한국 기관지확장증 Diagnostic Bundle : Delphi 연구 결과

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Agenda

- Why a diagnostic bundle matter?
- How the expert consensus made during modified Delphi survey?
- The results of consensus recommendations
- Discussion points

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Disease heterogeneity

- Hallmark of bronchiectasis
  - radiology
  - clinical manifestations
  - microbiologic diagnosis
  - pulmonary function test
  - etiology

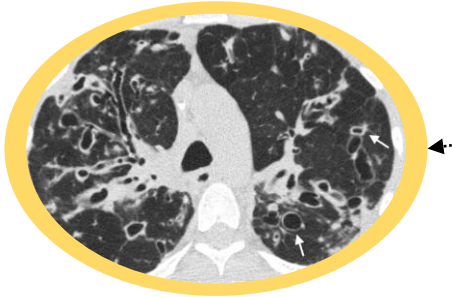


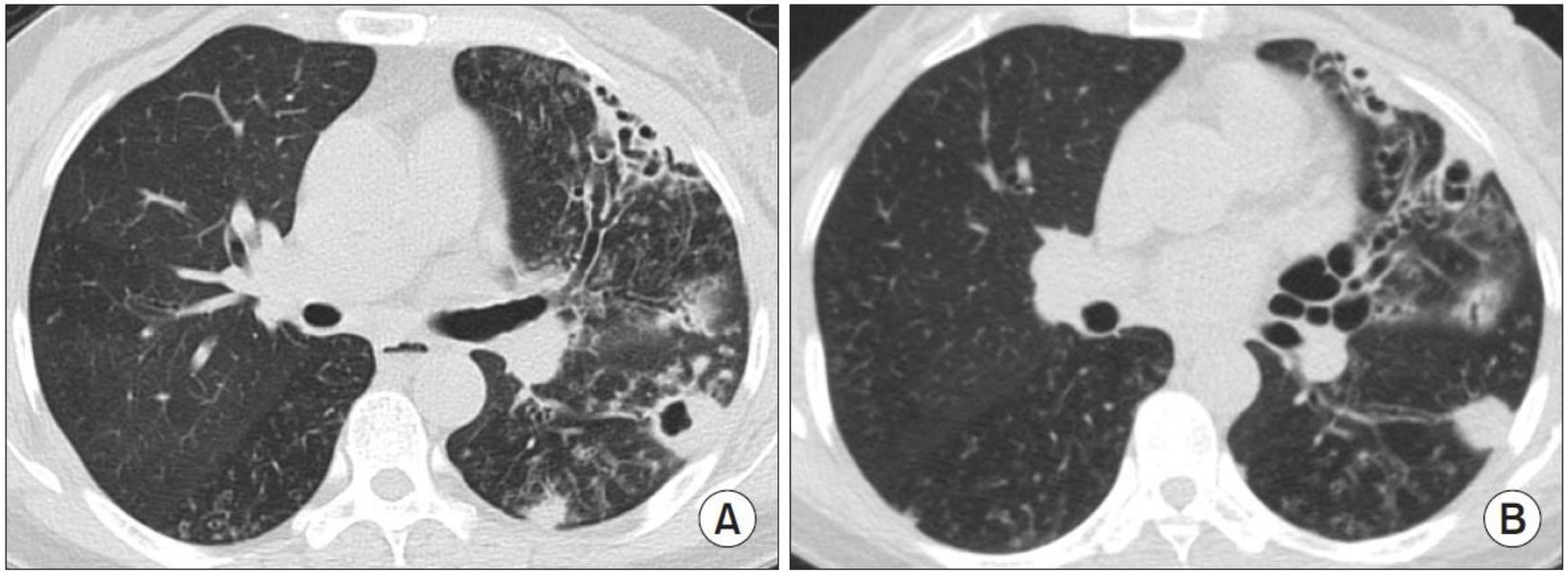
Image: https://www.mskcc.org/

Bronchiectasis etiology

- Congenital
  - Cystic fibrosis
  - Primary ciliary dyskinesia
  - Alpha-1 anti-trypsin deficiency
  - Primary Immunodeficiency
- Idiopathic
- Acquired
  - Post-infective
  - Post-obstructive
  - GERD/aspiration
  - Secondary Immunodeficiency
  - Connective tissue disease
  - Inflammatory bowel disease
  - COPD
  - Asthma
  - ABPA

