Full application for an addition of a test categories in the EDL

Survey response 1

Response ID
48

Date submitted
1980-01-01 00:00:00

Last page
1

Start language
en

1. Name of test category

Name of the test category addressed in the original submission:
Pneumocystis PCR

2. Pre-submission information

Please indicate your pre-submission response ID: [Pre-submission ID]
255

3. Applicant’s information (primary contact person):

Contact person, name and information of the person submitting the application: [LAST NAME, First name]
DENNING, David

Contact person, name and information of the person submitting the application: [Email address (...@....)]
ddenning@gaffi.org

Contact person, name and information of the person submitting the application: [Phone number (+country code) phone number no spaces]
447802482193

Contact person, name and information of the person submitting the application: [Other information]
www.GAFFI.org

4. Applicant’s information (secondary contact person):

[Last name, First name]

[Email address (...@....)]
5. Details of the organization making the submission (if applicable)

<table>
<thead>
<tr>
<th>Name of the organization making the submission (if applicable):</th>
<th>Global Action Fund for Fungal Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the organization making the submission (if applicable):</td>
<td>Rue Le Corbusier 12  1208 Geneva</td>
</tr>
<tr>
<td>Name of the organization making the submission (if applicable):</td>
<td><a href="http://www.GAFFI.org">www.GAFFI.org</a></td>
</tr>
<tr>
<td>Name of the organization making the submission (if applicable):</td>
<td>447802482193</td>
</tr>
</tbody>
</table>

6. Details of the organizations supporting the application:

<table>
<thead>
<tr>
<th>Please provide up to three organizations supporting your application including a. Organization name, b. Contact person, c. Email address:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal PCR Initiative: <a href="https://www.isham.org/working-groups/european-aspergillus-PCR-initiative-eapcri">https://www.isham.org/working-groups/european-aspergillus-PCR-initiative-eapcri</a>  Dr P. Lewis White, <a href="mailto:lewis.white@wales.nhs.uk">lewis.white@wales.nhs.uk</a></td>
</tr>
</tbody>
</table>

7. Public health impact of the disease/condition:
Pneumocystis pneumonia (PCP) is a life-threatening illness of largely immunosuppressed patients such as those with HIV/AIDS [1]. However, when diagnosed rapidly and treated, survival rates are high. The etiologic agent of PCP is Pneumocystis jirovecii, a human-only fungus that has co-evolved with humans and could be considered a commensal, which does not grow on microbiological agar. Other mammals have their own Pneumocystis species.

AIDS-related PCP in adults has a variable incidence - from 5.9 to 55% and in children from 5-49% [1]. In the 1980s, during the HIV pandemic, PCP was one of the most prevalent AIDS defining diseases in the developed world and this remains an issue in cases of undiagnosed HIV, particularly in resource limited countries. [2] There are thought to be about 400,000 PCP cases in advanced HIV infection annually and >100,000 in those with other immunosuppressive diseases. [3] Cotrim prophylaxis is partly protective, reducing the from 19.2 to 5.2 cases per 100 patient years in HIV patients in the USA [3]. Among babies and children with HIV, PCP is relatively common in many parts of the world; In South Africa, PCP occurred in 43 children (21.3%) with hypoxic pneumonia of whom 33 (76.7%) were HIV-infected. [4]

In addition to patients diagnosed with HIV, there is an ever-increasing susceptible HIV-negative population at risk of Pneumocystis jirovecii pneumonia (PcP) [6-11]. Patients with solid tumours or suffering from haemato logical malignancy, solid organ transplant recipients (SOT), or with autoimmune and inflammatory conditions receiving immuno-modulating therapies (e.g. high dose corticosteroids or anti-TNF therapy) and patients diagnosed with primary immune deficiencies, are at increased risk of PPP. [11, 12] Generally, the incidence of disease is low (12 months). [8-10, 13, 14] However, the epidemiology of PcP is changing, associated with more aggressive immunosuppressive and immuno-modulatory approaches when managing other conditions (haematology, SOT (particularly renal Tx), auto-immune conditions (rheumatoid arthritis and vasculitis) and pre-existing respiratory conditions (CORD)). [6, 7]

Untreated the mortality is 100%. In AIDS, in high income countries the mortality is about 10%, but in LMICs about 30% [1]. The day 30 all-cause mortality overall is ~28%, ranging from 10-62%, but is higher in HIV-negative patients due to fulminant disease. [4]. In addition to high dose cotrimoxazole, adjunctive corticosteroids reduce mortality in AIDS in moderate and severe cases, but are unhelpful in non-AIDS cases. Second-line therapy requires clindamycin + primaquine.

