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Global survey of physician testing practices for non-tuberculous mycobacteria

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Take home message:

Testing for non-tuberculous mycobacteria is influenced by underlying disease, symptoms and radiological changes. For some patients, such as those initiating macrolide therapy, guidelines are not being followed and clear testing recommendations are needed.

Abstract:

Background Certain patients are at greater risk of developing non-tuberculous mycobacterial pulmonary disease (NTM-PD), including those with lung conditions such as bronchiectasis. Testing for non-tuberculous mycobacteria (NTM) in patients at risk is necessary to identify NTM-PD and start appropriate management. The aim of this survey was to evaluate current testing practices for NTM and identify testing triggers.

Methods Physicians (n=455) who see ≥1 patient with NTM-PD in a typical 12-month period and test for NTM as part of practice from Europe, the USA, Canada, Australia, New Zealand and Japan participated in a 10-min anonymised survey on NTM testing practices.

Results Bronchiectasis, chronic obstructive pulmonary disease (COPD) and use of immunosuppressants were the factors most likely to prompt testing among physicians in this survey (90%, 64% and 64%, respectively) with radiological findings the most common reason leading to considering NTM testing in patients with bronchiectasis and COPD (62% and 74%, respectively). Macrolide monotherapy in patients with bronchiectasis and inhaled corticosteroid use in patients with COPD were not important triggers for testing (15% and 9% of physicians, respectively). Persistent cough and weight loss triggered testing in >75% of physicians. Testing triggers were markedly different for physicians in Japan, with CF prompting testing in fewer physicians compared with other regions.

Conclusions Testing for NTM is influenced by underlying disease, clinical symptoms or radiological changes, but clinical practice varies considerably. Adherence to guideline recommendations for NTM testing is limited in certain patient subgroups and varies across regions. Clear recommendations on NTM testing are needed.

Introduction

Non-tuberculous mycobacterial pulmonary disease (NTM-PD) is a rare, difficult-to-treat lung condition that is associated with a substantial patient burden [1–4]. The prevalence of NTM-PD is increasing globally, [5] and recent predictions estimate many patients are undiagnosed [6, 7]. NTM-PD is associated with significant mortality [8–11] therefore timely diagnosis is important. However, NTM-PD can be challenging to diagnose because of a low index of suspicion and symptoms that are non-specific and overlap with those of coexisting lung conditions [12, 13].

Certain patient groups have been demonstrated to have an increased risk of NTM-PD, such as those with underlying lung conditions including non-cystic fibrosis bronchiectasis, chronic

obstructive pulmonary disease (COPD) and cystic fibrosis (CF) as well as those treated with immunosuppressants and systemic or inhaled steroids [14, 15]. Other commonly associated factors include low body mass index and thoracic skeletal abnormalities [16, 17]. Testing for non-tuberculous mycobacteria (NTM) in patients at risk is important to identify NTM-PD early and start treatment in appropriate patients; early recognition, diagnosis and treatment may prevent disease progression [4, 18, 19].

A patient survey highlighted the need to raise awareness of NTM among all healthcare professionals including primary care physicians as well as the need for faster diagnosis and access to NTM-PD specialists [20]. A physician survey of perceived risk of NTM-PD in patients with bronchiectasis across Europe found physicians understand the risk of NTM-PD and associated morbidity in patients with bronchiectasis, however, most do not test for NTM-PD even in circumstances where guidelines recommend it [21]. The aim of the current survey was to evaluate current testing practices for NTM across geographies and identify testing triggers and adherence to current guideline recommendations.

Methods

Physicians from Europe (UK, France, Germany, Italy, Spain and the Netherlands), the USA, Canada, Australia, New Zealand and Japan were invited to participate in a 10-min anonymised survey on NTM testing practices via a secure online platform. Physicians invited to take part were recruited as part of the SERMO clinician networking platform (London, UK) panel members and recruitment took place via email. All panellists active in the past 365 days who were registered as practicing in the target specialties of respiratory medicine, pulmonary medicine, internal medicine, or infectious diseases were invited to be screened on study eligibility. Inclusion criteria were set for the parameters of NTM caseload and testing; physicians were required to see at least one patient with NTM-PD in a typical 12-month period and requested or refered for NTM testing as part of their practice. Target sample sizes for each country were designed in consideration of 1) the estimated number of physicians seeing NTM within the target specialties and 2) specialty-specific response rates observed on prior surveys in the field of NTM. A breakdown of response rates observed in this study are shown in supplementary table S3.

The survey was conducted in the physician's native language. Physicians received honorarium for completing the survey in line with current accepted standards. All registered panellist credentials were verified against bodies that maintain official registers of pulmonologists in each country. SERMO processes are in line with ISO 20252.

The survey instrument was developed in consultation with a range of stakeholders including external experts (Michael Loebinger, Royal Brompton Hospital, UK and Jakko van Ingen, Radboudumc, the Netherlands) and Insmed B.V., the Netherlands and implemented by Porterhouse Insights, UK. Respondents were recruited by Porterhouse Insights. Informed consent was collected, in adherence with the British Healthcare Business Intelligence Association and Market Research Society and the European Pharmaceutical Market Research Association guidelines [22, 23].

The survey was conducted between 6 August and 2 September 2021. The full survey questionnaire included 5 screening questions and 14 survey questions on NTM testing practice (see supplementary tables S1 and S2). The survey data were analysed using contingency tables that were created using QPSMR version CL 64 2021.2c. Descriptive statistics were employed looking at the sub-groups and populations with the use of T-tests to highlight statistically significant differences.

Results

Survey respondent demographics

Overall, 455 physicians completed the survey across Europe (61%; n=276), North America (23%; n=104), Australasia (5%; n=25) and Japan (11%; n=50). The majority were in the specialty of pulmonology or respiratory medicine (63%; n=288), with smaller numbers in internal medicine (11%; n=49) and infectious diseases (25%; n=113). A full breakdown of respondents' countries and specialties are presented in table 1. Physicians' caseloads varied with 42% seeing >10, 28% seeing 6–10 and 29% seeing ≤5 patients with NTM-PD in a typical 12-month period.

Patient profiles prompting NTM testing

Most regions were generally aligned regarding the patient profiles that prompted testing. Patients with bronchiectasis were the most frequently tested for NTM, with 90% of physicians globally considering testing patients with this condition (figure 1). For those who tested patients with bronchiectasis (n=409), testing was primarily considered following the results of radiological examination (62%; n=254) or on presentation of specific clinical symptoms (such as weight loss or haemoptysis) (56%; n=230), while few considered testing patients at initial presentation (24%; n=100) (figure 2).

In contrast, macrolide use was rarely mentioned, with 24% of physicians overall considering testing for NTM in patients receiving long-term macrolide therapy (figure 1) and a similarly low number considered testing patients with bronchiectasis before initiating macrolide monotherapy (15%; n=61) (figure 2). The number of physicians testing for NTM in patients with bronchiectasis using ICS was even lower (7%; n=28).

COPD and use of immunosuppressants were considered important, prompting testing in 64% of physicians globally (figure 1). In physicians who specified testing for NTM in patients with COPD (n=293), almost three-quarters considered testing following the results of radiological examinations (74%; n=218) or on presentation of specific clinical symptoms (73%; n=213) (figure 3). Few physicians considered testing all adults with COPD (9%; n=27). There was greater variability observed between countries for frequent exacerbations as a trigger for NTM testing in patients with COPD, with 23% and 78% of physicians in Japan and Canada, respectively, reporting this as a relevant trigger.