Etiology evaluation

- May improve patients' symptoms and long-term outcomes

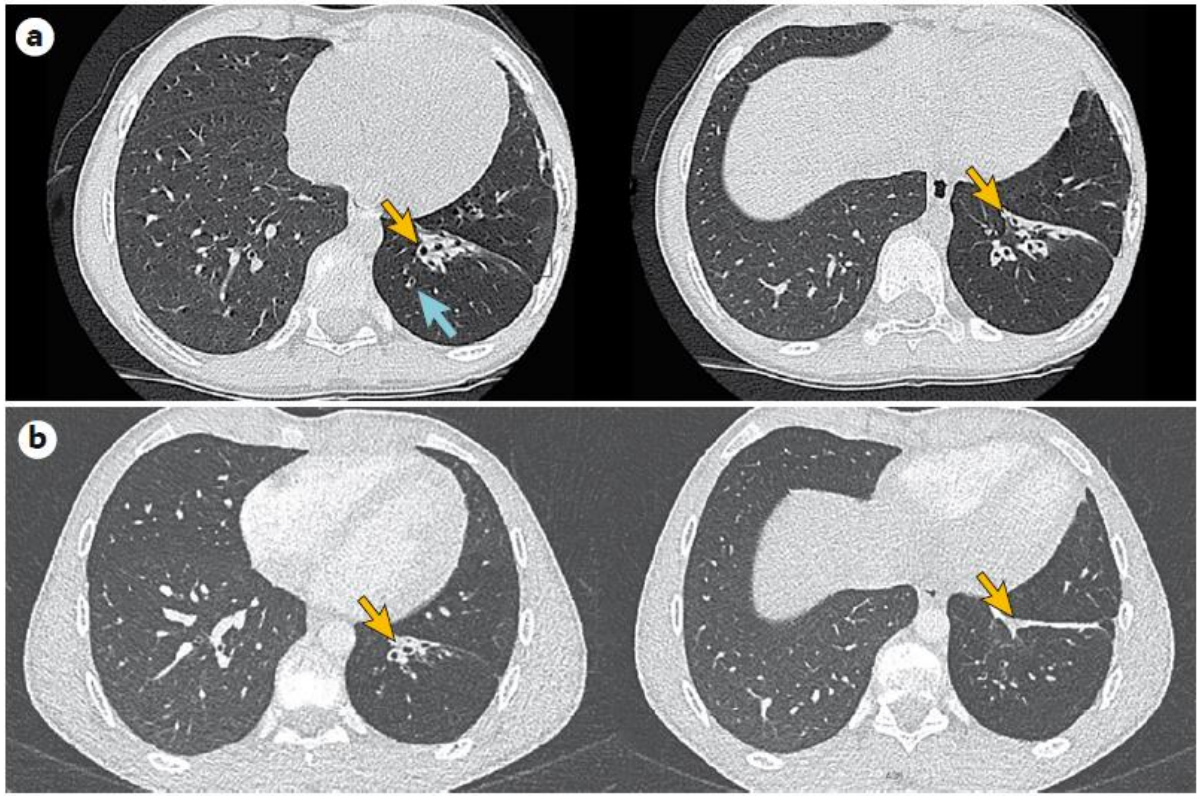


61/F with *M. avium* pulmonary disease
- 12-month of treatment

Kwon *et al. Tuberc Respir Dis* 2019;82:15

Etiology evaluation

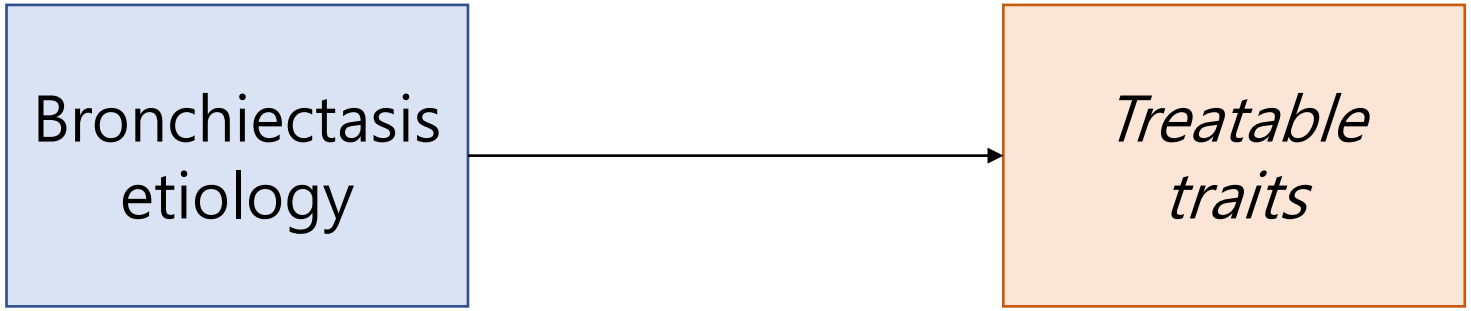
- Might even terminate bronchiectasis



5-year-old child
- common variable immunodeficiency
- >3 years of IV immunoglobulins

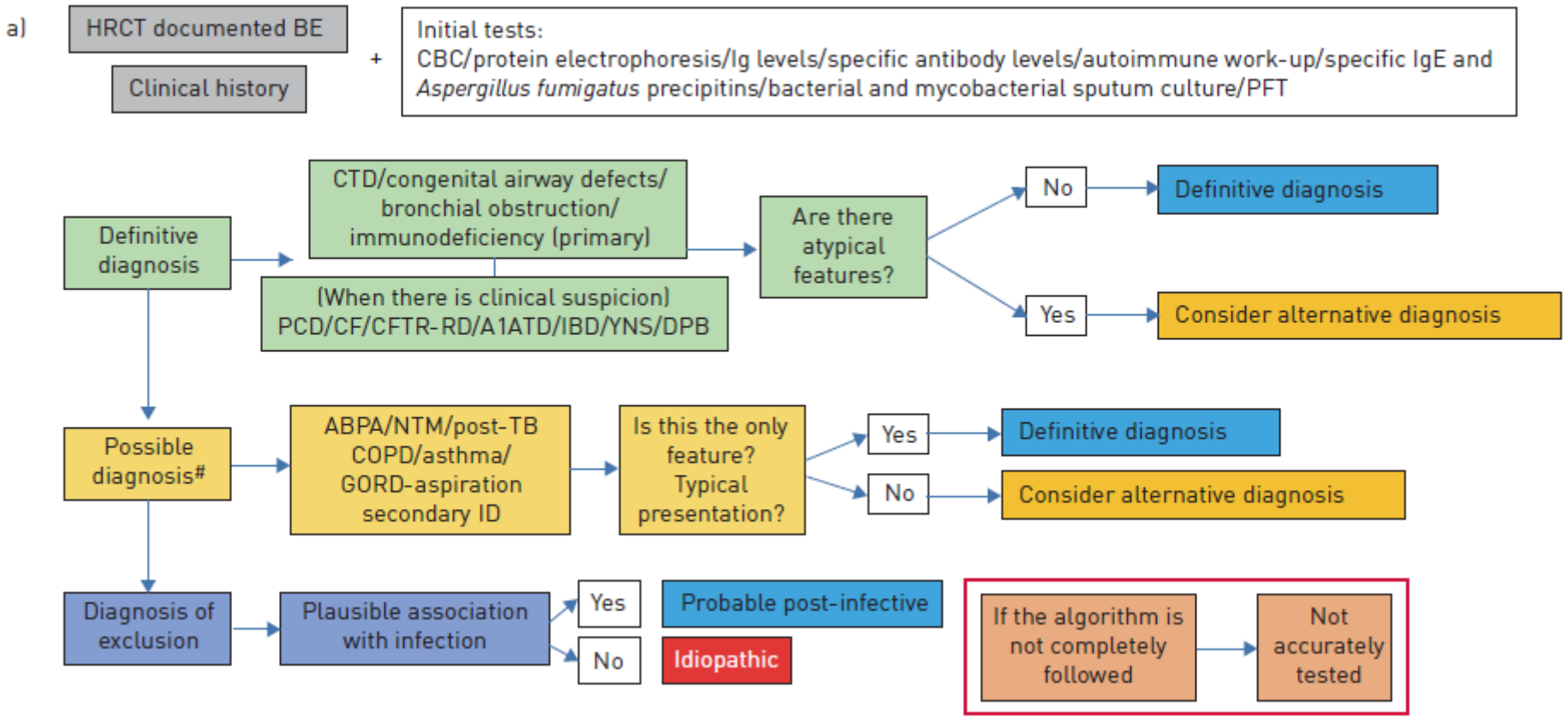
Gailard *et al. Eur J Radiol* 2003;47:215