The historical difficulties in diagnosing PcP (lack of culture and poor sensitivity of microscopic investigation) has resulted in many cases being diagnosed on clinical suspicion [3]. Clinically, signs are non-specific, typically bilateral chest infection presents with respiratory signs of distress, which can be mild in the HIV-positive but typically more severe in HIV-negative. Radiological signs can be absent in the early stages, but when present although typical of PcP, are generally non-specific (bilateral ground glass opacification, leading to consolidation) and could also represent the underlying condition [15, 16]. With the advent of modern diagnostics techniques (real-time PCR and (1-3)-β-D-glucan (BDG)) there is no reason for a laboratory based diagnosis not being achieved.

Please detail the public health relevance of conditions addressed with the proposed test and add references:

1) Pneumocystis pneumonia Briefing document: https://www.gaffi.org/media/fact-sheets/
3) GAFI Roadmap: https://www.gaffi.org/roadmap/
8. Potential public health impact of the test:

Please explain in which way the proposed test benefits public health. Please detail your response and add references:

The development of highly sensitive, non-culture based tests have enabled laboratories to diagnose PCP more readily and exclude disease when tests are negative. PCP is currently not confirmable in the laboratory in babies and children without Pneumocystis PCP - nasopharyngeal washes have a high predictive value.

Pneumocystis pneumonia (PCP) in AIDS is often diagnosed empirically based on a subacute onset of cough, breathlessness out of proportion to the radiological abnormalities and subtle, bilateral chest X-ray changes, in the context of a low CD4 cell count. Co-trimoxazole (trimethoprim-sulphamethoxazole, Bactrim®, Septrin®) is the most effective agent for both prevention and therapy of PCP. A low dose is effective for prophylaxis, but a 3-week course of high and potentially toxic doses is required for effective therapy. The differential diagnosis of PCP is broader in children as bacterial pneumonia is more common. If a precise diagnosis could be achieved in most cases of PCP, much inappropriate use of co-trimoxazole would be prevented.

Rates of PCP among newly hospitalized adults with advanced HIV infection are highly variable (less than 1% to 60%), with rising rates as gross domestic product increases. [1] Without adequate diagnostics available, many patients will unnecessarily receive high dose co-trimoxazole with or without corticosteroids for 3 weeks. If the actual number of PCP cases in patients with AIDS is 400,000, then 100,000s may be given co-trimoxazole unnecessarily, with toxicity rates as high as 90%. [2,3] Early detection and diagnosis of PCP can help prevent unnecessary hospitalization and cost. Outpatient sputum PCP PCR is possible in hours, and assuming that 25% of PCP cases are mild, immediate diagnosis and use of oral therapy will potentially avoid 100,000 admissions to hospital annually, or even more if the diagnosis is ruled out and patients are not admitted for unnecessary PCP therapy. Mild PCP responds well to treatment, and prevents progression to moderate or severe infection.

 provision of rapid Pneumocystis diagnostics will enable early diagnosis, allow discontinuation of broad spectrum antibiotics if positive and discontinuation of high dose cotrimoxazole and corticosteroids if negative. Missed PCP diagnoses, obscured by concurrent bacterial infection, will be minimized. Pneumocystis PCR should be widely available for all respiratory samples serving large immunocompromised populations. These diagnostics will also definitively improve outcome for non-AIDS immunocompromised patients for the same reasons as in AIDS.