Of physicians who specified testing for NTM in patients on immunosuppressants (n=291), 66% (n=192) of them consider testing for NTM in certain patients using steroids including corticosteroids (figure 4), yet few tested patient with COPD who were receiving ICS (9%; n=27) (figure 3). Few physicians considered receiving anticancer agents (19%) or anti-tumour necrosis factor-alpha (anti-TNFα) inhibitors (10%) as important prompts to test for NTM.

Physicians in Japan considered different patient profiles for NTM testing compared with other regions. More physicians in Japan considered testing for NTM in patients with asthma (38% versus 24% globally) or age (42% versus 24% globally) compared with other cohorts (figure 1). Additionally, only 20% of physicians in Japan considered testing in patients with CF.

In contrast, CF was an important prompt for testing in all other regions (53–70% of physicians), particularly in European countries (70%). In the physicians who specified testing for patients with CF (60%; n=274), half (50%; n=137) considered testing all adults with CF. Physicians in Canada and Australia/New Zealand were more likely to consider testing all adults with CF compared with other regions (71% and 73%, respectively). Physicians in the USA and Japan were more likely to consider testing patients following the results of radiological examinations (50% and 60%, respectively) than testing all adults with CF (43% and 40%, respectively).

Symptoms prompting NTM testing

Signs and symptoms that most commonly prompted NTM testing were persistent cough and weight loss, with >75% of physicians globally considering each of these symptoms as a trigger to test (figure 5). Assessing the correlations between primary symptoms and specific patient factors, such as underlying respiratory conditions, was not possible. Haemoptysis, increased or purulent sputum and fatigue were also frequently mentioned (71%, 70% and 66%, respectively) whereas physicians rarely considered testing for NTM important for patients with persistent reflux.

There was marked variability in the symptom profiles frequently prompting testing for NTM across regions, with physicians in Japan reporting different symptom profiles compared with other countries (figure 5). Physicians with larger NTM-PD caseloads (>10 patients annually) were significantly more likely ($P<0.05$) to test a patient with increased or purulent sputum, fever, increased exacerbation frequency or worsening lung function compared with those with smaller caseloads (≤10 patients annually).

Risk factor combinations prompting NTM testing

The majority of physicians considered testing for NTM in patients presenting with a combination of symptoms and underlying disease, but generally underlying disease alone, with the exception of bronchiectasis, or medication alone rarely triggered NTM testing without the presence of clinical symptoms (figure 6). Combinations of symptoms without underlying disease or medication use were more likely to prompt testing for physicians in Japan compared with other regions. Respondents indicated they would test patients for NTM when a combination of symptoms or clinical conditions were present; on average five different risk factors were needed to prompt testing for NTM.

Symptom profiles that included persistent cough with weight loss were the most frequently mentioned, with 62% of physicians mentioning this combination of symptoms in at least one of their patient profiles that would prompt testing for NTM. Physicians also frequently mentioned profiles including persistent cough with persistent fatigue (49% of physicians) as well as persistent cough with bronchiectasis (48%), followed by combinations containing weight loss with fatigue (47%) and persistent cough with sputum production (46%).

NTM testing patterns

Upon worsening of clinical symptoms, most physicians repeated testing every 6 months. Physicians in Japan were more likely to not repeat microbiological testing compared with other regions (14% versus 3–5% of physicians, respectively) and perform radiological testing every 6 months (80% versus 54–67%, respectively). Physicians who saw >10 patients with NTM-PD per year were significantly more likely ($P<0.05$) to conduct microbiological testing every 6 months compared with those with ≤10 patients per year, but no differences were seen for radiological imaging between physicians managing different caseloads of NTM-PD patients.

Overall, mycobacterial sputum cultures were the tests most used to rule out NTM infection (91%). However, in Japan, high-resolution computed tomography scans and direct molecular tests were the more commonly used (76% and 74%, respectively), with mycobacterial sputum culture considered by 62% of physicians.

Reasons not to test for NTM were varied with many physicians choosing not to test patients without specific symptoms suggesting NTM-PD. In the USA and Australia/New Zealand many physicians decide against testing for NTM because they believe their patient is too frail to receive treatment for NTM-PD (39% and 36%, respectively). Other reasons physicians cited for not testing for NTM included ones related to lack of sufficient infrastructure, for example, lack of access to microbiological laboratories (22%), insufficient funding (12%) and lack of expert support (12%) in Europe, whereas 21% of physicians in the USA did not test because there was no satisfactory patient pathway to refer or manage patients after testing (figure 7).

Discussion

Results from this survey indicate a high threshold for NTM testing among physicians globally, but it is clear that certain symptoms, radiological changes and predisposing conditions are important drivers to test for NTM. Persistent cough and weight loss were key clinical symptoms prompting testing for respondents, suggesting that they are commonly testing patients with more advanced disease. The patients considered for testing most often were those with bronchiectasis followed by COPD, with

radiological features specifically being the most common reason for NTM testing in these patients. However, despite growing evidence [14, 24, 25] and/or guideline recommendations, macrolide monotherapy in patients with bronchiectasis and ICS use in patients with COPD were not important triggers for testing in this survey.

There were marked differences in the symptom and disease profiles that prompted testing among physicians in Japan compared with other regions, particularly for CF, which was considered an important risk factor to prompt testing by only 20% of physicians in Japan, compared with 60% globally. However, CF is rare in Asian populations and physicians in Japan are less likely to see these patients, potentially leading to CF being considered less relevant for testing for these physicians.

Guidelines on NTM testing for patients with predisposing conditions are limited to bronchiectasis and CF. Regional bronchiectasis guidelines, including the European Respiratory Society guidelines, recommend testing for NTM when NTM is suspected as the cause of bronchiectasis or at initial evaluation, in patients with radiological or clinical features of NTM-PD or prior to initiating long-term antibiotic therapy such as macrolide monotherapy [26–32]; some guidelines also recommend regularly testing all patients with bronchiectasis, where possible [26, 29–31]. CF recommendations specify that cultures for NTM should be performed annually in spontaneously expectorating individuals with a stable course [33]. No guidelines or recommendations specifically address testing for NTM in patients with COPD. Findings from this survey showed that 90% of physicians considered testing patients with bronchiectasis for NTM, most commonly following the results of a radiology exam or on presentation of specific clinical symptoms, in line with guideline recommendations. These findings support recent reports by Wagner *et al*., who demonstrated in a European survey that 85% of physicians tested at least some of their patients with bronchiectasis [21]. Data from the EMBARC registry also highlighted wide regional variation in testing frequency in the UK, ranging from 8.3 to 35.5% of patients with bronchiectasis [34]. In the current survey, 60% of physicians considered testing patients with CF and only 50% of these tested all adults with CF despite guideline recommendations. Patients with CF are often treated in specialised CF centres and therefore physicians who participated in the survey may not see these patients or only see them as part of shared care constructions, leading them to be less likely to consider these patients for NTM testing. It was notable that in this patient group in the USA and Japan testing was more likely to be considered after suspicions raised following radiology exams. These results may suggest that radiological examinations in vulnerable patients are undertaken regularly in these countries.