Etiology evaluation



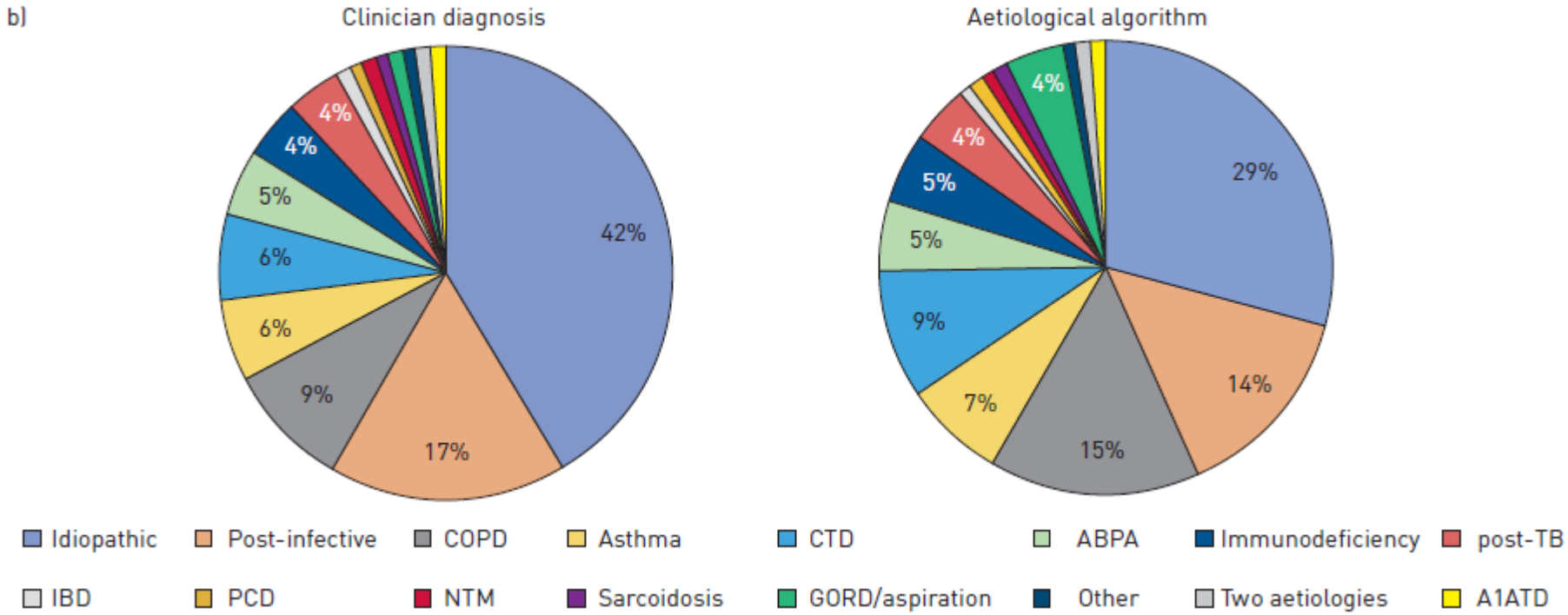
- **Crucial role** in the management of bronchiectasis