9. Clinical utility of the proposed test/potential impact of the test on patient management and care
High dose co-trimoxazole (sulphamethoxazole/trimethoprim) is the standard therapy for PCP, best given IV initially for very ill patients. A switch to oral is usually after 3-10 days depending on progress and severity. Moderate and severe PCP (judged by hypoxaemia) responds better if corticosteroids are used concurrently, for 10 days to 3 weeks, in AIDS patients. [1,2] A few data support corticosteroid therapy in children with HIV, but it is often not used because of clinical uncertainty. Adjuvant corticosteroid therapy has not been yet evaluated properly in non-HIV infected patients, although not to influence outcome based on retrospective studies. If the diagnosis of PCP can be excluded, then corticosteroids can be avoided, reducing the risk of other infections.

Complications of therapy are common including nausea, vomiting, skin rash, neutropenia and abnormal liver function tests. Mild cases can be treated with all oral therapy, using co-trimoxazole, dapsone, or atovaquone. Second line therapy is preferably a combination of clindamycin and primaquine; IV pentamidine, can be used for cotrimoxazole intolerance.

Untreated PCP is fatal. Management by highly experienced clinicians leads to 85-90% survival in AIDS patients and ~50% in non-AIDS patients. Once improved, AIDS patients can be started on antiretroviral agents (ARVs) and most make an excellent clinical recovery, without residual lung disease, and immunological recovery.

P. jirovecii circulates in immunocompetent hosts through air continuously in the human population1. It is present in exhaled air close to patients with PCP, amounts decreasing the further the sampling moved away from patients. Direct person-to-person transmission has now been documented [3], and some genotypes may be more transmissible or virulent than others. [4-6] All hospitalized patients with PCP should be isolated in single rooms and that vulnerable patient groups should be kept away from them. Transmission has also occurred from carrier patients, making more complicated the prevention of transmission. [6]


10. Systematic reviews of the clinical accuracy of the test

<table>
<thead>
<tr>
<th>Meta-analytical review of PcP PCR on respiratory generates excellent sensitivity ≥97% and the subsequent negative predictive value (NPV) ≥99% is sufficient to rule-out PcP when PCR is negative. [1-3] Despite the detection of possible Pneumocystis colonization, positivity in respiratory samples readily confirms disease as shown by the positive likelihood ratios (LR+ ≥10). [1-3]</th>
</tr>
</thead>
</table>
11. Primary studies of clinical accuracy of the test
The current gold standard for confirming a diagnosis remains histological and/or microscopic identification of ascus (cysts containing ascospores) and trophic forms of Pneumocystis in clinical specimens, usually respiratory samples using conventional or immuno-fluorescent (IF) antibody stains. Standard microscopic investigation is highly subjective and this can influence specificity, sensitivity which is dependent on the fungal burden. While IF-microscopy improves sensitivity, it is still sub-optimal (67%). [1] A 4-way comparison of different microscopy and staining techniques on 313 respiratory specimens found the best to IF. [2] The sensitivity and specificity of Calcofluor white stain (CW) were 73.8 and 99.6%, respectively. The sensitivity and specificity of Grocott-Gomori methenamine silver stain (GMS) were 79.4 and 99.2%, respectively. The sensitivity and specificity of Diff-Quik stain were 49.2 and 99.6%, respectively. The sensitivity and specificity of Merifluor Pneumocystis stain were 90.8 and 81.9%, respectively. Only CW and GMS had positive and negative predictive values of >90%.

PCR testing has been applied to a range of specimen types (BAL fluid, NBL, blood). PCR testing of BAL fluid is preferred, but positivity in upper airway samples (sputum, induced sputum, oral washes and nasopharyngeal aspirates), once thought to represent detection of transient colonization, likely reflects a significant burden lower in the respiratory tract and is specific for PCp. [3] Expectorated and induced sputum samples have been studied in Africa and have good sensitivity. [4,5] In Namibia, 475 samples were analysed and 25 (5.3%) samples were positive for P. jirovecii; 17 (3.6%) using both qPCR and GMS staining and eight (1.7%) using qPCR only. [4] P. jirovecii was present in 8/150 (5.3%) HIV-positive and tuberculosis (TB) smear-negative patients, and in 12/227 (5.3%) TB smear-negative patients with an unknown HIV status. In South Africa, P. jirovecii was identified in 51% (156/305) and 67% (204/305) of specimens using IF and qPCR, respectively. [5] The cut-off value for the qPCR that best predicted the IFA results was 78 copies/5 μl (area under ROC curve 0.92). The sensitivity and specificity of qPCR using this cut-off was 94.6% and 89.1%, respectively, compared with the IFA.