Guideline recommendations are frequently not being followed with respect to which patients should be tested: in this survey 24% of physicians globally tested patients for NTM at initial

presentation of bronchiectasis and very few physicians tested patients with bronchiectasis prior to receiving long-term macrolide monotherapy (15%). Results are similar to a survey of testing practice in patients with bronchiectasis in Asia Pacific that noted that 21% of physicians performed acid-fast bacilli smear tests and cultures at the initial visit [35]. Findings from previous surveys also report low levels of testing in patients with bronchiectasis prior to initiating long-term macrolide therapy [21, 34]. Macrolides are the backbone of NTM-PD therapy and macrolide monotherapy in the presence of NTM infection is a risk factor for macrolide resistance [25, 36]; therefore, testing patients for NTM when considering use of macrolides should be undertaken, in line with guidelines, to retain possible future treatment options.

The decision to test for NTM should consider the overall patient profile, and is usually based on a combination of factors, rather than individual clinical symptoms or patient types. Patients receiving immunosuppressants who also present with respiratory symptoms or have predisposing conditions may be at risk of NTM-PD and testing is warranted. For example, it is well-established that anti-TNFα therapies are associated with an increased risk for NTM disease including NTM-PD and experts advise a low threshold to test for NTM in these patients [37, 38]. In this survey, physicians were most likely to consider testing for NTM in patients presenting with combinations of symptoms that included persistent cough and weight loss, suggesting many physicians look for at least one of these symptoms before testing or they are the most consistently presented symptoms in patients. Physicians generally did not consider testing for NTM in patients with underlying disease or using certain medications without the presence of clinical symptoms suggestive of NTM-PD and physicians considered clinical symptoms in combination with underlying disease to be the most important prompt for testing. It is likely that certain symptoms prompt testing primarily in patients with other indicators of clinical suspicion for NTM-PD, for example, underlying bronchiectasis. Survey data cannot explore in detail correlations between multiple symptoms prompting clinical suspicion and in which patients.

Experts who see many patients with NTM-PD are more likely to have their clinical suspicion of NTM infection raised following a broad range of, often, non-specific or diffuse symptoms with the most common suspicious symptoms including persistent cough, haemoptysis, night sweats, weight loss, persistent fatigue, increased or purulent sputum, fever and an increase in exacerbation frequency of their underlying condition. Use of ICS in patients with COPD, anti-TNFα therapies and persistent reflux have been linked to an increased risk for NTM-PD and are also considered important prompts to test by experts [14, 15, 39]. These factors were considered less important by physicians in the survey, suggesting clear disparities between physician practice and expert opinion.

These survey data highlight different physician's approaches to NTM testing, influenced by factors such as access to mycobacteriological laboratories or in some cases because respondents believed testing was not useful in patients they deemed too frail to complete the challenging and lengthy treatment regimens required to treat NTM-PD appropriately. Tolerable, shorter and more effective treatments are urgently needed to lower the threshold to treat. In addition, supportive therapies aimed at airway clearance may provide benefit for patients deemed too frail for antibiotic therapies, providing an argument to test and diagnose even in those too frail to treat. [40] Importantly, some of the testing approaches identified in this survey suggest that some patient groups may be missing out on appropriate testing. Limitations inherent to surveys and their design, with a risk of selection and perception bias in the questionnaire, apply to this research. The combination of symptoms and risk factors that lead physicians to test a particular patient for NTM can be considered as subjective and can be difficult to capture in surveys in general. In addition, survey participation was limited to physicians who see ≥1 patient with NTM per year and who test for NTM as part of clinical practice. It would be important to survey NTM testing practices in physicians who do not manage patients with NTM-PD, as it is likely that this group does not test appropriately and may even further highlight the disparities in testing practices between physicians and experts who frequently see patients with NTM-PD.

In conclusion, testing for NTM is influenced by underlying disease and the presence of clinical symptoms or radiological changes. However, clinical practice varies considerably across geographies and is not aligned with existing recommendations for NTM testing in certain patient subgroups. The symptoms that often trigger testing for NTM are those seen in later-stage NTM-PD, which can potentially lead to late diagnoses of NTM-PD with a negative impact on patient outcomes. Including NTM-PD in other respiratory disease guidelines, such as COPD, with clear recommendations on NTM testing, monitoring and management in these patient groups is warranted.

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Author contributions:

All authors were involved in the development of the survey questionnaire. All authors critically appraised the manuscript and reviewed and approved the final draft.

Conflict of interest:

MRL reports receiving honorarium from Insmed, Astra Zeneca, Chiesi, Grifols, Savara, Armata, Parion, Zambon, 30T, Electromed and AN2 Therapeutics; JvI reports honorarium for speaking or advisory boards from Boehringer-Ingelheim, Janssen Pharmaceuticals, Insmed,

Spero Therapeutics, Paratek and AN2 Therapeutics; RvdL is an employee of Insmed B.V.; MO is an employee of Insmed Germany GmbH.

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TABLE 1 Survey respondent demographics

Country	Specialty				
	Pulmonology/respiratory medicine	**Internal medicine**	**Infectious diseases**	**Other**	**Total**
France	33	3	14	–	50
Germany	28	10	11	1	50
Italy	26	10	14	–	50
Spain	33	4	13	1	51
UK	33	4	12	1	50
The Netherlands	20	–	5	–	25
USA	42	–	32	1	75
Canada	22	2	5	–	29
Australia	23	–	1	–	24
New Zealand	1	–	–	–	1
Japan	27	16	6	1	50
Total	288	49	113	5	455

