European Dermatology Forum

Guideline on the Management of Mycoplasma genitalium Infections

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2015 European guideline on *Mycoplasma genitalium* infections

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Introduction

Mycoplasmas, the trivial name for members of the class Mollicutes, are the smallest free-living micro-organisms. They lack the rigid cell wall of other bacteria so that they resist penicillins and other β-lactams (Taylor-Robinson *et al.*, 2000). The mycoplasmas isolated commonly from humans belong to the family Mycoplasmataceae. This family comprises the genus *Mycoplasma*, and the genus *Ureaplasma*, which hydrolyses urea. In the urogenital tract, the relevant species are *M. genitalium, U. urealyticum, U. parvum,* and *M. hominis. M. hominis* and the ureaplasmas will not be dealt with in the present guideline.

Mycoplasma genitalium was first isolated in 1980 from two of 13 men with non-gonococcal urethritis (NGU) (Tully *et al.*, 1981). It is an extremely slow-growing and fastidious bacterium, and its role as a pathogen in human disease was not established until the first diagnostic PCRs were developed in the early 1990's (Jensen *et al.*, 1991; Palmer *et al.*, 1991).

Male NGU was the first syndrome unequivocally associated with *M. genitalium* infection (Jensen *et al.*, 1993; Horner *et al.*, 1993) and in a meta-analysis including 37 studies up to 2010 (Taylor-Robinson & Jensen, 2011), *M. genitalium* was associated with a pooled OR of 5.5 for NGU. In the 29 studies where information on chlamydial infection was available, *M. genitalium* was associated with a pooled OR of 7.6 for non-chlamydial non-gonococcal urethritis (NCNGU). The prevalence of *M. genitalium* in men with NCNGU ranges from 10% to 35% (Taylor-Robinson & Jensen, 2011), thus contributing significantly to the overall burden of disease. In comparison, *M. genitalium* is detected in only 1% to 3.3% of men and women in the general population (Andersen *et al.*, 2007; Oakeshott *et al.*, 2010; Manhart *et al.*, 2007). In women, several studies have demonstrated the association between *M. genitalium* and urethritis, cervicitis, endometritis, and pelvic inflammatory disease (PID) (Cohen *et al.*, 2002; Manhart *et al.*, 2003; Cohen *et al.*, 2005; Anagrius *et al.*, 2005; Falk *et al.*, 2005). In a recent meta-analysis (Lis *et al.*, 2015), significant associations were found between *M. genitalium* and cervicitis (pooled odds ratio (OR) 1.66), and pelvic inflammatory disease (pooled OR 2.14). While there are less data in pregnancy, *M. genitalium* has been associated with preterm birth (pooled OR 1.89), and spontaneous abortion (pooled OR 1.82), but the prevalence of *M. genitalium* in pregnant women has generally been low in many European settings (Oakeshott *et al.*, 2004; Peuchant *et al.*, 2015) and therefore, the relative importance of *M. genitalium* as a cause of adverse pregnancy outcome in Europe is probably rather small.

Serological studies and studies based on detection of *M. genitalium* using NAATs have also shown an association with increased risk of tubal factor infertility (pooled OR 2.43). In sub-analyses that accounted for co-infections, Lis et al found these associations to be stronger and more statistically significant (Lis *et al.*, 2015).

Persistence of *M. genitalium* after treatment is associated with recurrent or persistent NGU. In men with persistent NCNGU after doxycycline therapy, as many as 41% were found to be *M. genitalium* positive (Wikström & Jensen, 2006), and 91% of patients with persistent *M. genitalium* infection experienced persistent urethral symptoms compared to 17% of patients in whom *M. genitalium* was eradicated (Bradshaw *et al.*, 2008). In a recent meta-analysis (Jensen & Bradshaw, 2015), a total of 21 studies on the efficacy of treatment of *M. genitalium* positive urethritis were included as they presented data on the presence of urethritis in patients where antibiotic treatment failed to eradicate the infection. In the 19 studies where data on men with persistent and eradicated *M. genitalium* infection could be evaluated, 220 (77%) of the 285 patients with persistent *M. genitalium* infection had persistent urethritis, compared to only 78 (16%) of the 499 patients where *M. genitalium* was successfully eradicated ($p<0.0001$). Persistent *M. genitalium* was associated with a pooled odds ratio of 26 (95% CI = 11 to 57) for persistent urethritis (signs and/or symptoms). This analysis clearly demonstrates that failure to eradicate *M. genitalium* leads to persistent or recurrent signs and symptoms of urethritis in the vast majority of men with persistent infection and that diagnosis and optimal treatment is extremely important. The role of *M. genitalium* in facilitating HIV transmission, in particular in Sub-Saharan Africa (Vandepitte *et al.*, 2014; Mavedzenge *et al.*, 2012; Manhart, 2012) is another reason for concern when eradication fails due to inappropriate treatment.