In children, Pneumocystis PCR is invaluable for diagnosis. In South Africa, 202 children [median age 3.2 months] were studied; 124 (61.4%) were HIV infected. [6] PCP was identified in 109 (54%) children using PCR, compared to 43 (21%) using IF and Grocott staining (p < 0.0001). Most PCP cases (88, 81%) occurred in HIV-infected children. All 21 cases (19%) occurring in HIV-negative children had another risk factor for PCP. In India, 94 immunocompromised children with pneumonia were investigated for PCP. [7] PCR detected P. jirovecii in 14 children. The occurrence of PCP in HIV-infected children was 43% (6/14), renal disease on immunosuppressants 45% (4/9), primary immune deficiency 19% (2/11) and malignancies on chemotherapy 4% (2/57).

The presence of Pneumocystis DNA in blood samples is a poor prognostic marker. Detection of DNA in the plasma of HIV-positive patients was significantly higher in deceased patients (79%) compared to survivors (14%), as was the burden of disease (deceased: 54610 copies/ml vs survivors: 935 copies/ml). [8] PCR has been used to determine prognosis. In a study of 81 HIV-negative PCp patients with respiratory failure that were initially PCR positive, PCp PCR negative conversion was associated with a good prognosis, generating a hazard ratio of 0.433 (95% CI: 0.203-0.928, P = 0.031). [9] Performance of PCR may vary between HIV-positive and HIV-negative patients. The lower burden encountered in HIV-negative patients may lower sensitivity, but PCR specificity remains high. [3] Nevertheless, PCR negativity when testing BAL fluid can be used to exclude disease irrespective of the underlying condition (ECIL Guidelines A-II recommendation). [3]
Please attach the publications you make reference to:

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[("title":"Das Children India","comment":"","size":193.02,"name":"Das%20Induced%20sputum%20in%20children%20India%20J%20Trop%20Pediatr%202014.pdf","filename":"fu_wwhkw22z9ajmgwt","ext":"pdf" ),
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("title":"Choi Pneumocystis blood poor prognosis","comment":"","size":1192.851,"name":"Choi%20Pneumocystis%20DNA%20blood%20PLOS%20ONE%202018.pdf","filename":"fu_jscany742dd7xgq","ext":"pdf" ),
("title":"Nowaseb Sputum PCP PCR and grocott","comment":"","size":752.316,"name":"Nowaseb%20Sputum%20PCP%20Namibia%20J%20Infect%20Dev%20Ctries%202014.pdf","filename":"fu_u3nt2i3vyw8p3be","ext":"pdf" )]
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12. Systematic reviews of the clinical utility/impact of the test on patient management and care

Please describe any systematic reviews of studies on the impact of the test result in clinical practice on diagnosis, treatment and patient outcomes or state if none are available (please refer to the guidance document):

In the context of LMICs, almost no real-life studies of the role of PCP PCR have been conducted because of unavailability of the test. We did review the topic recently but it is not a systematic review as this is probably not possible with the current state of knowledge [1]:

"Globally, Pneumocystis pneumonia (PCP) remains a common and lethal infection in both HIV-positive and HIV-negative patients, particularly in developing countries where rates of PCP increases with rising GDP. Pneumocystis jirovecii cannot be cultured in routine clinical laboratories; thus diagnosis relies on microscopy, histology, serology and/or polymerase chain reaction (PCR) of the Pneumocystis DNA. Most of these methods are expensive and require training. Accessing lower respiratory tract specimens in young children is often challenging and only PCR testing of nasopharyngeal aspirates is useful. Early treatment with high-dose co-trimoxazole is effective therapy; however, adverse reactions are common along with reports of emerging resistance. Improved outcomes are associated with adding corticosteroid to treatment in those with moderate/severe PCP, although this has not been studied in resource-poor settings. This review compares the available diagnostic techniques in relation to their suitability for use in resource-poor settings. We also addressed the non-availability of the alternative medications in these regions."


