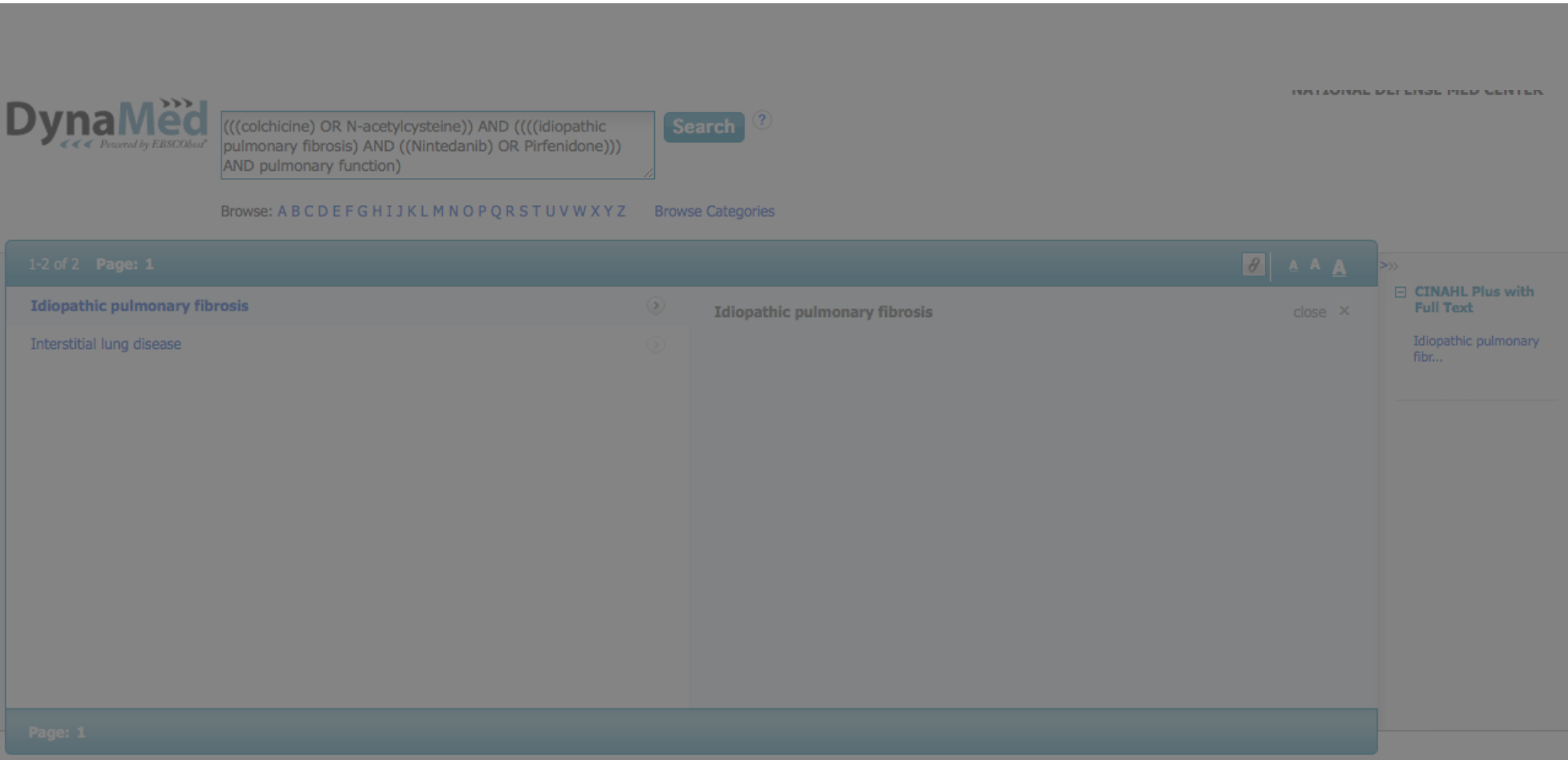

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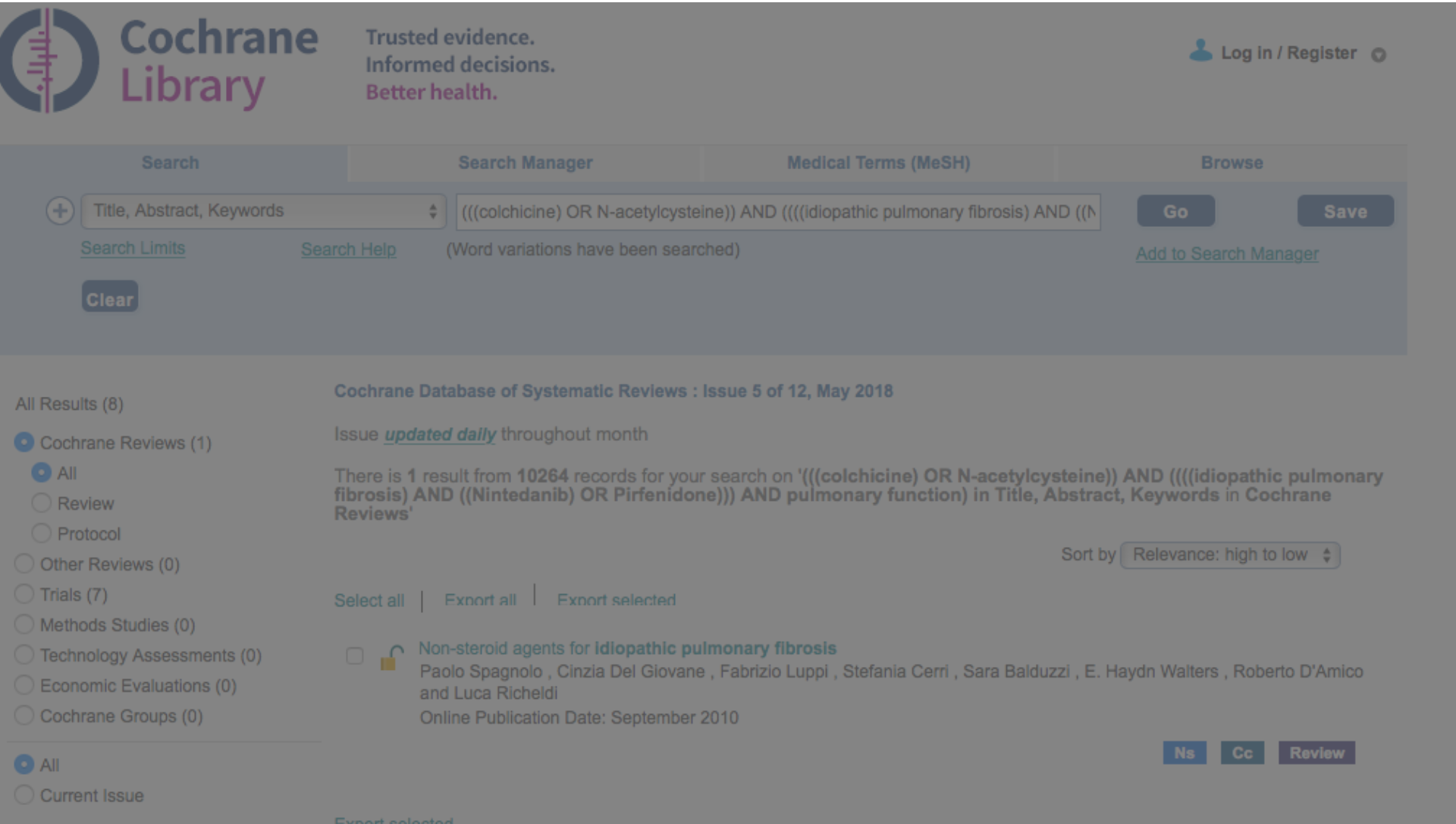