Standardized etiologic algorithm



Araujo *et al. Eur Respir J* 2017;50:1701289

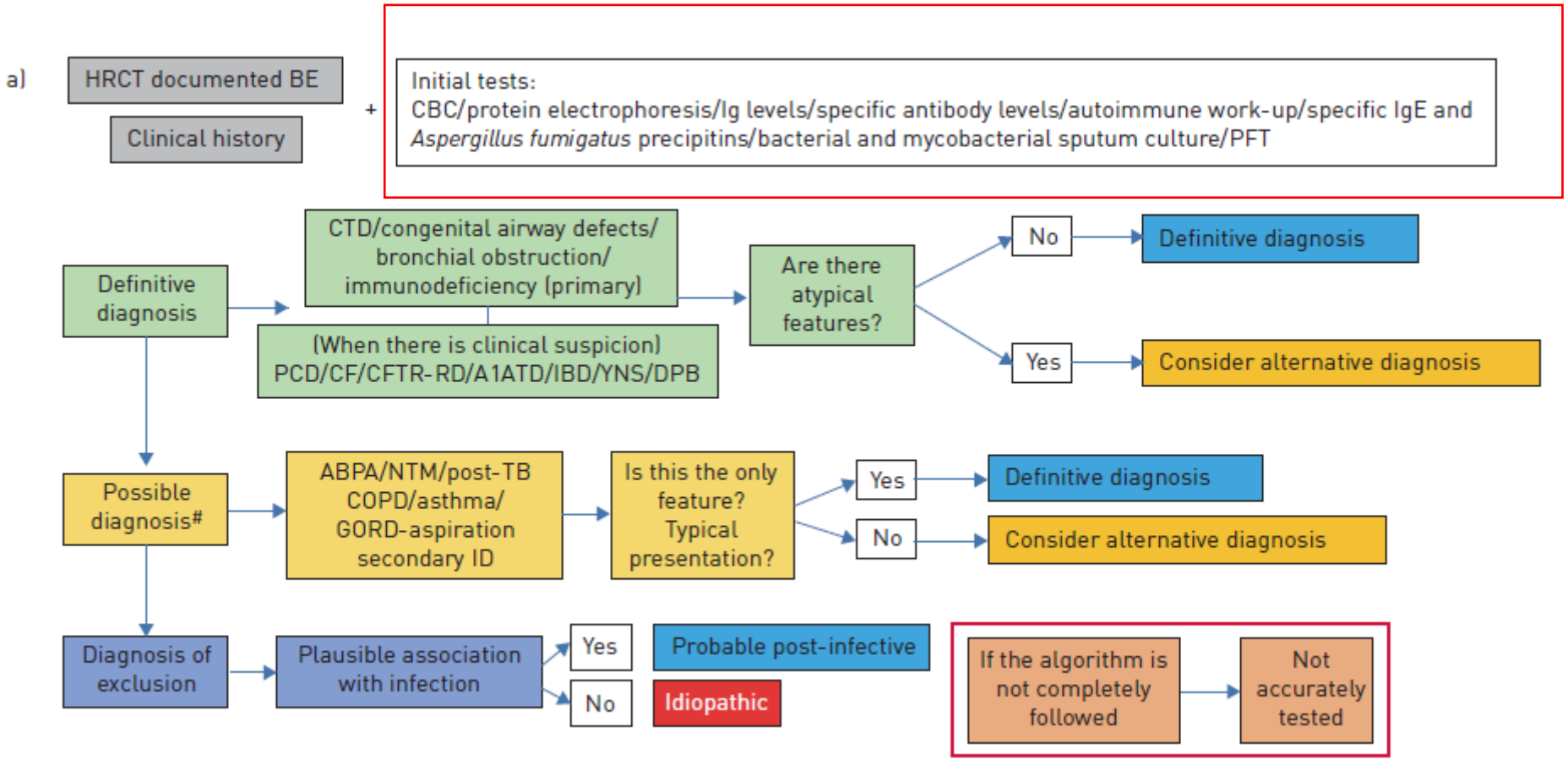
Standardized etiologic algorithm



Idiopathic etiology: **42%** → **29%**

Araujo *et al. Eur Respir J* 2017;50:1701289

Standardized etiologic algorithm



Araujo *et al. Eur Respir J* 2017;50:1701289

ERS Guideline 2017

- Minimum bundle
  - CBC with differential count
  - Serum immunoglobulin (A, G, M)
  - ABPA testing
    - Serum IgE level, specific IgE and IgG, *Aspergillus* skin test
  - Routine sputum culture

  Other testing as dictated by clinical data
    - Mycobacterial culture

Polverino *et al. Eur Respir J* 2017;50:1700629

BTS Guideline 2019

- <u>All patients</u>
  - CBC with differential count
  - Serum immunoglobulin (A, G, M)
  - ABPA testing
  - Routine and mycobacterial sputum culture (stable state)
  - Specific Ab levels against capsular polysaccharide pneumococcal vaccine
  - Spirometry

- Patients with supporting clinical features
  - Reflux and aspiration
  - PCD
  - CF

Hill *et al. Thorax* 2019;74:1

Minimum bundle suggested tests

	BTS 2019	ERS 2017	Separ 2017	Saudi 2017	Portuguese 2016	New Zealand 2015
Differential blood count	O	O	O	O		O
IgG, IgA, IgM	O	O	O	O	O	O
ABPA-specific IgE	O	O		O	O	O
Total IgE	O	O	O	O		O
Sputum bacterial & mycobacterial culture	O	O	O	O	O	O
Spirometry	O		O	O	O	O
Alpha1-antitrypsin					**O**	
Serum protein electrophoresis			O	O	O	
Specific *S. pneumoniae* Ab	O			O		

Amati et al. Semin Respir Crit Care Med 2021;42:513

Why develops a diagnostic bundle?

- Geographical heterogeneity in Bronchiectasis

- Changes in Korea
  - Epidemiologic studies
  - Korean Bronchiectasis Registry – KMBARC
  - KATRD Bronchiectasis Study Group

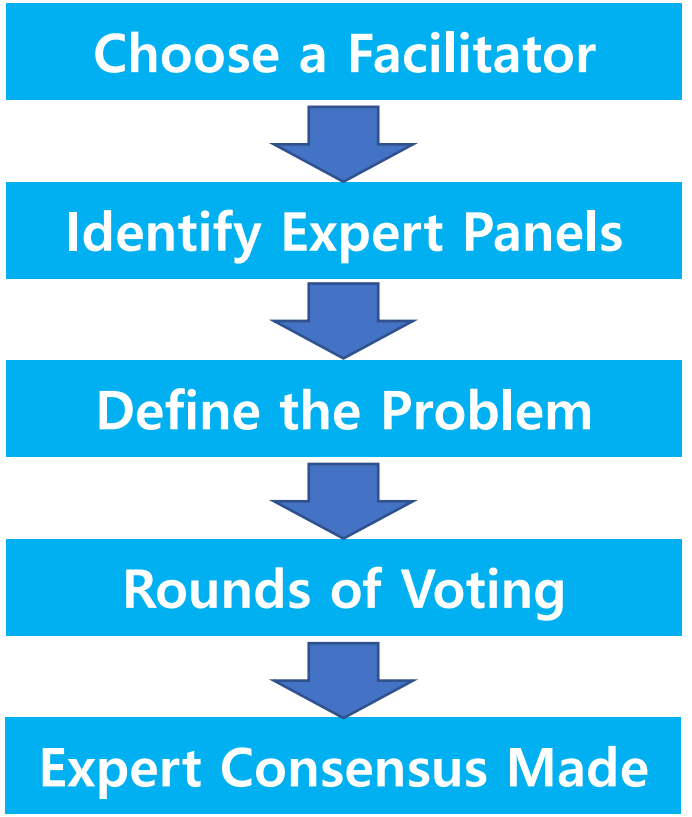
Agenda

- Why a diagnostic bundle matter?
- How the expert consensus made during modified Delphi survey?
- The results of consensus recommendations
- Discussion points