Please attach the reviews you make reference to:

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[("title":"Oladele PCP in resource poor settings","comment":"","size":715.926,"name":"Oladele%20PCP%20in%20resource%20poor%20settings%20in%20%20J%20%20Underserved%202018.pdf","filename":"fu_djg6g825xrgf78","ext":"pdf" )]
```

13. Primary studies of the clinical utility/impact of the test on patient management and care

Please briefly describe any primary studies of the clinical utility/impact of the test on patient management and care, or state if none are available (please refer to the guidance document):

This topic is covered in the sections above.
Numerous guidelines recommend Pneumocystis PCR as a component of managing complex immunocompromised patients. The WHO Advanced HIV Disease guidelines do not specifically recommend any diagnostic approach.


7) Donnelly JP et al. 2nd revision of the EORTC/MSG criteria Clinical Infectious Diseases 2019. In press

Please attach the guidelines that you are referring to:

- Donnelly JP et al. 2nd revision of the EORTC/MSG criteria Clinical Infectious Diseases 2019. In press
Please download and complete the table in Annex I with commercially available IVD products in the test category, and include the information listed for each one. Please upload the completed file back and all the relevant test Instructions For Use (Package Inserts):

Filecount - Please download and complete the table in Annex I with commercially available IVD products in the test category, and include the information listed for each one. Please upload the completed file back and all the relevant test Instructions For Use (Package Inserts):

1

16. Training requirements

Considering the tests mentioned in 15 above, what in general are the training requirements?:
Significant training required

17. Equipment required

Considering the tests mentioned in 15 above, please describe in general terms what, if any, equipment is required other than that provided with the test:
See Annex 1
Extraction and real-time PCR equipment necessary as well as positive displacement pipettes and other 'clean' facilities.

18. Energy requirements

Considering the tests mentioned in 15 above, what, if any energy source is required for performance of the tests?:
Continuous electrical power

Considering the tests mentioned in 15 above, what, if any energy source is required for performance of the tests?: [Other]

19. Landscape reviews

Please list any landscape reviews describing the different test technologies and their use or state if none available:
The recent review by Guegan and Robert-Gangneux provides an excellent summary of the molecular diagnosis of PcP, including commercially available assays (Se: 60-100%; Sp: 82-100%). [1]


Please attach the documents referred to in this question:

Filecount - Please attach the documents referred to in this question:
1

20. Cost and Cost-effectiveness
Please provide a summary of data on comparative cost and cost-effectiveness or state if not available:

| No review of this is available. Costs per assay are shown in Annex 1, if available. Not the development of the first freeze-dried assay (Amplex), which will greatly reduce shipping cost and enable transport to centres without a major airport. This is a recent launch and potentially transformational. We cannot certain the cost per assay or the equipment cost, but notable that no extraction system required and time to assay result is 25 minutes. |

21. Ethical issues

Please detail any important ethical considerations related to the proposed test category and any consequences of its use:

| No specific ethical issues |

22. Equity and human rights issues

Please indicate if it reduces inequities and increases accessibility or if the test may prove inaccessible to some populations:

| No specific equity or human rights issues |

Signature

| Through the electronic signature below, I acknowledge that I have provided appropriate information to support this submission. I acknowledge that WHO reserves the right to format and select the information provided as necessary and agree that the information will be publicly disclosed by WHO. [Electronic Signature (type your full name to sign):] David Denning |

2019-11-17 | Through the electronic signature below, I acknowledge that I have provided appropriate information to support this submission. I acknowledge that WHO reserves the right to format and select the information provided as necessary and agree that the information will be publicly disclosed by WHO. [Date (yyyy-mm-dd):] | 2019-11-17 |