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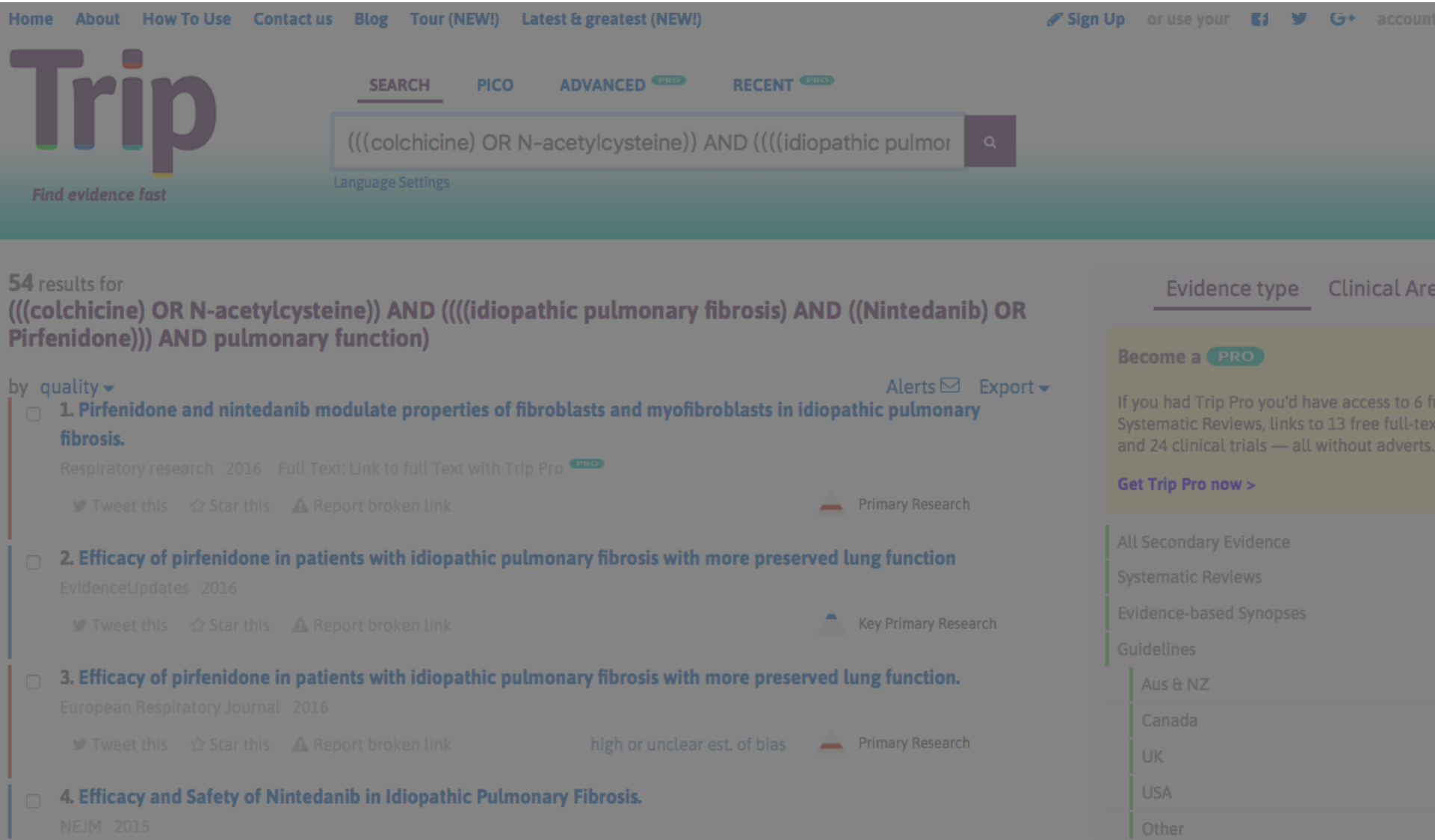