Transmission

Transmission is primarily by direct genital-genital mucosal contact with inoculation of infected secretions as illustrated by a high concordance rate of identical DNA types in sexual partners (Hjorth *et al.*, 2006). Genital-anorectal transmission has been shown (Edlund *et al.*, 2012) and may play a role as *M. genitalium* is commonly found in the anal mucosa (Soni *et al.*, 2010; Lillis *et al.*, 2011) and the organism can be cultured from this site (Jensen, unpublished). Oral-genital contact is less likely to contribute to any significant extent, as carriage of *M. genitalium* in the oro-pharynx is low. Mother-to-child transmission at birth has not been systematically studied, but *M.*

genitalium has been detected in the respiratory tract of new-born children (Luki *et al.*, 1998). The risk of contracting *M. genitalium* per sexual encounter has not been determined, but because *M. genitalium* is present in lower concentration in genital tract specimens than *C. trachomatis* (Walker *et al.*, 2011), it could be considered slightly less contagious than chlamydia.

There are no estimates of the global burden of disease. Prevalence estimates are variable as a wide variation in the sensitivity of detection assays is present and there is no agreed gold standard. In STI patients, the prevalence is usually from 60 to 85% of that of *C. trachomatis*, but in the general population, the ratio is generally significantly lower (Andersen *et al.*, 2007; Manhart *et al.*, 2007).

Compared to *C. trachomatis*, the prevalence of *M. genitalium* infected patients appear to peak approximately 5 years later for both men and women and to remain higher in the older age-groups (Jensen *et al.*, 2004; Salado-Rasmussen & Jensen, 2014)

Clinical features

Urogenital infections

Symptoms and signs in women:

- Among STD clinic attendees, 40 – 75% are asymptomatic (Falk *et al.*, 2005; Anagrius *et al.*, 2005)
- Symptoms are related to cervical and urethral infection and include increased or altered vaginal discharge (<50%), dysuria or urgency (30%) and, rarely, inter-menstrual or post coital bleeding or menorrhagia (Falk *et al.*, 2005; Anagrius *et al.*, 2005; Bjartling *et al.*, 2012).
- Cervicitis
- Rectal and pharyngeal infections are usually asymptomatic
- Lower abdominal pain (<20%) should raise suspicion of pelvic inflammatory disease (PID)

Complications in women (Lis et al., 2015):

- PID (endometritis, salpingitis)
- Tubal factor infertility (probably)
- Sexually acquired reactive arthritis (SARA) (Taylor-Robinson *et al.*, 1994)

Symptoms and signs in men (Taylor-Robinson & Jensen, 2011)

- 70% symptomatic (Falk *et al.*, 2004)
- Urethritis (acute, persistent, and recurrent)
- Dysuria
- Urethral discharge
- Balanoposthitis has been associated with *M. genitalium* infection in one study (Horner & Taylor-Robinson, 2010)

Complications in men:

- SARA (Taylor-Robinson *et al.*, 1994)
- Epididymitis

Ocular infections

Ocular infections can result in conjunctivitis in adults (Björnelius *et al.*, 2004) but is not systematically studied. Neonatal conjunctivitis has not been systematically studied

<u>Indications for laboratory testing</u> [IV; C]

- Symptoms or signs of urethritis in men
- Mucopurulent cervicitis
- Cervical or vaginal discharge with risk factor for STI
- Intermenstrual or post-coital bleeding
- Acute pelvic pain and/or PID
- Acute epididymo-orchitis in a male aged <50 years
- Screening of persons with high-risk sexual risk behavior (age <40 years, >3 new sexual contacts in the last year, more than 5 life-time partners and never screened)
- Sexual contact of persons with an STI or PID in particular contacts of *M. genitalium* infected persons
- MSM should be regularly screened, including anal sampling
- Before termination of pregnancy or other procedures that breaks the cervical barrier.