Delphi method

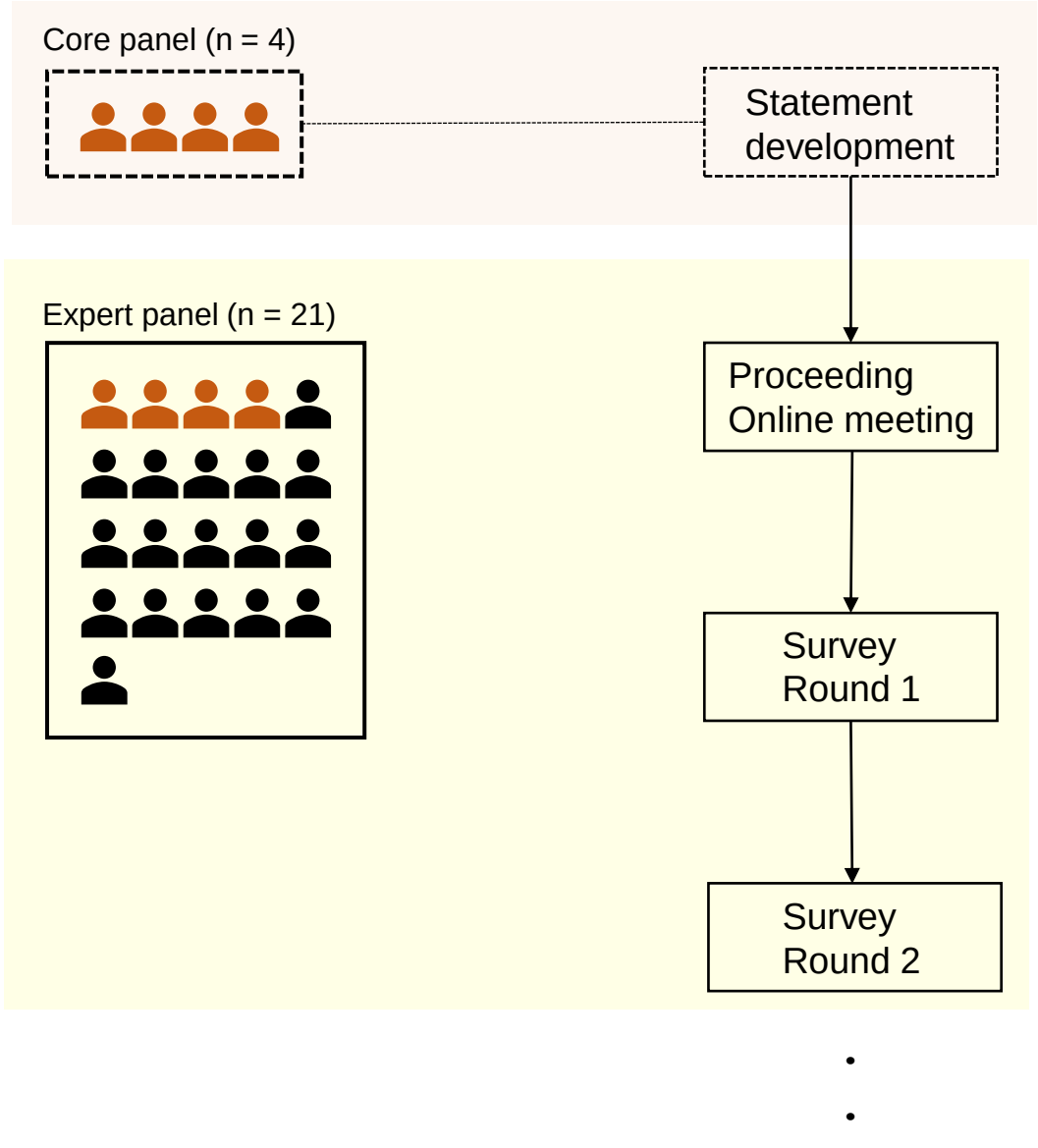
- Healthcare settings
  - Reliable means of determining consensus
  - for a defined clinical problem

- modified Delphi method
  - expert interaction (face-to-face meeting)



Eubank et al. BMC Medical Research Methodology 2016;16:56
What is Delphi Method https://www.youtube.com/watch?v=ESxuo1CePZI

Process of a modified Delphi method



Statement development

- Core panel (n = 4)
  - YMO, SWR, HL, HC




- Based on
  - International Bronchiectasis Practice Guidelines
    - ERS 2017
    - BTS 2019
  - KMBARC baseline data
  - Recent research results
    - Aspergillosis diagnostic tests
    - Sinus exam

Expert panel

- 기관지확장증 연구회 (n = 16)
  - KHY, YBP, JHL, DKK, YSK, SWL, CK, CKR, SJL, HYP, JYJ, JHL