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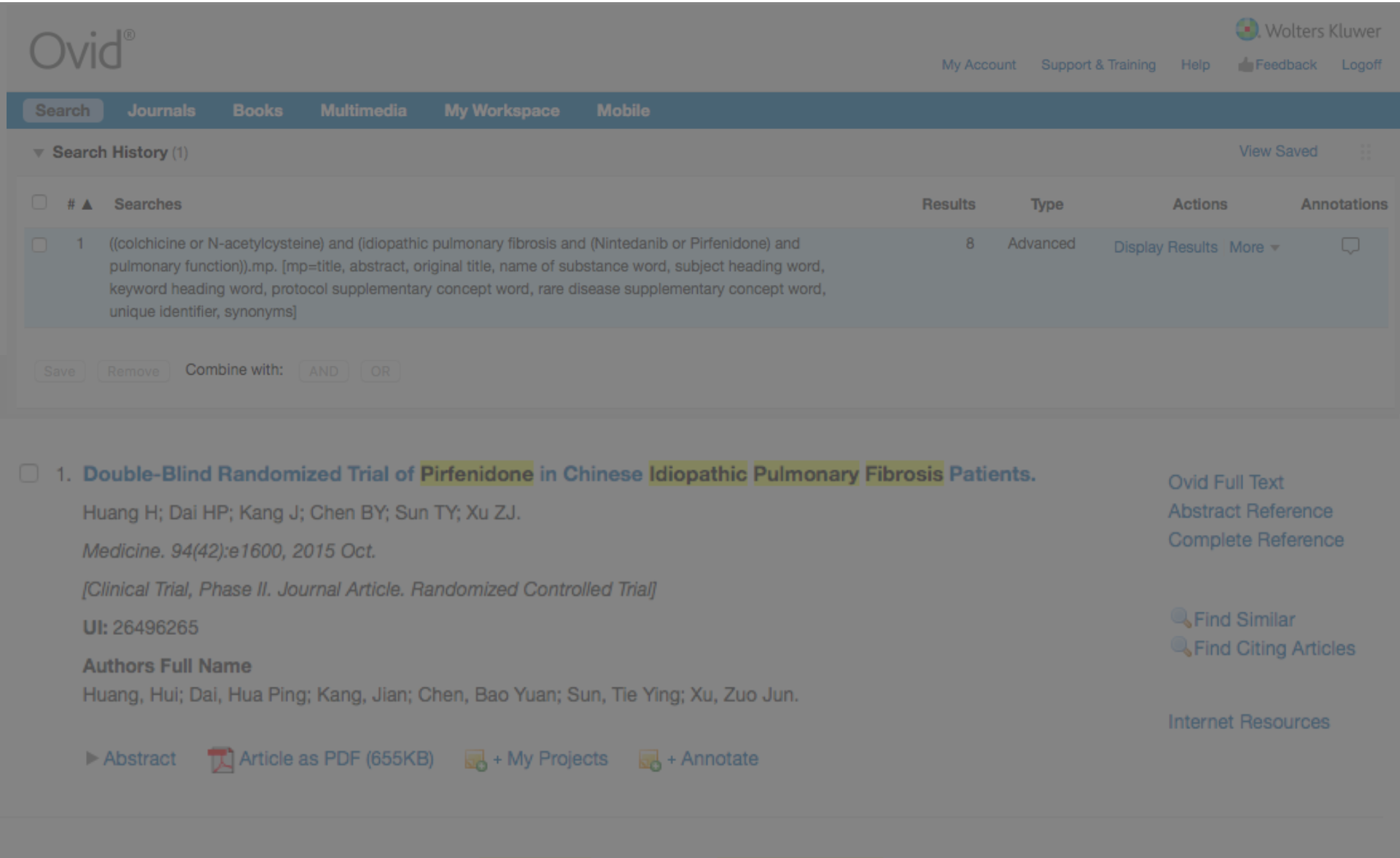