Laboratory diagnostics [III; B]

Recommended diagnostic assays:

Nucleic acid amplification tests (NAATs) identifying *M. genitalium* specific nucleic acid (DNA or RNA) in clinical specimens are the only useful methods for diagnosis, due to the difficulties in isolating *M. genitalium* by culture (Hamasuna *et al.*, 2007; Jensen *et al.*, 1996) and in the absence of specific and sensitive diagnostic serological assays (Taylor-Robinson & Jensen, 2011) [III; B]. However, at present no commercially available NAAT assays have been evaluated up to the US FDA approval standard, and the CE marked tests on the market suffer from very limited validation. Consequently, it is extremely important that diagnostic laboratories carefully validate any commercial or in-house assays and participate in external quality assurance assessment (EQA) schemes such as the EQUALIS EQA scheme (http://www.equalis.se/sv/vaar-verksamhet/extern-kvalitetssaekring/kvalitetssaekringsprogram/m-r/mycoplasma-genitalium-nukleinsyra-288-2015/). This EQA scheme has demonstrated substantial differences in the sensitivity of participating laboratories. In Russia, routine diagnostics for *M.genitalium* with commercially available tests manufactured in Russia is widely used. The tests were internationally validated and have sensitivity range from 74 to 100% and 100% specificity for different types of clinical samples obtained from men and women (Shipitsyna *et al.*, 2009).

With the widespread macrolide resistance in Europe, it is strongly recommended that all positive tests are followed up with an assay capable of detecting macrolide resistance mediating mutations. A variety of methods are available for this purpose (Jensen *et al.*, 2008; Twin *et al.*, 2012; Jensen, 2012; Touati *et al.*, 2014; Salado-Rasmussen & Jensen, 2014; Wold *et al.*, 2015), and the main determinant for the selection of an assay is the practical aspects from a laboratory point of view, and the sensitivity measured as the proportion of screening positive tests capable of being resistance typed. The latter aspect varies significantly between assays.

Determination of moxifloxacin resistance can also be carried out using molecular methods although the correlate between mutations in parC and in vitro moxifloxacin resistance is less clear. The current assays are based on conventional sequencing of a PCR amplified fragment of parC (Deguchi *et al.*, 2001). At present, detection of moxifloxacin resistance mediating mutations is probably not indicated on a routine basis in Europe, as the level of resistance is low (app 5%)

(Pond *et al.*, 2014) but it may be considered in the Asia-Pacific region where moxifloxacin resistance is more common (Shimada *et al.*, 2010; Couldwell *et al.*, 2013; Kikuchi *et al.*, 2014) or in patients having acquired the infection in this region.

Specimens

Due to the various assay formats used in different laboratories, it is difficult to make firm conclusions regarding the optimal sample type. Provided that the sample extraction procedure includes processing of the urine sample to provide a concentration step, first void urine (FVU) from men and women provide a good diagnostic specimen which may be self-obtained (Jensen *et al.*, 2004). Vaginal swab (physician or self-collected) also provide an appropriate sensitivity (Hardick *et al.*, 2006; Wroblewski *et al.*, 2006; Carlsen & Jensen, 2010). Anal samples are useful in MSM where as many as 70% of the infection will be missed if this site is not sampled (Reinton *et al.*, 2013), but may also be relevant in women at risk (Lillis *et al.*, 2011). The association between an anal infection and symptoms is uncertain, but the infection is likely to be transmitted if not detected and treated.

In most settings it will be appropriate to use the same sampling procedure as for *C. trachomatis* testing. However, some transport media designed for *C. trachomatis* NAAT will lyse *M. genitalium*, and may provide a poor sensitivity in an in-house assay. This should be careful evaluated for all in-house assays and even for assays where a validated collection and nucleic acid purification kit is not included [III B].

Screening and repeat testing

- Screening in low-risk, asymptomatic populations is not recommended [IV, C]. The diagnostic yield will be low and concern has been raised that active case finding will lead to treatment with azithromycin with subsequent augmentation of the problems with macrolide resistance (see below).
- Test of cure samples should be collected no earlier than three weeks after start of treatment [IV, C]. In patients responding to treatment, *M. genitalium* will be undetectable within one week in most patients, but may become temporarily false negative in patients failing treatment (Falk *et al.*, 2015).