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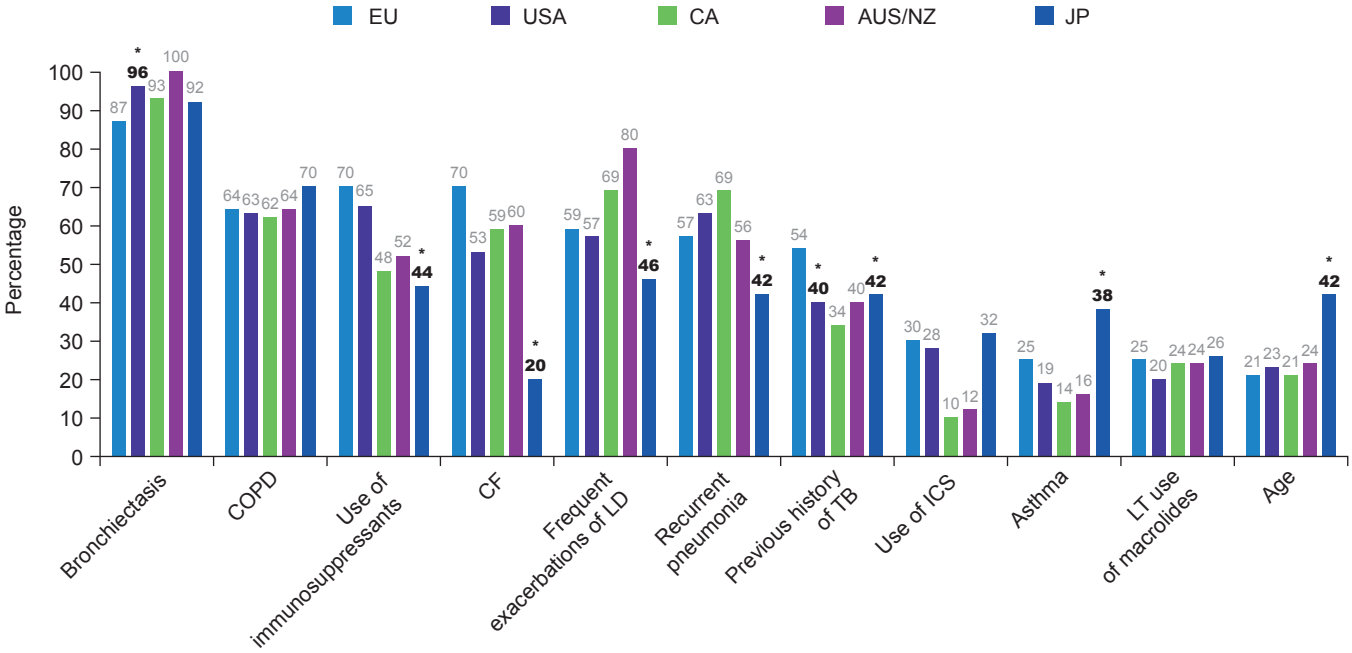
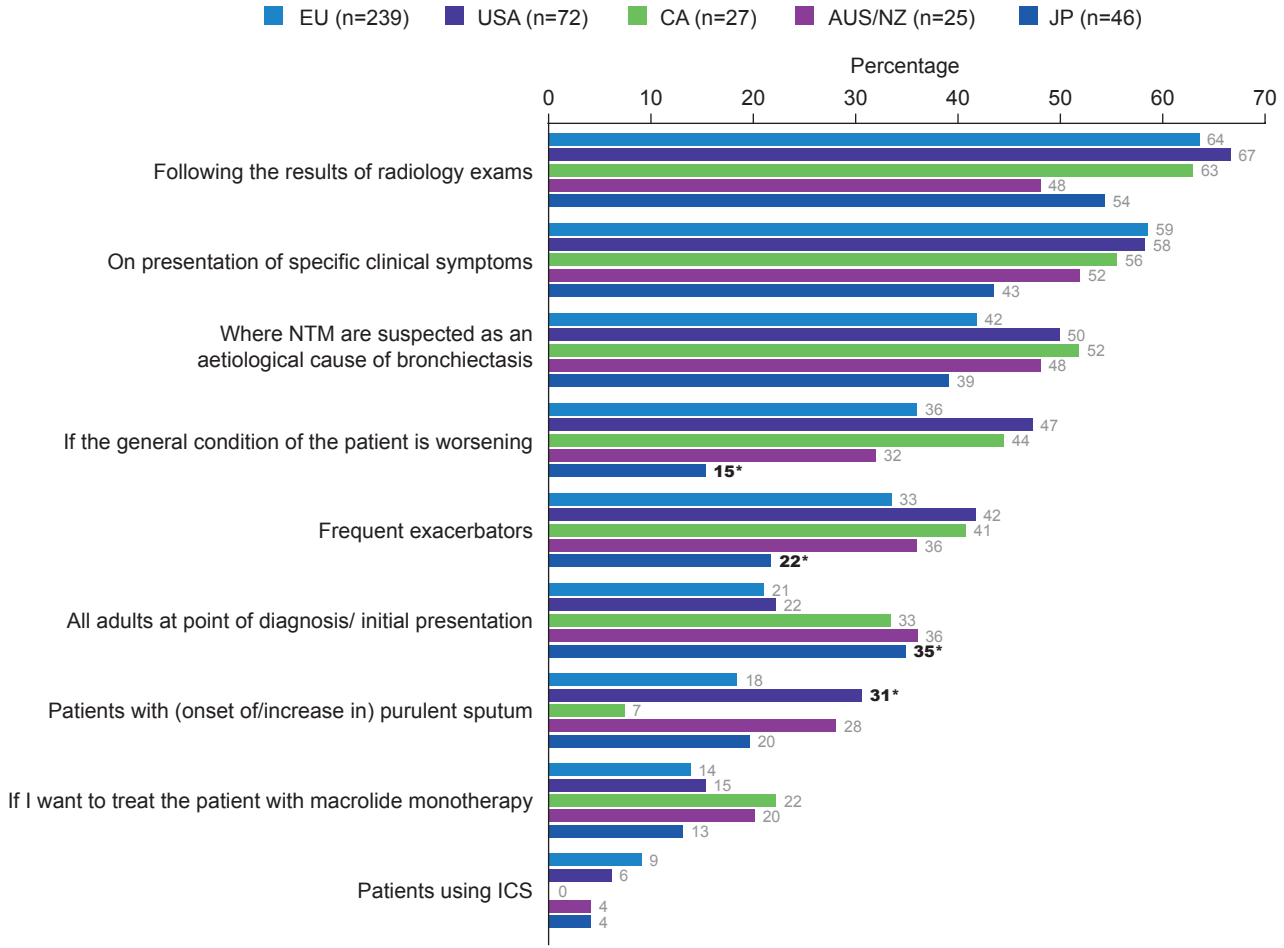
Figure 1. Factors that prompt testing for non-tuberculous mycobacteria infection.



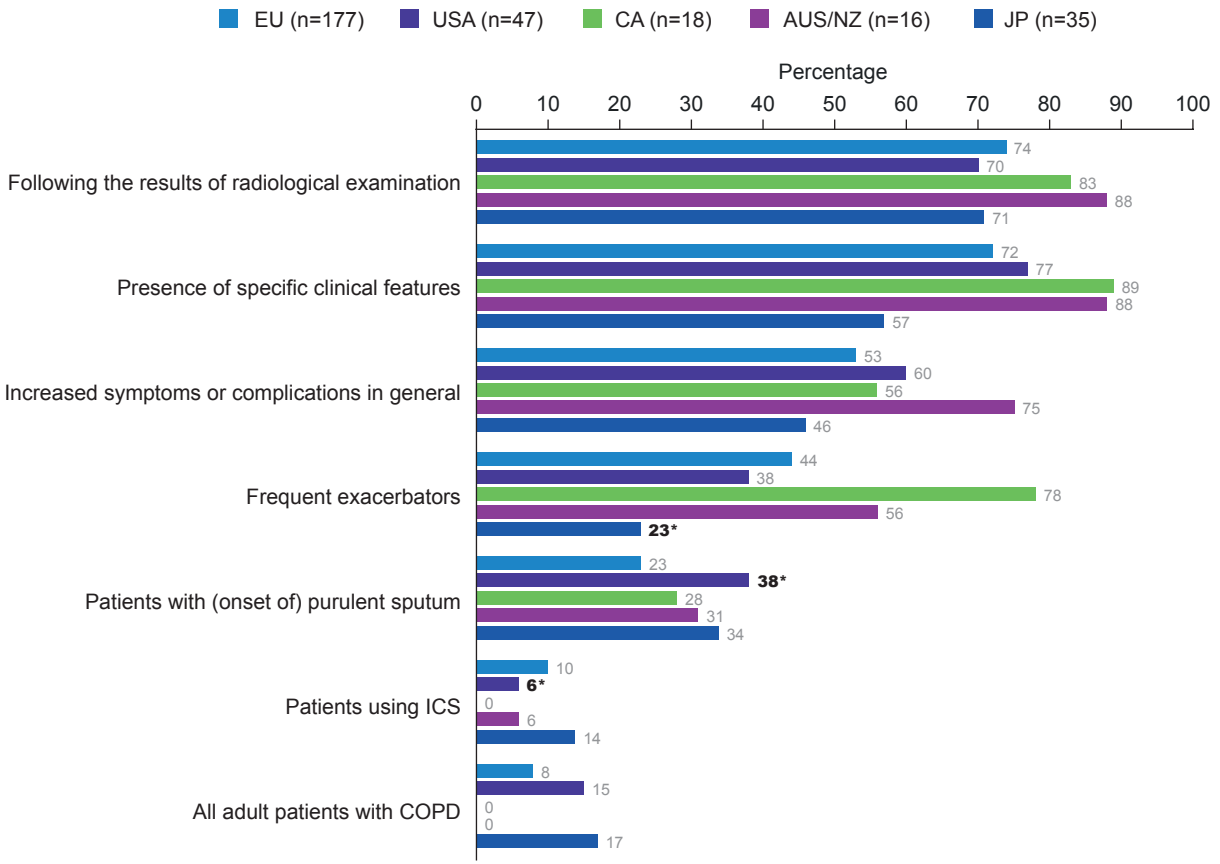
*P<0.05 versus at least one other region.
AUS/NZ: Australia/New Zealand; CA: Canada; CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; EU: Europe; ICS: inhaled corticosteroids; JP: Japan; LD: lung disease; LT: long term; TB: tuberculosis.