Primary Database

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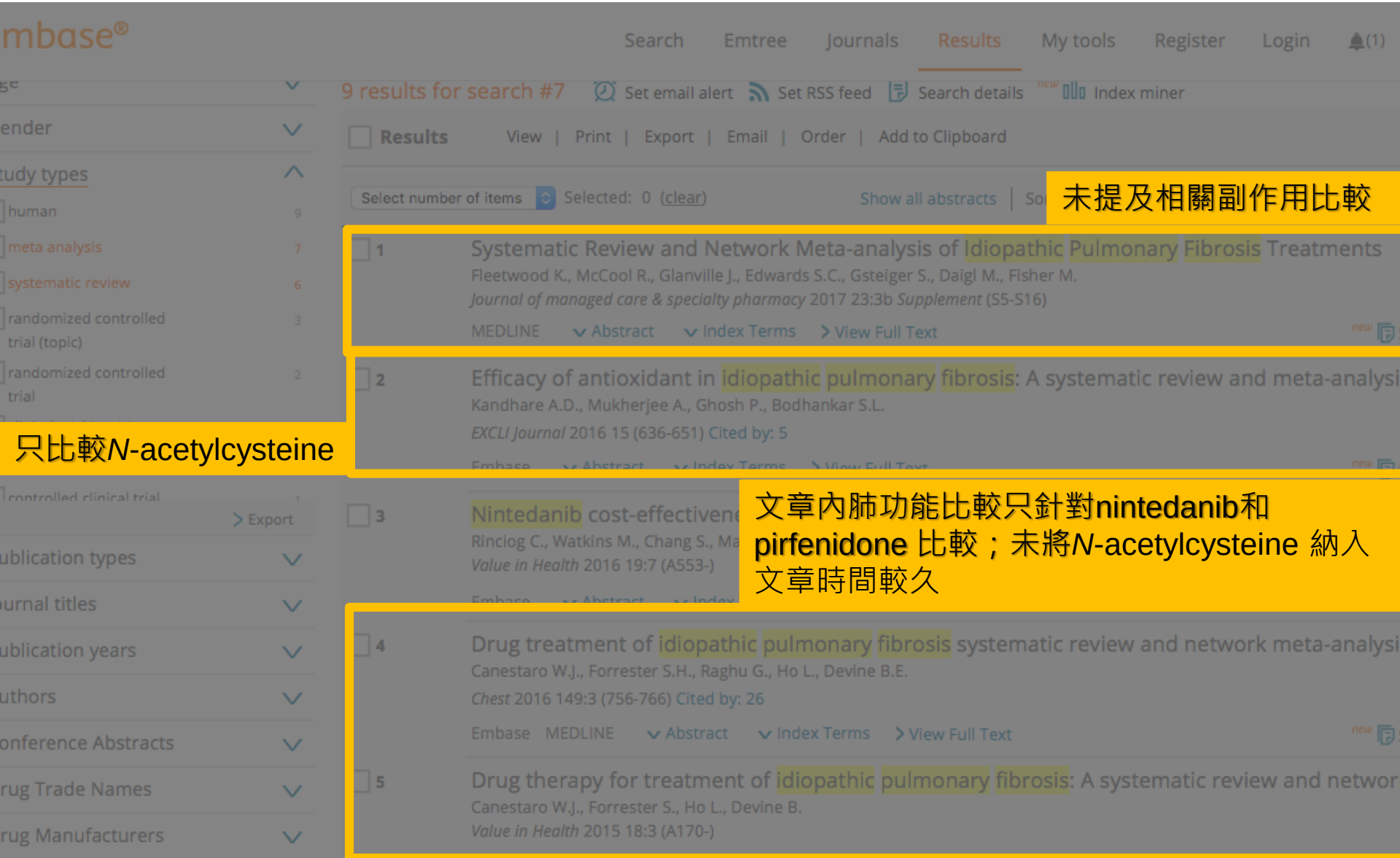

Primary Database

PubMed www.pubmed.gov

PubMed (((colchicine) OR N-acetylcysteine)) AND ((((idiopathic pulmonary fibrosis) AND ((Nintedanil Search

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Clinical Trial (2)
Diagnosis/Broad (13)
Etiology/Broad (14)
Prognosis/Broad (12)
Review (15)
Therapy/Broad (26)
Taiwan (0)

Search results

未提及相關副作用比較

1. Systematic Review and Network Meta-analysis of **Idiopathic Pulmonary Fibrosis** Treatments.
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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2. **Pirfenidone**, **nintedanib** and **N-acetylcysteine** for the treatment of **idiopathic pulmonary 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
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3. New treatments in **idiopathic pulmonary fibrosis**.
Strâmbu I.
Pneumologia. 2016 Ju
PMID: 29542881
Similar articles