Management of patients

Information, explanation and advice for the patient

- Patients with *M. genitalium* infection should be advised to abstain from unprotected sexual contact until they and their partners have completed treatment, their symptoms have resolved, and their test of cure negative [IV; C].
- Patients with *M. genitalium* infection (and their sexual contacts) should be given information about the infection, including details about transmission, prevention and complications. It is recommended that both verbal and written information be provided [IV; C].
- Patients with anal infection including MSM should be informed about the risk of transmission from this site and that the infection may be more difficult to eradicate. Consequently, a test of cure is important.
- Patients with *M. genitalium* infection should be screened for other STIs, including *C. trachomatis*, *N. gonorrhoeae*, syphilis, HIV, and *T. vaginalis* where appropriate [IV; C].

Pregnancy

- *M. genitalium* infections during pregnancy may be associated with a slight increase in the risk of spontaneous abortion and preterm birth (Lis *et al.*, 2015). In macrolide susceptible infections, a five-day-course of azithromycin is generally acceptable. The choice of drugs for treatment in macrolide resistant infections is important and often difficult because of their possible adverse effects on foetal development and pregnancy outcome. In many cases, the risk associated with treatment with the available antibiotics would appear to outweigh the risk of adverse pregnancy outcome, and treatment, especially in women with infection with a macrolide resistant *M. genitalium* strain, may be considered postponed until after delivery. Although little is known about transmission during birth, the neonate should be observed for signs of infection, primarily conjunctivitis and respiratory tract infection [IV; C].

Indications for therapy [IV; C]

- Identification of *M. genitalium* specific nucleic acid in a clinical specimen.
- On epidemiological grounds if a recent sexual contact has confirmed *M. genitalium* infection (ideally specimens for *M. genitalium* NAAT should be collected before treatment).

Therapy

Treatment of individuals with *M. genitalium* urogenital infection prevents sexual transmission and probably complications, including PID (Oakeshott *et al.*, 2010) and tubal-factor infertility (Lis *et al.*, 2015).

M. genitalium has demonstrated a remarkable capability of developing resistance to all antimicrobials used until today. Unfortunately, only few antimicrobial classes have activity against mycoplasmas including tetracyclines, macrolides, and fluoroquinolones.

Doxycycline has been shown in several controlled trials to have a poor efficacy in eradicating *M. genitalium* (Björnelius *et al.*, 2008; Mena *et al.*, 2009; Schwebke *et al.*, 2011; Manhart *et al.*, 2013) with microbiological cure rates between 30 and 40%, whereas azithromycin given as a 1 g single dose generally has proven more effective with cure rates in early studies (Björnelius *et al.*, 2008; Mena *et al.*, 2009) at approximately 85%, but with a declining efficacy to 40% in the most recently conducted trial with inclusion of patients between 2007 and 2011 (Manhart *et al.*, 2013). The declining efficacy is caused by a rapidly increasing prevalence of macrolide resistance, most likely due to widespread use of azithromycin as a 1g single dose without test of cure, resulting in selection of resistant strains.

Azithromycin given as an extended regimen with 500 mg day one followed by 250 mg days 2-5 (1.5g total dose) has been recommended as the primary choice of treatment of *M. genitalium* infections in Scandinavia. This is based on the reported effect of extended azithromycin on the closely related *M. pneumoniae* (Schönwald *et al.*, 1990), and approval of this regimen for treatment of pneumonia from the regulatory bodies. In a recent meta-analysis comparing studies with extended and 1g single dose azithromycin, microbiological cure rates of 88 and 81%, respectively (p=0.026) were found (Jensen & Bradshaw, 2015). It should be noted, however, that a large proportion of the patients receiving extended azithromycin had it as a second line treatment,

most often after doxycycline. Using extended azithromycin or other macrolide antibiotics after failure with the 1g single dose regimen will not eradicate *M. genitalium*.