Figure 2. Reasons prompting testing for non-tuberculous mycobacteria infection in patients with bronchiectasis.



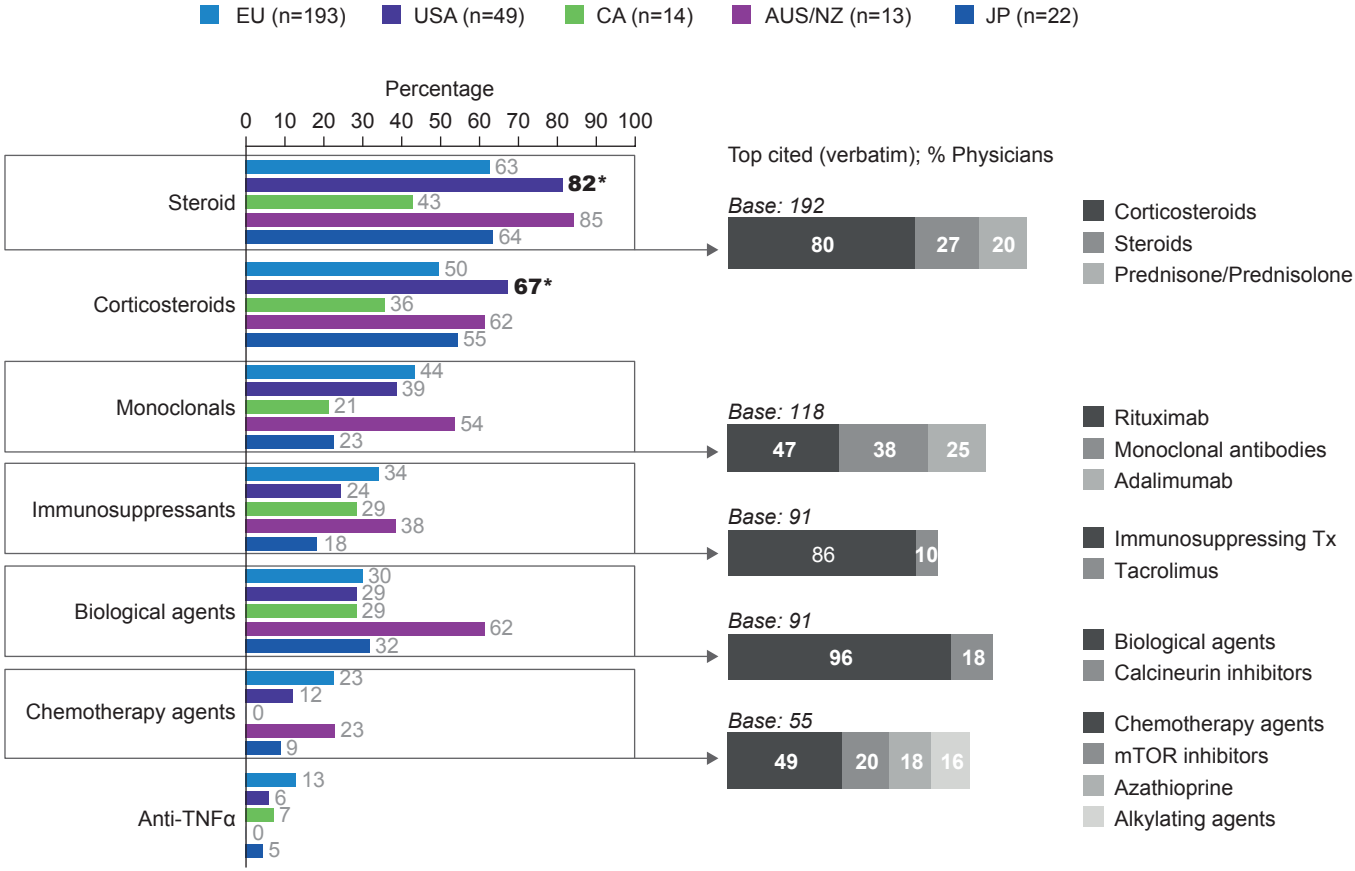
*P<0.05 versus at least one other region.
AUS/NZ: Australia/New Zealand; CA: Canada; EU: Europe; ICS: inhaled corticosteroids; JP: Japan; NTM: non-tuberculous mycobacteria.

Figure 3. Reasons prompting testing for non-tuberculous mycobacteria infection in patients with chronic obstructive pulmonary disease.



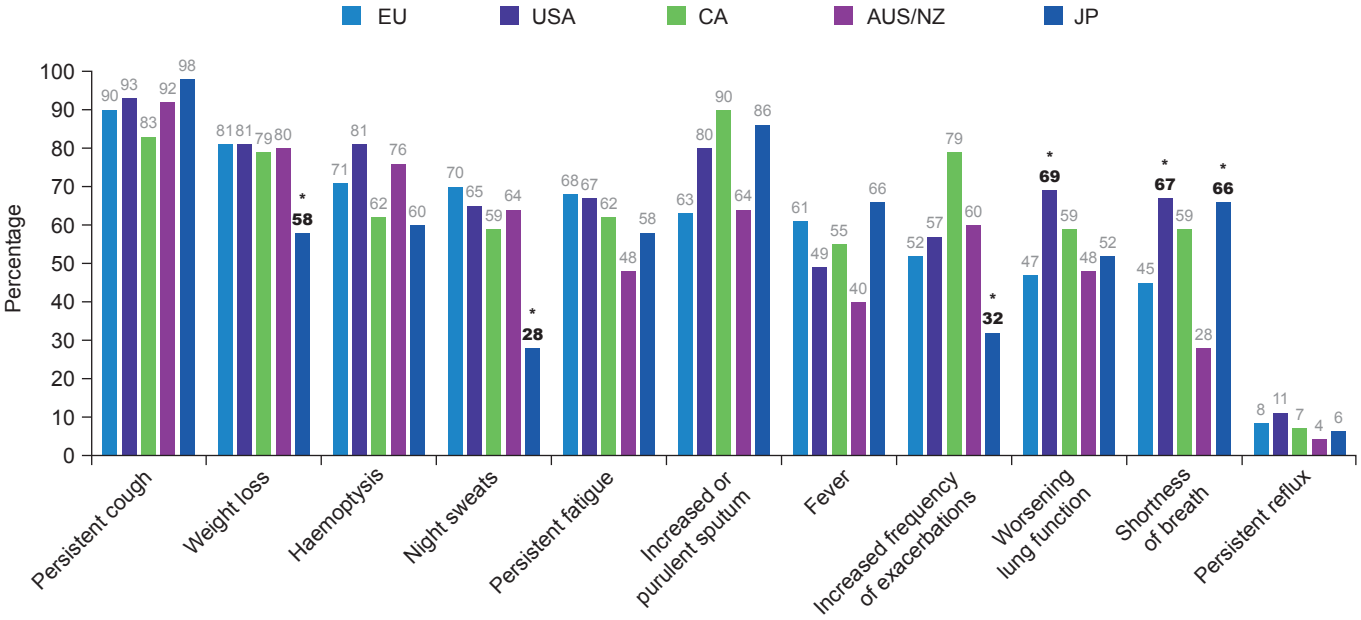
*P<0.05 versus at least one other region.
AUS/NZ: Australia/New Zealand; CA: Canada; COPD: chronic obstructive pulmonary disease; EU: Europe; ICS: inhaled corticosteroids; JP: Japan.