文章內肺功能比較只針對nintedanib和pirfenidone 比較；未將*N*-acetylcysteine 納入

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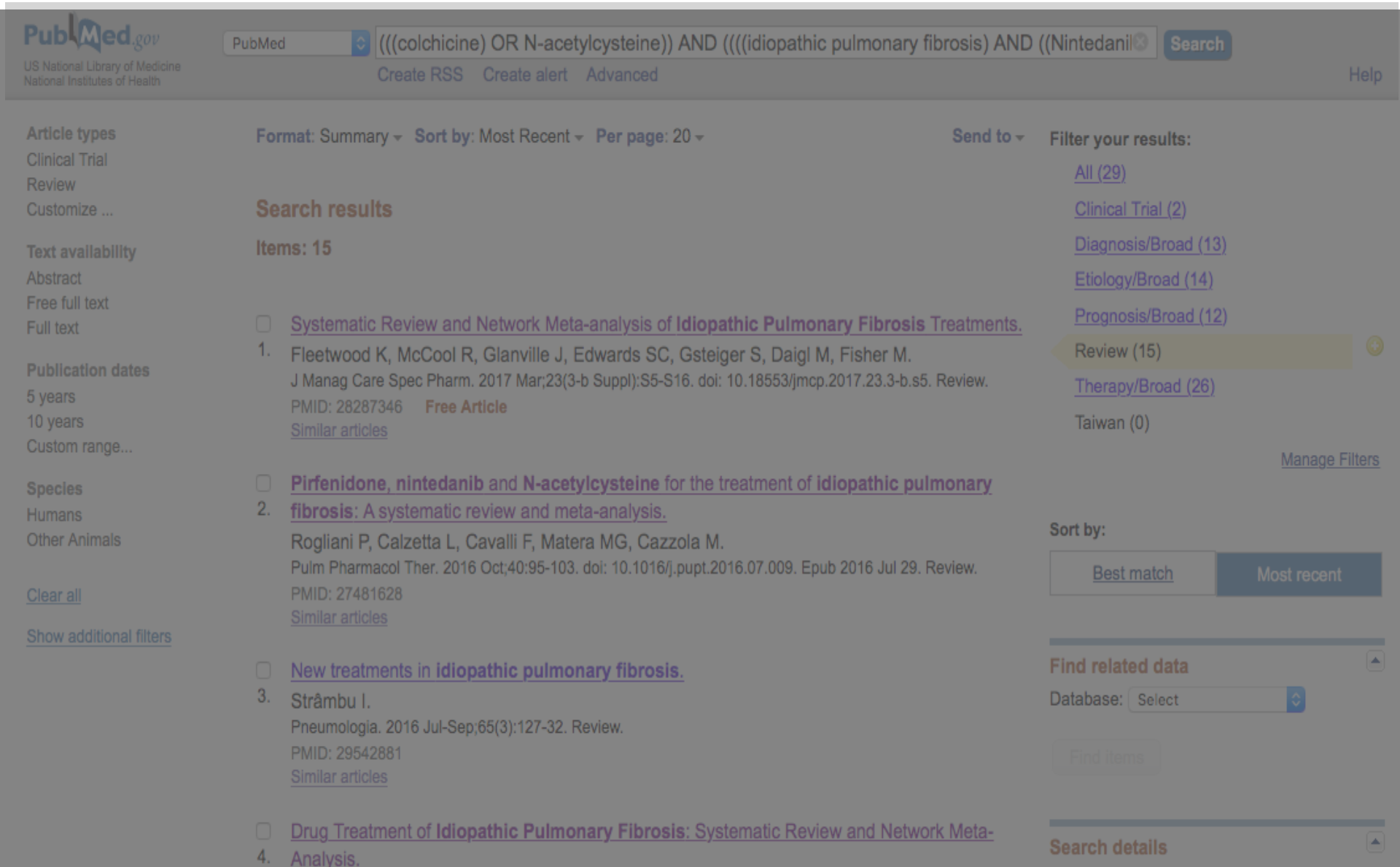
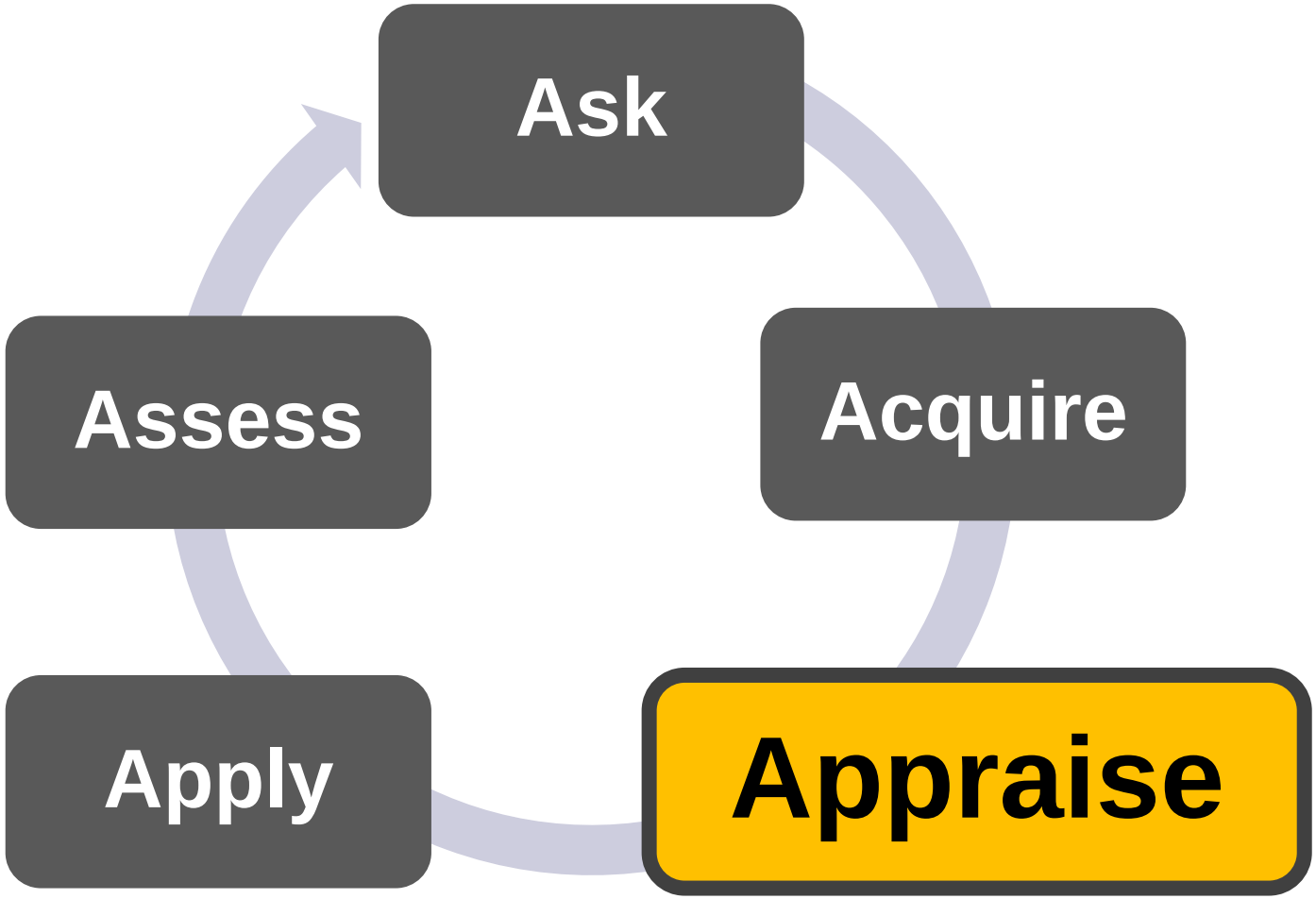
4. Drug Treatment of **Idiopathic Pulmonary Fibrosis**: Systematic Review and Network Meta-Analysis.
Canestaro WJ, Forrester SH, Raghu G, Ho L, Devine BE.