It has been proposed that azithromycin 1g single dose may be more likely to select for macrolide resistance compared to the extended regimen (Horner *et al.*, 2014). An observational study (Anagrius *et al.*, 2013) has examined the development of resistance after extended azithromycin. This study found that none of 77 patients treated with extended azithromycin developed resistance. In contrast, 10% of 318 patients treated with a 1 g azithromycin in six studies developed resistance during treatment, lending support to the concept that single dose therapy appears to be associated with induction of resistance compared to extended regimens. On the other hand, a recent study clearly documented that resistance can be selected also during the extended azithromycin, as three of 46 (6.5%) patients with pre-treatment susceptible strains developed resistance after treatment, comparable to one of 10 (10%) receiving the 1 g single dose (Falk *et al.*, 2015).

Macrolide resistance rates varies significantly geographically, but where azithromycin 1g single dose is used for treatment of NGU, it is usually found in 30-45% of samples (Salado-Rasmussen & Jensen, 2014; Pond *et al.*, 2014; Kikuchi *et al.*, 2014; Nijhuis *et al.*, 2015) and in Greenland where azithromycin is widely used, a resistance rate of 100% has been reported (Gesink *et al.*, 2012). Another macrolide, josamycin, is widely used in Russia for treatment of *M .genitalium* positive patients as first line treatment. In a recently published study, josamycin given as 500 mg three times a day for 10 days showed a 93.5% eradication rate in males with urethritis caused by macrolide susceptible *M. genitalium* (Guschin et al., 2015). Macrolide resistance to this 16-membered macrolide was reported with approximately the same rate as for azithromycin but the mutation was selected at the A2062G position of the 23S rRNA gene (different from the A2058G/A2059G mutations described for azithromycin). In vitro, this mutation resulted in resistance of *M. pneumoniae* to pristinamycin but no cross resistance with azithromycin (Pereyre *et al.*, 2004).

Moxifloxacin is the most commonly used second line antimicrobial. Moxifloxacin is bactericidal and generally well tolerated, and in early studies, it appeared to have a cure rate approaching 100% (Bradshaw *et al.*, 2006; Jernberg *et al.*, 2008; Bradshaw *et al.*, 2008; Anagrius *et al.*, 2013). However, a declining cure rate for moxifloxacin has been observed, primarily in patients from the

Asia-Pacific region with treatment failures in up to 30%. A significant proportion of the *M. genitalium* strains had concurrent macrolide resistance mediating mutations leaving very few available treatment options (Terada *et al.*, 2012; Couldwell *et al.*, 2013; Gundevia *et al.*, 2015; Bissessor *et al.*, 2015).

Pristinamycin is the only antimicrobial with documented activity in patients failing both azithromycin, moxifloxacin, and in many cases also extended dosage doxycycline (100 mg twice daily for 14 days) (Bissessor *et al.*, 2015). In Europe, it is registered only in France, but can be acquired after special permit in most European countries. It should only be used in the maximal recommended dose of 1g four times a day for 10 days (oral) as these patients are facing their last known active antimicrobial therapy. A dose reduction is not advisable since some of the multidrug resistant strains have an elevated MIC of 0.5 mg/l (Jensen, unpublished) which may lead to failure with lower doses.

Recommended treatment for uncomplicated *M. genitalium* infection in the absence of macrolide resistance mediating mutations *[IIb;B]*

- Azithromycin 500 mg on day one, then 250 mg od days 2-5 (oral)
- Josamycin 500 mg 3 times daily for 10 days [IV.C]

Recommended treatment for uncomplicated macrolide resistant *M. genitalium* infection *[IIb;B]*

- Moxifloxacin 400 mg od for 7 - 10 days (oral). The optimal duration of treatment is uncertain and a few observational studies have found higher cure-rate after longer treatment in cervicitis (Terada *et al.*, 2012)

Recommended second line treatment for uncomplicated persistent *M. genitalium* infection *[IIb;B]*

- Moxifloxacin 400 mg od for 7 - 10 days (oral)

Recommended third line treatment for persistent *M. genitalium* infection after azithromycin and moxifloxacin *[III;B]*

- Doxycycline 100 mg two times daily for 14 days can be tried and will eradicate *M. genitalium* from approximately 30% of the patients, but the patient must be informed about the poor eradication rate and accept to comply with advice regarding sexual abstinence or condom use.
- Pristinamycin 1g four times daily for 10 days (oral). The patient should be informed about the need to comply strictly with the dosage scheme.