Figure 4. Immunosuppressant therapies prompting testing for non-tuberculous mycobacteria infection.



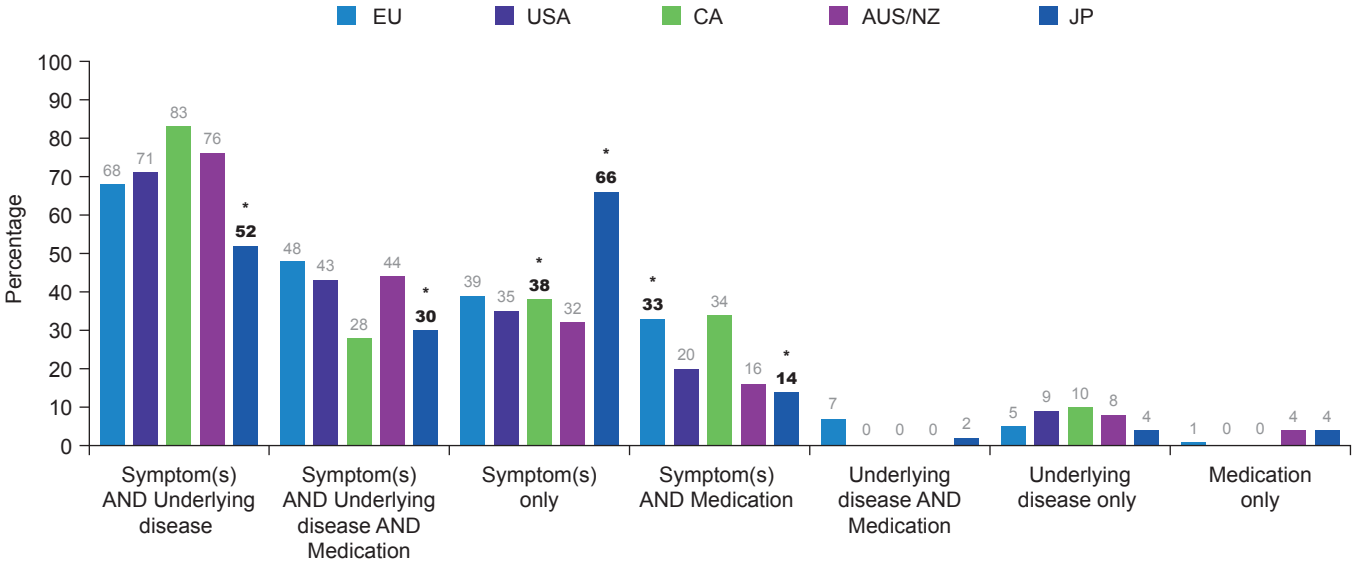
*P<0.05 versus at least one other region.
AUS/NZ: Australia/New Zealand; CA: Canada; EU: Europe; JP: Japan; mTOR: mechanistic target of rapamycin; TNF: tumour necrosis factor; Tx: treatment.

Figure 5. Clinical symptoms that prompt testing for non-tuberculous mycobacteria infection.



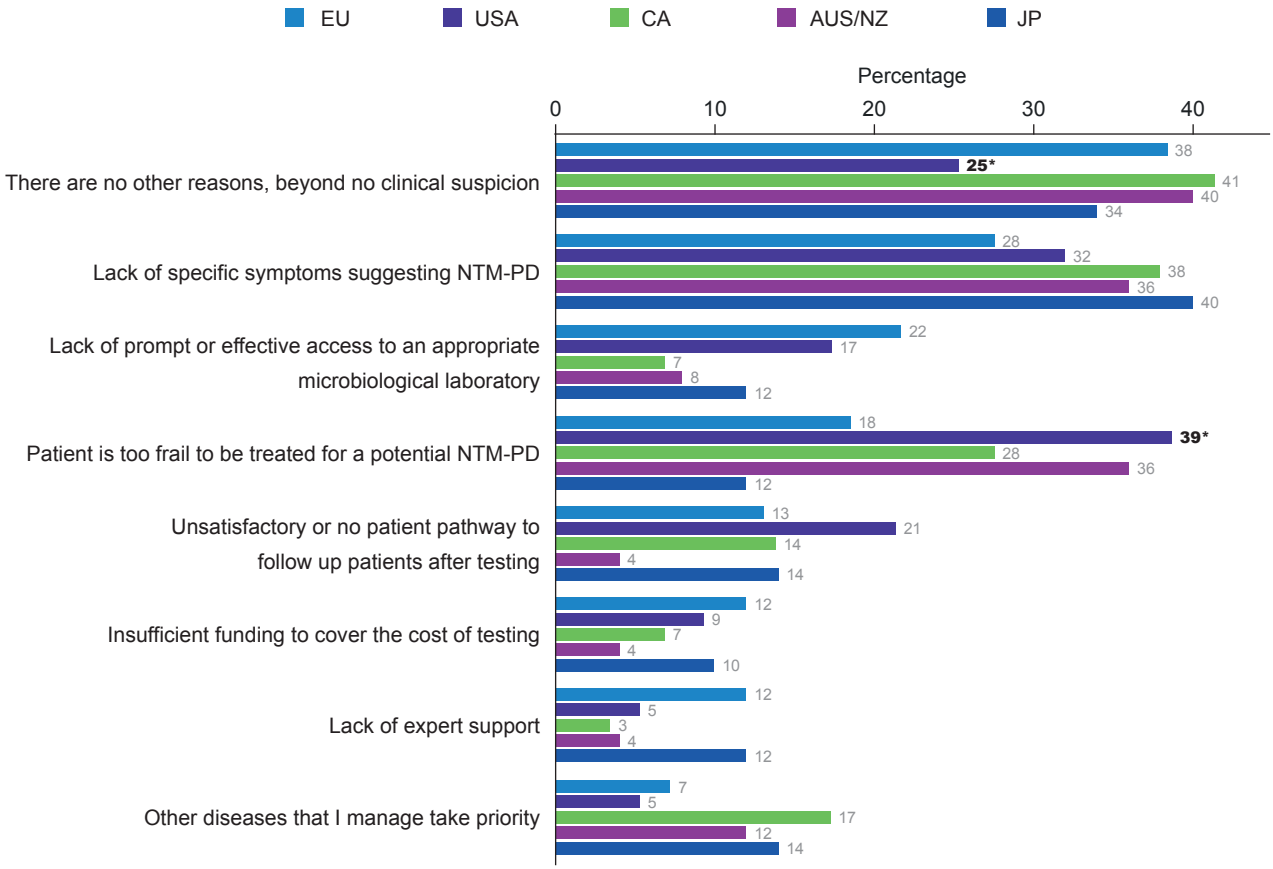
*P<0.05 versus at least one other region.
AUS/NZ: Australia/New Zealand; CA: Canada; EU: Europe; JP: Japan.