Search details
(("colchicine"[MeSH Terms

Primary Database

airiti Library 華藝線上圖書館





Critical appraisal

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

Pulmonary Pharmacology & Therapeutics 40 (2016) 95–103

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

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

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[c] 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)

CASP Systematic Review Checklist	CASP Qualitative Checklist
CASP Randomised Controlled Trial Checklist	CASP Case Control Checklist
CASP Diagnostic Checklist	CASP Cohort Study Checklist
CASP Economic Evaluation Checklist	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.

☑ Yes ☐ Can't tell ☐ No

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 is reasonable to do so?

Due to high heterogenecity : I square>50%

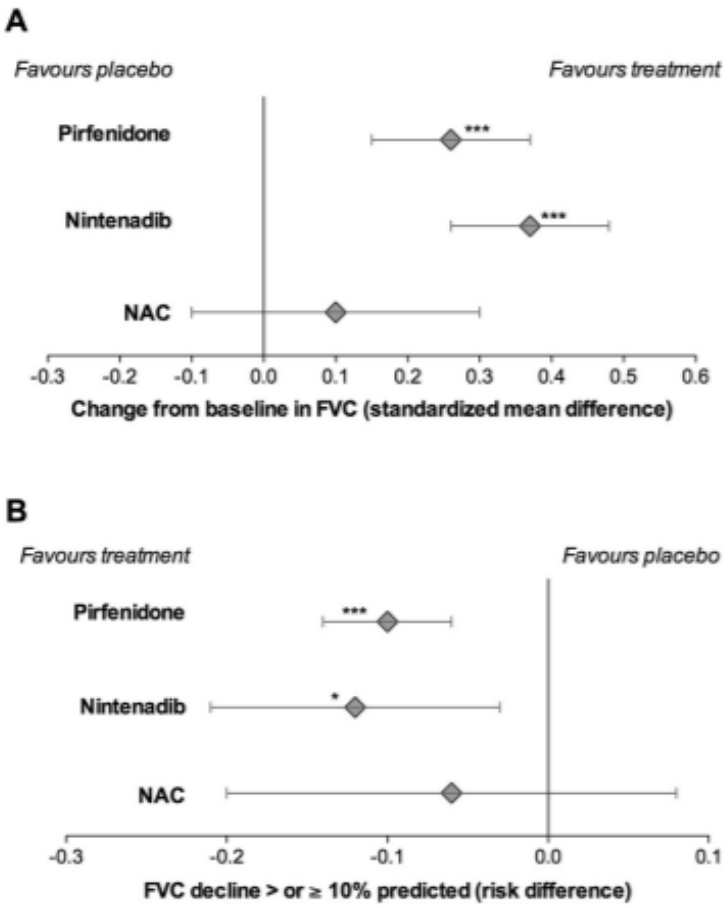
The analysis was performed via a binary random-effects model [20–23]. Values have been expressed as mean difference (MD), standardized MD (SMD), or risk difference (RD) and 95% confidence interval (CI) for the impact of pirfenidone, nintedanib and NAC on the examined variables.