Recommended treatment for complicated *M. genitalium* infection (PID, epididymitis) *[IV;C]*

- Moxifloxacin 400 mg od for 14 days (oral) (Judlin *et al.*, 2010)

<u>Management of sexual contacts</u>

- Contact notification should be performed and documented by appropriately trained professionals at the time of diagnosis to improve outcome [IV;C]
- Sexual contacts should be contacted and offered testing together with counseling and treatment for *M. genitalium* infection (same antimicrobial as index patient) and testing for other STIs [IV; C]
- All sexual contacts within the preceding 6 months of onset of symptoms or diagnosis should ideally be evaluated, tested and treated [IV; C].
- If sexual contacts do not attend for evaluation and testing, epidemiological treatment should be offered with the same regimen as given to the index patient [IV; C]

Follow-up and test of cure (TOC)

A TOC should be routinely performed in all patients due to the high prevalence of macrolide resistance either present pre-treatment or developing during treatment with azithromycin and in the absence of routine testing for fluoroquinolones resistance [IV; C]. This recommendation differs from the BASHH and CDC guidelines (Workowski & Bolan, 2015; Horner *et al.*, 2015) where TOC for asymptomatic cases is not recommended. However, it is a clinical experience that many patients enter a stage of few or no symptoms after treatment, but with persistent carriage and subsequent risk for spread of resistance in the community.

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APPENDICES

Search strategy

A Medline search was conducted in May 2015 using PubMed. The search heading was kept broad (Mycoplasma genitalium) to include epidemiology, diagnosis, antimicrobial resistance, drug therapy, clinical trials and prevention and control. Only publications and abstracts in the English language were considered. The Cochrane library was searched for all entries related to mycoplasma. Sexually transmitted diseases guidelines produced by the US Centers for Disease Control (www.cdc.gov/std/) and the British Association for Sexual Health and HIV (www.bashh.org) were also reviewed.

Gianfranco Spiteri – ECDC representative, Sweden, (app.

List of contributing organisations

This guideline has been produced on behalf of the following organisations: the European Branch of the International Union against Sexually Transmitted Infections (IUSTI Europe); the European Academy of Dermatology and Venereology (EADV); the European Dermatology Forum (EDF); the Union of European Medical Specialists (UEMS). The European Centre for Disease Prevention and Control (ECDC) and the European Office of the World Health Organisation (WHO-Europe) also contributed to its development.

Levels of Evidence

Ia. Evidence obtained from metaanalysis of randomised controlled trials.

Ib. Evidence obtained from at least one randomised controlled trial.

IIa. Evidence obtained from at least one well designed study without randomisation.

IIb. Evidence obtained from at least one other type of well designed quasi-experimental study.

III. Evidence obtained from well designed non experimental descriptive studies such as comparative studies, correlation studies, and case control studies.

IV. Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of Recommendations

A (Evidence levels Ia, Ib)

Requires at least one randomised control trial as part of the body of literature of over all good quality and consistency addressing the specific recommendation.

B (Evidence levels IIa, IIb, III)

Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence IV)

Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

Conflicts of interests

The Work Under Consideration for Publication **2015 European guideline on *Mycoplasma genitalium* infections**					
		Jørgen Skov Jensen	**Marco Cusini**	**Mikhail Gomberg**	**Harald Moi**
1	Grant	no	no	no	no
2	Consulting fee or honorarium	no	no	no	no
3	Support for travel to meetings for the study or other purposes	no	no	no	no
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no	no	no	no
5	Payment for writing or reviewing the manuscript	no	no	no	no
6	Provision of writing assistance, medicines, equipment, or administrative support	no	no	no	no
7	Other	no	no	no	no

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	no	no	no	no
2	Consultancy	yes	yes	yes	yes
3	Employment	no	no	no	no
4	Expert testimony	yes	yes	yes	yes
5	Grants/grants pending	no	no	no	no
6	Payment for lectures including service on speakers bureaus	yes	yes	yes	yes
7	Payment for manuscript preparation	no	no	no	no
8	Patents (planned, pending or issued)	no	no	no	no
9	Royalties	no	no	no	no
10	Payment for development of educational presentations	no	no	no	no
11	Stock/stock options	no	no	no	no
12	Travel/accommodations/meeting	yes	yes	yes	yes

	expenses unrelated to activities listed**				
13	Other (err on the side of full disclosure)	no	no	no	no

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no	No	No	no