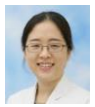













  - YMO, SWR, HL, HC

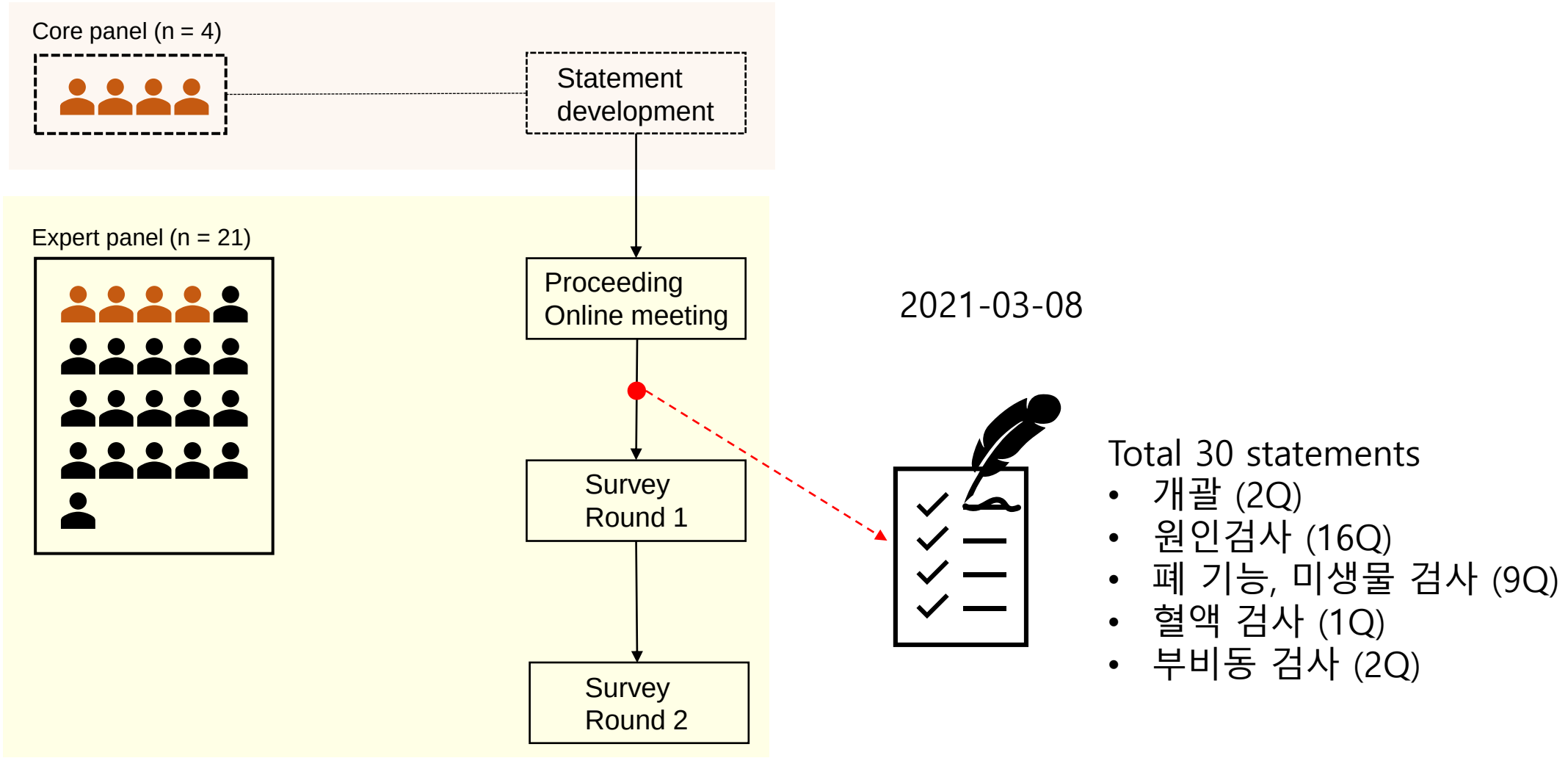
- COPD 연구회 (n = 2)
  - KHM, JGJ


- 결핵 연구회 (n = 2)
  - KWJ, BWJ


- 소아청소년과 (n = 1)
  - EHC

YJK

Process of a modified Delphi method



Statements for Survey Round 1

Section 1. Overview	
Q1	Standardized diagnostic bundle for bronchiectasis is useful in clinical practice
Q2	Additional tests should be performed in patients aged < 50 years without definite cause (tests for PCD, CF, A1AD, immunodeficiency)
Section 2. Tests to search for the causes of bronchiectasis	
Q3	All patients should receive chest CT when first diagnosed with bronchiectasis.
Q4	All patients should receive tests related to ABPA.
Q5	Tests related to ABPA should be performed in patients with asthma history.
Q6	Serum Ig levels (Ig G, Ig A, Ig M) should be measured in all patients.
Q7	Serum Ig levels (Ig G, Ig A, Ig M) should be measured only when immunodeficiency suspected (recurrent infections).
Q8	Baseline level of specific Ab to *S. pneumoniae* capsular polysaccharides should be measured in all patients.

Statements for Survey Round 1

Q9	Repetitive measurement of level of specific Ab to *S. pneumoniae* capsular polysaccharides should be done 4-8 weeks after pneumococcal 23 polyvalent vaccine injection in all patients.
Q10	Baseline level of specific Ab to *S. pneumoniae* capsular polysaccharides should be measured only when immunodeficiency suspected (recurrent infections).
Q11	Repetitive measurement of level of specific Ab to *S. pneumoniae* capsular polysaccharides should be done 4-8 weeks after pneumococcal 23 polyvalent vaccine injection only when immunodeficiency suspected, and the baseline level was low.
Q12	Autoimmune markers (FANA, RF, anti-CCP, ANCA) should be measured in all patients.
Q13	Autoimmune markers should be measured only when rheumatologic diseases are suspected.
Q14	When PCD suspected, clinicians should refer patients to institutions where diagnostic tests are available.
Q15	Questionnaires of high diagnostic sensitivity should be used for differential diagnosis of PCD in patients aged < 50 years without definite cause

Statements for Survey Round 1

Q16	When A1AD suspected, clinicians should refer patients to institutions where diagnostic tests are available.
Q17	In patients aged < 50 years without definite cause and show panacinar emphysema, A1AD tests should be performed.
Q18	When CF suspected, clinicians should refer patients to institutions where diagnostic tests are available.
Section 3. Pulmonary function tests and microbiological tests	
Q19	Pre-BD spirometry should be performed in all patients.
Q20	Post-BD spirometry should be performed in all patients.
Q21	Diffusing capacity should be measured if indicated.
Q22	Lung volume should be measured if indicated.
Q23	Sputum gram stain and bacteria culture in all patients.
Q24	Sputum AFB stain and culture in all patients.

Statements for Survey Round 1

Q25	Sputum fungus culture in all patients.
Q26	All patients should receive tests for chronic pulmonary aspergillosis.
Q27	Tests for chronic pulmonary aspergillosis should be performed only patients with chronic pulmonary diseases and CPA suspected.
Section 4. Laboratory tests	
Q28	All patients should receive CBC and blood chemistry (LFT, BUN, Cr, CRP).
Section 5. Paranasal sinus tests	
Q29	All patients should receive PNS X-ray.
Q30	All patients should receive PNS CT.

Survey Round 1

2021-03-24 ~ 2021-04-15

번호	구분	문항	매우 동의	동의	보통	비동의	전혀 비동의
3	원인 검사	기관지확장증 첫 진단 시에 모든 환자에서 흉부 전산화 단층 촬영을 시행해야 한다.	1	2	3	4	5
4		기관지확장증 첫 진단 시에 모든 환자에서 Allergic bronchopulmonary aspergillosis 관련 검사를 시행해야 한다(CBC, total IgE, Specific IgE or skin test for *Aspergillus fumigatus*). *(배경: 2017년 유럽호흡기학회 기관지확장증 진료 지침[이하, 2017 ERS Guideline]과 2019 BTS Guideline은 필수 검사로 추천, ABPA는 영국 기관지확장증 원인의 1~11% 차지, KMBARC Baseline 데이터 분석 결과 33% 환자에서 ABPA 검사 시행)*	1	2	3	4	5
5		Allergic bronchopulmonary aspergillosis 관련 검사는 천식 병력이 있는 환자에게서만 시행해야 한다.	1	2	3	4	5
6		기관지확장증 첫 진단 시에 모든 환자에서 serum immunoglobulin level (IgG, A, M)을 측정해야 한다 (B 세포 면역 검사). *(배경: 2017 ERS 및 2019 BTS Guideline은 필수 검사로 추천, 면역 저하 질환은 유럽 기관지확장증 원인의 5~6% 차지 [immunoglobulin 보충으로 예후를 크게 호전시킬 수 있기 때문], KMBARC Baseline 데이터 분석 결과 16.7% 환자에서 immunoglobulin 검사를 시행하였으며, 검사 환자의 2~5.4%에서 감소 확인)*	1	2	3	4	5
		수정 및 추가의견:					