Figure 6. Combinations that prompt testing for non-tuberculous mycobacteria infection.



*P<0.05 versus at least one other region.
AUS/NZ: Australia/New Zealand; CA: Canada; EU: Europe; JP: Japan.

Figure 7. Reasons physicians choose not to test for non-tuberculous mycobacteria infection, beyond that of no clinical suspicion.



*P<0.05 versus at least one other region.
AUS/NZ: Australia/New Zealand; CA: Canada; EU: Europe; JP: Japan; NTM-PD: non-tuberculous mycobacterial pulmonary disease.

Supplementary materials

Supplementary Table S1. Screening questions

	SCREENING		
#	Question	Code	Route
S0	Country		BASE =ALL AUTO CODE
		France	1
		Germany	2
		Italy	3
		Spain	4
		UK	5
		Netherlands	6
		USA	7
		Canada	8
		Australia	9
		New Zealand	10
		Japan	11
S1	Do you <u>see</u> patients with **non-tuberculous mycobacterial (NTM) lung disease** as part of your practice?		SINGLE CODE
	Yes	1	➔ CONTINUE
	No	2	➔ CLOSE
S2	How many patients with non-tuberculous mycobacterial (NTM) lung disease do you **typically <u>see</u> in a 12 month period**?		SINGLE CODE
	Zero patients/none	1	➔ CLOSE
	1 patient	2	➔ CONTINUE
	2–5 patients	3	➔ CONTINUE
	6 to 10 patients	4	➔ CONTINUE
	More than 10 patients	5	➔ CONTINUE
S3	And do you <u>test</u> patients for non-tuberculous mycobacterial (NTM) lung disease as part of your practice?		SINGLE CODE
	Yes	1	➔ CONTINUE
	No	2	➔ CLOSE
S4	What is your primary medical specialty? Select one that best applies		SINGLE CODE
	Pulmonology/Respiratory medicine	1	➔ CONTINUE
	Internal Medicine	2	➔ CONTINUE
	Infectious Diseases	3	➔ CONTINUE
	Other *please write in*_____	4	➔ CONTINUE
S5	ASK IF INTERNAL MEDICINE ONLY: Do you have a secondary specialty in pulmonology?		
	Yes	1	➔ CONTINUE
	No	2	➔ CONTINUE

	RESPONDENT MUST SEE AND TEST NTM-LUNG DISEASE PATIENTS

Supplementary Table S2. Survey questionnaire

	SECTION A		
#	Question	Code	Route
A1a	Which clinical symptoms would prompt you to test for NTM infection in a patient? *Check those that apply and/or write in any others in the box below* Persistent cough Weight loss Increased or purulent sputum Fever Persistent fatigue Shortness of breath Night sweats Worsening lung function Haemoptysis Increased frequency of exacerbations Gastroesophageal reflux Other clinical symptoms *please specify – write in*_____ *please use 1 row per symptom*_____ _____	 **1** **2** **3** **4** **5** **6** **7** **8** **9** **10** **11** **12** **13** **14**	**MULTI CODE**
	IF A1 = 8 ASK A1B		
A1b	You indicate that "*worsening lung function*" is a clinical symptom that would prompt you to test for NTM infection in a patient – at what level of decline would you begin to test on this basis? **FEV1 & FVC** % decline of: Less than 10% 10–20% 21–30% More than 30% Other please write in_____	 1 2 3 4 5	**SINGLE CODE**

A1c	In patients that you test for NTM infection based on worsening clinical symptoms how often would you repeat sputum (microbiological) testing or radiological imaging? Do not repeat test Every 6 months Annually Every 2 years Every 5 years Other please specify:_____	**Microbiological testing** 1 2 3 4 5 6	**Radiological imaging** 1 2 3 4 5 6
	ASK ALL		
A2a	Which of the following specific patient types, if any, do you test or monitor for NTM infection? *Check all that apply* COPD Bronchiectasis Asthma Cystic fibrosis (CF) Age Use of immunosuppressant therapies (e.g. biologicals or immunosuppressant drugs) Use of inhaled corticosteroids Use of long-term macrolide antibiotics Patients with a previous history of tuberculosis (TB) Patients with recurrent pneumonia Patients with recurrent and frequent exacerbations of their underlying lung condition None **(EXCLUSIVE) – SKIP TO A16**	 **1** **2** **3** **4** **5** **6** **7** **8** **9** **10** **11** **12**	**MULTI CODE**
A2b	**IF MORE THAN 5 CODES SELECTED AT PREVIOUS QUESTION, ASK:** And of these, which 5 do you consider to be the most important to test or monitor for NTM infection? **INSERT CODES SELECTED FROM PREVIOUS QUESTION, AND MULTICODE 5 OF THEM** ➔ **THESE CODES TO BE CARRIED THROUGH TO QUESTION LOOPS TO FOLLOW**		
PATIENT TYPE LOOPED QUESTIONS			
	IF A2a = 1 ASK A3 QUESTIONS ON ONE SCREEN IF POSSIBLE		

A3a	Which COPD patients do you test or monitor for NTM infection? *Check all that apply* All adult patients with COPD Following the results of radiological examination – physical features in the lung that lead to suspicion of NTM infection Presence of specific clinical features (such as weight loss, haemoptysis) that lead to suspicion of NTM infection Increased symptoms or complications in general that lead to suspicion of NTM infection Frequent exacerbators Patients with (onset of) purulent sputum Patients in receipt of ICS Other COPD patient type *Please write in*_____	 **1** **2** **3** **4** **5** **6** **7** **8**	**MULTI CODE- EXCEPT CODE '1' – EXCLUSIVE CODE**
A3b	And is severity in COPD a rationale for testing or monitoring for NTM infection? No Yes – at GOLD stage I – at GOLD stage II – at GOLD stage III – at GOLD stage IV	 1 2 3 4 5	**SINGLE CODE** **IF YES CODED – POP UP SECOND PART OF ANSWER AND REQUIRE CODE**
	IF A2a = 2 ASK A4 QUESTIONS ON ONE SCREEN IF POSSIBLE		

A4a	Which bronchiectasis patients do you test or monitor for NTM infection? *Check any of the following statements that apply* All adult patients with bronchiectasis are tested at point of diagnosis/initial presentation Following the results of radiology exams, showing physical features of the lung which lead to the suspicion of NTM infection On presentation of specific clinical symptoms (such as weight loss, haemoptysis) which lead to the suspicion of NTM infection Where NTM are suspected as an aetiological cause of bronchiectasis If I want to treat the patient with macrolide monotherapy Frequent exacerbators If the general condition of the patient is worsening Patients with (onset of/increase in) purulent sputum Patients in receipt of ICS Other bronchiectasis patient type *Please write in*_____	**1** 2 3 4 5 6 7 8 9 10	**MULTI CODE- EXCEPT CODE '1' – EXCLUSIVE CODE**
A4b	And is severity in bronchiectasis a rationale for testing or monitoring for NTM infection? No Yes - 0 - 4 points* - 5 - 8 points* - ≥ 9 Points* *Severity criteria using the Bronchiectasis Severity Index[1] 1. EMBARC. Bronchiectasis Severity Index. https://www.bronchiectasis.eu/severity-assessment [Accessed June 2021]	**1** **2** **i** **ii** **iii**	**SINGLE CODE** **IF YES CODED – POP UP SECOND PART OF ANSWER AND REQUIRE CODE**
	IF A2a = 3 ASK A5 QUESTIONS ON ONE SCREEN IF POSSIBLE		