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 ?



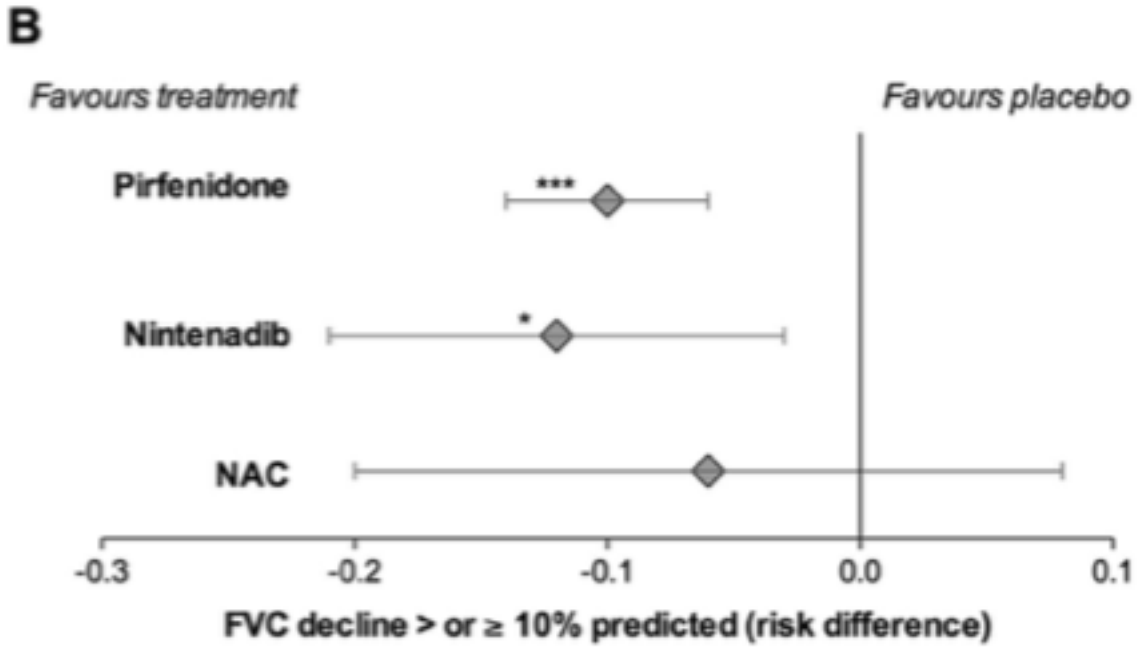
FVC decline

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?



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

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

Yes | Can't tell | No

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_{CO} (% 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)	PaO2≥70 mmHg at rest; SpO2 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 SpO2 and the lowest SpO2 during a 6MET; the lowest SpO2 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%; FEV1/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/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

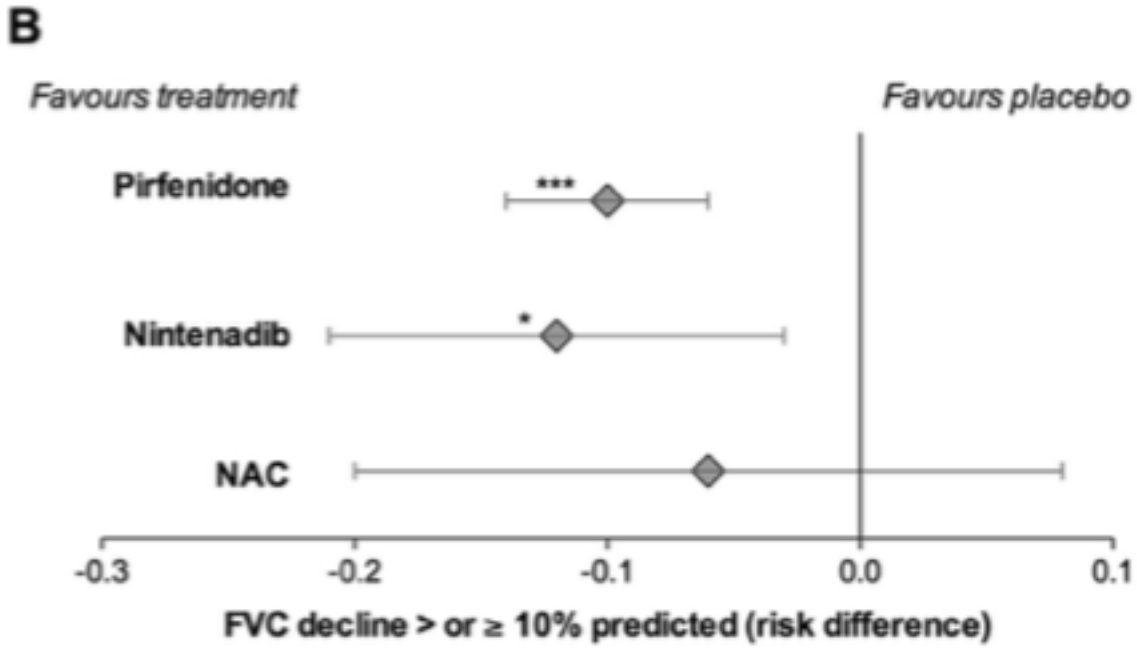
Adverse events were reported in 12 RCTs (treated n = 2,261, placebo n = 1604).