Survey Round 1

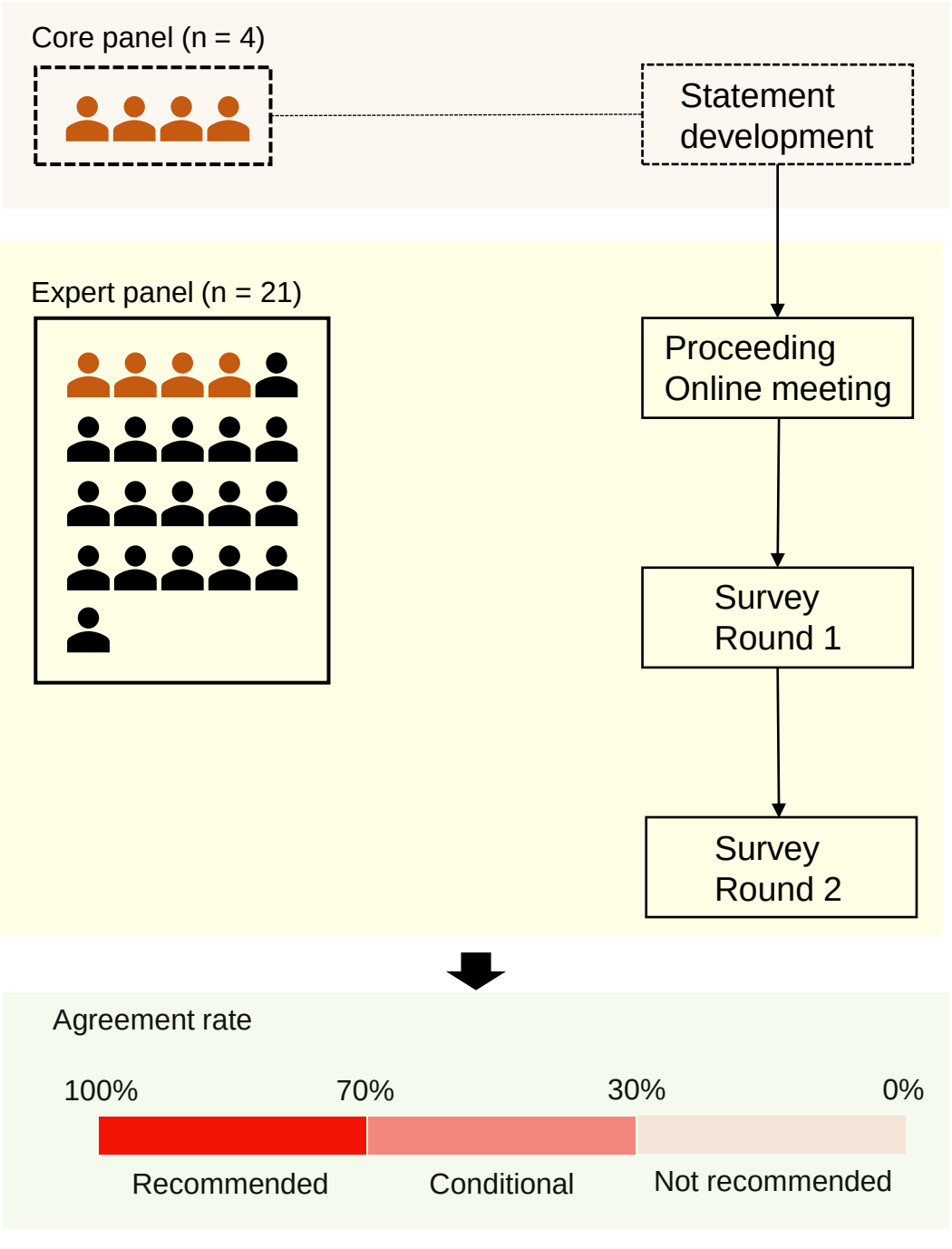
2021-03-24 ~ 2021-04-15

31	종 합	1차, 2차 설문의 전문가 패널 의견을 종합한 결과(답신한 패널 최소 12명 이상의 문항에 대해서)를 통한 검사 권고 여부의 적절한 cut-off 는? *(예: 70%/30% cut-off: 70% 이상의 패널이 동의하면 해당 검사 권장, 30~69% 동의하면 해당 검사 시행은 담당 의사/환자 선택 사항, 30% 미만 동의하면 해당 검사 권장하지 않음)* A) 70%/30% cut-off B) 80%/30% cut-off C) 70%/20% cut-off D) 80%/20% cut-off

Survey Round 2

2021-05-07 ~ 2021-05-13

번호	구분	동의율/비동의율		문항	매우 동의	동의	보통	비동의	전혀 비동의
6	원인 검사	1차	60%/35%	Allergic bronchopulmonary aspergillosis 관련 검사는 천식 병력이 있는 환자에게서만 시행해야 한다.					
		2차 문항		Allergic bronchopulmonary aspergillosis 관련 검사는 천식 병력이 있는 기관지확장증 환자에게서만 시행해야 한다.	1	2	3	4	5
		수정 및 추가의견 :							
7		1차	40%/30%	기관지확장증 첫 진단 시에 모든 환자에서 serum immunoglobulin level (IgG, A, M)을 측정해야 한다 (B 세포 면역 검사). *(배경: 2017 ERS 및 2019 BTS Guideline은 필수 검사로 추천, 면역 저하 질환은 유럽 기관지확장증 원인의 5~6% 차지 [immunoglobulin 보충으로 예후를 크게 호전시킬 수 있기 때문], KMBARC Baseline 데이터 분석 결과 16.7% 환자에서 immunoglobulin 검사를 시행하였으며, 검사 환자의 2~5.4%에서 감소 확인)*					
		2차 문항		기관지확장증 첫 진단 시에 50세 미만의 젊은 환자에게서는 혈액 면역글로불린 측정 검사를 시행해야 한다.	1	2	3	4	5
8		1차	60%/30%	Serum immunoglobulin level (B 세포 면역) 검사는 면역 저하 질환이 의심되는 환자 (예: 반복적인 감염)에서만 시행해야 한다.					
		2차 문항		혈액 면역글로불린 측정 검사는 면역 저하 질환이 의심되는 환자에게서만 시행해야 한다.	1	2	3	4	5


Core panel (n = 4)
Statement development
Expert panel (n = 21)
Proceeding Online meeting
Survey Round 1
Survey Round 2
Agreement rate
100%
70%
30%
0%
Recommended
Conditional
Not recommended