A5a	Which asthma patients do you test or monitor for NTM infection? *Check any of the following statements that apply* All adult patients with asthma are tested at point of diagnosis/initial presentation Following the results of radiology exams, showing physical features of the lung which lead to the suspicion of NTM infection On presentation of specific clinical symptoms (such as weight loss, haemoptysis) which lead to the suspicion of NTM infection If I want to treat the patient with macrolide monotherapy Frequent exacerbators If the general condition of the patient is worsening Patients with (onset of/increase in) purulent sputum Patients in receipt of ICS Other asthma patient type *Please write in*_____	1 2 3 4 5 6 7 8 9	**MULTI CODE- EXCEPT CODE '1' – EXCLUSIVE CODE**
A5b	And is severity in asthma a rationale for testing or monitoring for NTM infection? No Yes – intermittent – mild persistent – moderate persistent Severe persistent Status asthmaticus	1 2 i ii iii iv v	**SINGLE CODE** **IF YES CODED – POP UP SECOND PART OF ANSWER AND REQUIRE CODE**
	IF A2a = 4 ASK A6 QUESTIONS ON ONE SCREEN IF POSSIBLE		

A6a	Which CF patients do you test or monitor for NTM infection? *Check any of the following statements that apply* All adults with CF are tested Following the results of radiology exams, showing physical features of the lung which lead to the suspicion of NTM infection On presentation of specific clinical symptoms (such as weight loss, haemoptysis) which lead to the suspicion of NTM infection If the general condition of the patient is worsening Other CF patient type *Please write in*_____	1 2 3 4 5	**MULTI CODE- EXCEPT CODE '1' – EXCLUSIVE CODE**
	IF A2a = 6 ASK A8 QUESTIONS ON ONE SCREEN IF POSSIBLE		
A8a	Which patients do you test or monitor for NTM infection based on age? *Check the following categories that apply* Those under 30 years old Those between 30 and 50 years old Those between 51 and 60 years old Those between 61 and 70 years old Those between 71 and 80 years old Those over 80 years old	**1** **2** **3** **4** **5** **6**	**MULTI CODE**
	IF A2a = 7 ASK A9 QUESTIONS ON ONE SCREEN IF POSSIBLE		
A9a	Which patients do you test or monitor for NTM infection based on their use of immunosuppressant therapies the include: • IV/oral corticosteroids; • biologics such as adalimumab, rituximab or others; • monoclonal antibodies such as basiliximab, daclizumab, trastuzumab; • immunosuppressant drugs including alkylating agents, folic acid antagonists, mTOR inhibitors, calcineurin inhibitors, Janus kinase inhibitors among others Please specify the drugs that prompt you to test for NTM infection Write in_____ Write in_____		**OPEN TEXT ALLOW UP TO FIVE ROWS**
	IF A2a = 10 ASK A10 QUESTIONS ON ONE SCREEN IF POSSIBLE		

A10a	Which patients with a previous history of tuberculosis (TB) do you test or monitor for NTM infection? *Check any of the following statements that apply* All adults with previous history of TB are tested Following the results of radiology exams, showing physical features of the lung which lead to the suspicion of NTM infection On presentation of specific clinical symptoms (such as weight loss, haemoptysis) which lead to the suspicion of NTM infection If the general condition of the patient is worsening	1 2 3 4	**MULTI CODE- EXCEPT CODE '1' – EXCLUSIVE CODE**
	NOW ASK ALL		

A11a In this question we are looking to explore which combination of symptoms/risk factors you would see in a patient that would increase your suspicion they might have NTM-PD and lead you to test for infection.

Please enter one combination per column
Combinations should be realistic, but may contain as many features you are likely to see together in clinical practice
Please use as many of the columns as you need, but at least 1

	Combination	Patient 1 **MUST PROVIDE SOME SELECTION**	Patient 2 **OPTIONAL**	Patient 3 **OPTIONAL**	Patient 4 **OPTIONAL**	Patient 5 **OPTIONAL**
	Persistent cough	○	○	○	○	○
	Weight loss	○	○	○	○	○
	Onset of/increase in purulent sputum	○	○	○	○	○
	Fever	○	○	○	○	○
	Persistent fatigue	○	○	○	○	○
	Shortness of breath	○	○	○	○	○
	Night sweats	○	○	○	○	○
	Worsening lung function	○	○	○	○	○
	Haemoptysis	○	○	○	○	○
	Increased frequency of exacerbations	○	○	○	○	○
	Gastroesophageal reflux disease and/or use of acid suppression medication (e.g. PPI)					
	Underlying disease – bronchiectasis					

	Underlying disease – COPD					
	Underlying disease – asthma					
	Underlying disease – CF					
	Underlying disease – history of TB					
	Morphological features (e.g. taller than average, elongated arm span >1.03 of individual's height, elderly [male or female] presence of pectus excavatum or scoliosis)					
	Medication use – oral corticosteroids					
	Medication use – IV corticosteroids					
	Medication use – Biologics (e.g. abatacept, rituximab, etc.)					
	Medication use – monoclonal antibodies (e.g. basiliximab, daclizumab)					
	Medication use – interferons (any type)					
	Medication use – Immunosuppressants (all classes e.g. mTOR inhibitors, calcineurin inhibitors, Janus kinase inhibitors etc.)					
	History of NTM isolation/disease					
	Other (please specify)					
A12	And are there any other reasons (other than those previously outlined) that would prompt you to test or monitor for NTM infection? No Yes IF YES please specify reasons:_____ _____			**1** **2**		**SINGLE CODE – IF YES SHOW OPEN TEXT BOX AND REQUIRE AT LEAST 5 CHARACTERS**

	ASK ALL		
A13	Which tests do you undertake to rule out NTM infection? Direct molecular tests for NTM organisms on primary sample Mycobacterial sputum culture Other microbiological tests please specify: _____ Lung function tests High resolution CT scan Other tests please specify:_____	 **1** **2** **3** **4** **5** **6**	**MULTI CODE**
A14	Are any of the below points reasons why you would <u>not test for NTM infection,</u> beyond that of no clinical suspicion? *Please select as many that apply to you* Insufficient funding to cover the cost of testing Lack of prompt or effective access to an appropriate microbiological laboratory Unsatisfactory or no patient pathway to follow up patients after testing Lack of expert support Other diseases that I manage take priority Patient is too frail to be treated for a potential NTM-PD Lack of specific symptoms suggesting NTM Other reason please specify _____ There are no other reasons **(EXCLUSIVE)**	 **1** **2** **3** **4** **5** **6** **7** **8**	**MULTI CODE**
	THANK AND CLOSE		
	AE REPORTING LINK SET UP FOR OPEN ENDED TEXT **WE WILL NEED ACCESS TO REVIEW FREE TEXT RESPONSES TO CHECK FOR ADVERSE EVENTS & REPORT WITHIN 1 BUSINESS DAY OF THE RESPONSE**		

Supplementary Table S3. Survey response rates

Country	Number of physicians invited	Number of physicians completing the screener	Non-response rate (%)
France	557	52	91
Germany	697	63	91
Italy	251	56	78
Spain	322	53	84

UK	572	55	90
The Netherlands	288	28	90
USA	134	78	42
Canada	96	30	69
Australia	724	25	97
New Zealand	72	1	99
Japan	351	56	84
Total	4064	497	88