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 (≥1/10) adverse events associated with the administration of approved dose of pirfeninone 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 (≥1/10) and 87% of common (≥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?

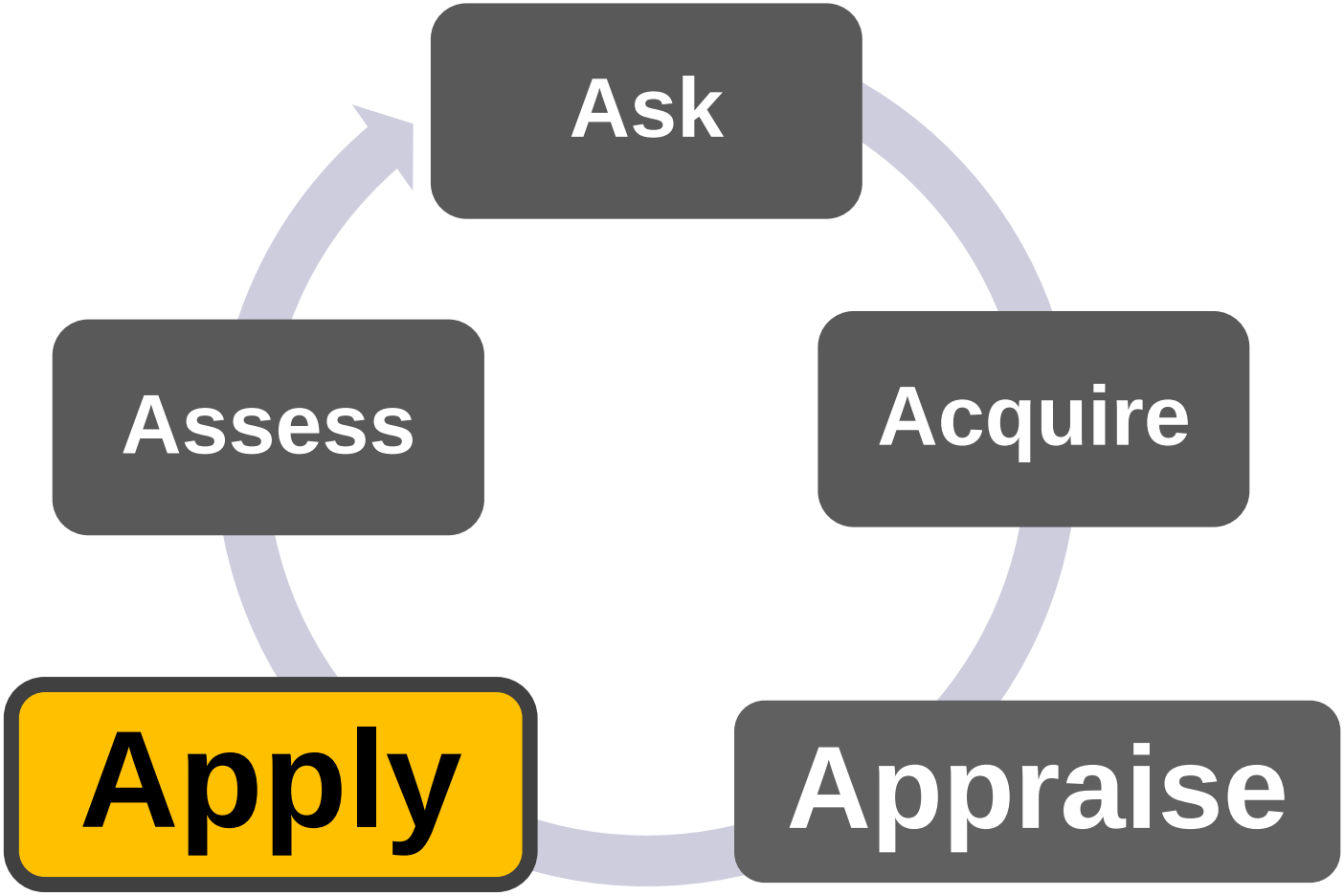


FVC decline

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)

回答病人問題

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)
How common is the problem?	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
Is this diagnostic or monitoring test accurate? (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
What will happen if we do not add a therapy? (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
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-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
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-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
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (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 ！