Agenda

- Why a diagnostic bundle matter?
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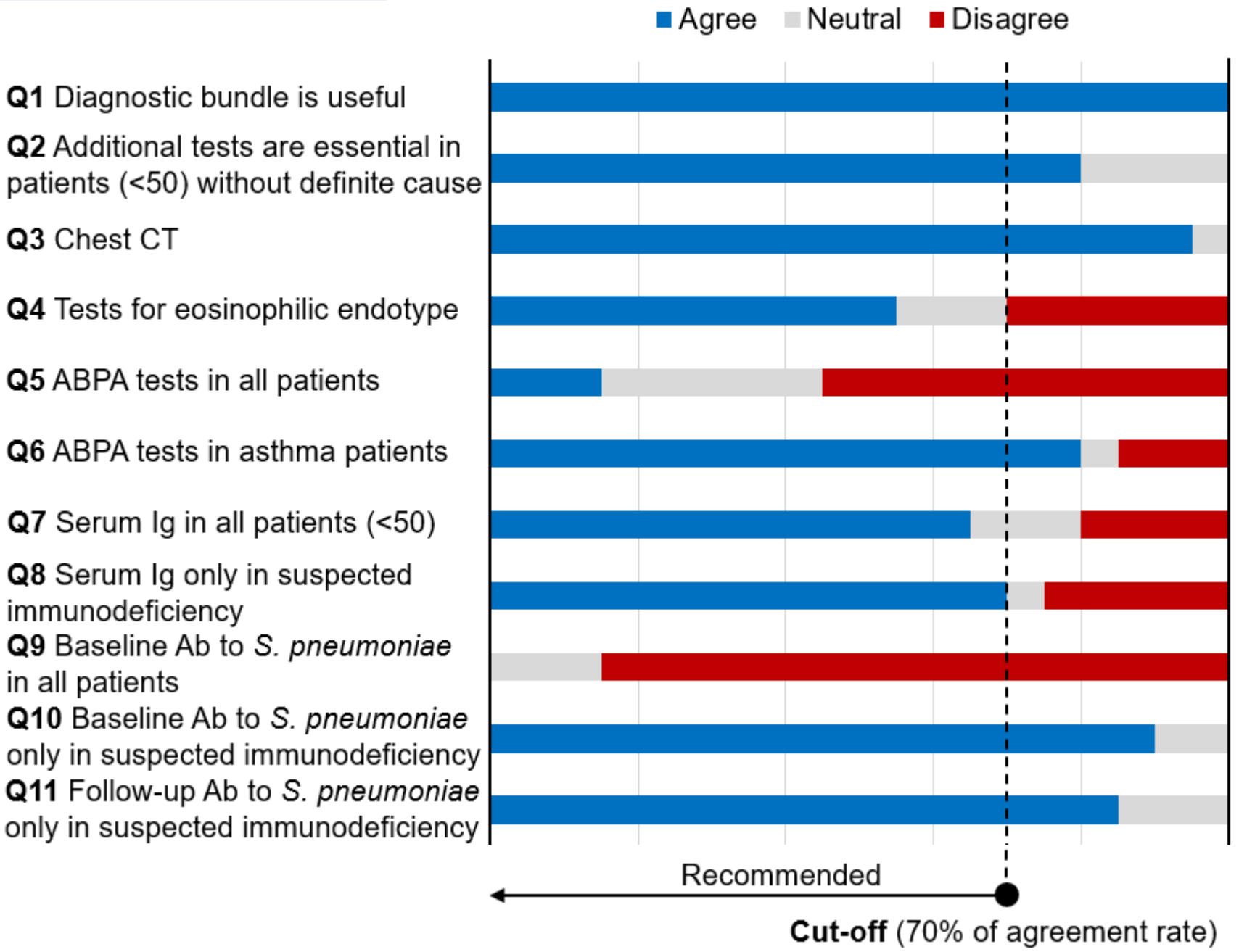
- The results of consensus recommendations
  - Agreement rate of Survey round 2
  - Summary of recommendations
- Discussion points

Response rate = 20/21 (95%)



Summary of recommendations

- **Recommended**
  - In all patients
    - chest CT
    - pre- and post-bronchodilator spirometry
    - sputum G/S & culture, sputum AFB stain & culture
    - CBC and blood chemistry (LFT, BUN, Cr, CRP)
    - PNS X-ray
  - In patients aged < 50 years without definite cause
    - additional tests beyond diagnostic bundle

Summary of recommendations

- **Recommended**
  - When indicated
    - ABPA tests – asthma history
    - Serum Ig – immunodeficiency suspected
    - Baseline and follow-up specific Ab to *S. pneumoniae* capsular polysaccharide – immunodeficiency suspected
    - Autoimmune markers – rheumatologic diseases suspected
    - Chronic pulmonary aspergillosis tests – when suspected

Summary of recommendations

- **Recommended**
  - Concerning rare diseases
    - Refer patients – suspected PCD, CF, A1AD
    - Patients aged < 50 years without definite cause – PCD questionnaire
    - Patients aged < 50 years without definite cause + panacinar emphysema – tests for A1AD

Summary of recommendations

- **Not recommended**
  - In all patients
    - ABPA tests
    - Baseline specific Ab to *S. pneumoniae* capsular polysaccharide
    - Sputum fungus culture
    - CPA tests
    - PNS CT

Summary of recommendations

- **Conditional**
  - In all patients
    - Test to check eosinophilic endotype (CBC, Total Ig E)
    - Diffusing capacity
    - Lung volume measurements
  - In patients aged < 50 years
    - Serum Ig (Ig G, Ig A, Ig M)
    - Autoimmune markers

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1

Bronchiectasis **Epidemiology**

- Why bronchiectasis increases?
  - More extensive use of **chest CT**
  - Increase in **life expectancy**
  - Rising prevalence
    - **Different diseases or conditions**
    - Associated with bronchiectasis

Amati *et al.* Semin Respir Crit Care Med 2021;42:513

2

Etiology to Phenotypes & Endotypes

Mucus
Mucus hypersecretion
vs Dry cough

Exacerbation
Frequent
vs Infrequent

Microbiology
Chronic infection
vs None

P. aeruginosa

NTM

Other bacteria

- Acquired
  - Post-infective
  - Post-obstructive
  - GERD/aspiration
  - Secondary Immunodeficiency
  - Connective tissue disease
  - Inflammatory bowel disease
  - COPD
  - Asthma
  - ABPA
- Congenital
  - Cystic fibrosis
  - Primary ciliary dyskinesia
  - Alpha-1 anti-trypsin deficiency
  - Primary Immunodeficiency
- Idiopathic

Neutrophilic inflammation

Eosinophilic inflammation

Impaired mucociliary clearance

Amati et al. Semin Respir Crit Care Med 2021;42:513

Summary

- Korean diagnostic bundle for bronchiectasis
  - A modified Delphi method
  - 21 experts and 30 statements
    - Recommended/conditional/not recommended

- Recommended
  - All patients: Chest CT, spirometry, sputum culture, CBC & blood che mistry, PNS X-ray
  - When indicated: ABPA, Serum Ig, autoimmune markers, CPA tests

- Future bronchiectasis clinical practice guideline

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