NICE advice

AdenoPlus point-of-care test for diagnosing adenoviral conjunctivitis

Medtech innovation briefing
Published: 15 December 2015

www.nice.org.uk/guidance/mib46

Summary

AdenoPlus is a point-of-care test for diagnosing acute adenoviral conjunctivitis in people of all ages, and can be used in any healthcare setting. Two prospective diagnostic accuracy studies showed the sensitivity of AdenoPlus to be 85% and 39.5%, and its specificity to be 98% and 95.5%, compared with existing laboratory tests. A box of 10 single-use AdenoPlus tests costs £150, excluding VAT. The test needs no additional equipment or consumables.

Product summary and likely place in therapy

- AdenoPlus is a point-of-care test for diagnosing adenoviral conjunctivitis in people of all ages.
- It is designed to be used in any setting where people present with eye conditions, such as primary care, urgent care services and ophthalmology services. If adopted, it

would be used as an alternative to existing laboratory tests that are currently carried out for managing persistent or high-risk infectious conjunctivitis.

Effectiveness and safety

- The published evidence summarised in this briefing comes from 3 studies including a total of 571 people.
- One US-based multicentre prospective diagnostic accuracy study compared the AdenoPlus test with both polymerase chain reaction (PCR) and viral cell culture with confirmatory immunofluorescence assay (CC-IFA) in 128 consecutive patients with suspected acute viral conjunctivitis based on clinical examination. AdenoPlus had a sensitivity of 85% and specificity of 98% compared with PCR, a sensitivity of 90% and specificity of 96% compared with CC-IFA, and a sensitivity of 93% and specificity of 98% compared with both CC-IFA and PCR.
- One UK-based prospective diagnostic accuracy study compared the AdenoPlus test with PCR in 109 consecutive patients presenting to an emergency eye unit with symptoms of acute adenoviral conjunctivitis. Compared with PCR, the AdenoPlus test had a sensitivity of 39.5% and a specificity of 95.5%. No adverse events were reported.
- The difference in reported sensitivity between the studies may have been caused by inadequate sampling of tear fluid for the reference standard test in the UK study.
- One cross-sectional epidemiological study done in France compared the AdenoPlus test with clinical diagnosis in 334 people with acute signs and symptoms of conjunctivitis for less than 7 days. The investigators believed the conjunctivitis was of viral origin in 89% of the people. This was confirmed by the AdenoPlus test in half of these people. No further information was reported that would allow the assessment of test accuracy.

Technical and patient factors

- AdenoPlus is a single-use diagnostic test. Each test kit comprises a sample collector, a test cassette and a buffer vial; the test result is available in around 10 minutes.
- The AdenoPlus test is intended to be used by healthcare professionals.

- The test is recommended for use within 7 days of developing a red eye consistent with infectious conjunctivitis.
- The sampling fleece used with the test is made of Dacron, which may cause allergic reactions in some people.

Cost and resource use

- A box of 10 single-use AdenoPlus tests costs £150, excluding VAT.
- No additional consumables are needed.

Introduction

Conjunctivitis is inflammation of the conjunctiva, the thin membrane that covers the front of the eye. It may be caused by infection, allergy or an external irritant. People with infectious conjunctivitis usually present with symptoms including an irritated red eye with a watery or purulent discharge. Symptoms often appear in one eye at first and then spread to the other eye. Most people with conjunctivitis are first treated by GPs rather than eye care specialists (Azari and Barney 2013). In England, there were 4.5 million GP consultations concerning the eye in 2011/12 (Health & Social Care Information Centre 2012). It has been estimated that infectious conjunctivitis was responsible for 41% of GP consultations about eye problems (Sheldrick et al. 1993).

Viral infection is the most common cause of infectious conjunctivitis, accounting for up to 75% of cases (Jhanji et al. 2015). Viral conjunctivitis is usually caused by adenovirus, which is highly contagious. Although adenoviral conjunctivitis tends to get better spontaneously, meaning that it is self-limiting, the person is still infectious for up to 14 to 21 days after infection (Kaufman 2011). Transmission of the infection is mostly by hand-to-eye contact, ocular secretions, respiratory droplets, and contact with ophthalmic care providers and their instruments (Azar et al. 1996).

Viral and bacterial conjunctivitis are difficult to distinguish based on symptoms alone. But, because most of the infections are self-limiting, laboratory confirmation is usually kept for recurrent conjunctivitis, and conjunctivitis that has not responded to medication (The College of Optometrists 2014). Laboratory tests include microscopy and either culture or polymerase chain reaction analysis of conjunctival swabs. The rate of clinical accuracy in diagnosing viral conjunctivitis is less than 50% compared with laboratory confirmation,

with many cases misdiagnosed as bacterial conjunctivitis (O'Brien et al. 2009). Only 36% of 300 UK-based GPs who completed a postal questionnaire believed that they could discriminate between viral and bacterial infection, and there was considerable variability in the use of individual signs to make a diagnosis of infectious conjunctivitis. The same survey found that 95% of GPs usually prescribe topical antibiotics (used to treat bacterial conjunctivitis) for infectious conjunctivitis despite 58% stating that they thought at least half of the cases were caused by viruses (Everitt and Little 2002). Social factors, including the need for children to attend day care or school and for parents to go to work, drive people to seek early treatment and contribute to a GP's decision to prescribe antibiotics for children with acute infectious conjunctivitis (Rose et al. 2006). Antibiotics are not needed for most patients, with 65% recovering without any treatment within 2 to 5 days of symptoms appearing (Rose 2007). Actions taken to slow the development and spread of antimicrobial resistance, including reducing inappropriate prescribing, led to a 3.8% fall in the number of prescriptions for antibiotics in primary care in 2013 compared with 2012 (Health & Social Care Information Centre 2013).

A test that could easily and reliably distinguish between bacterial and viral conjunctivitis could contribute to good antibiotic stewardship if it led to fewer antibiotics being prescribed.

Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

About the technology

CE marking

The AdenoPlus test is an in vitro diagnostic medical device for which the manufacturer (Rapid Pathogen Screening) received a CE mark in June 2011. The CE mark was revised in October 2012 when the product name was changed from Adeno Detector to AdenoPlus. The current UK distributor is Nicox Pharma SNC.

Description

AdenoPlus is a single use, point-of-care diagnostic test for adenoviral conjunctivitis. All human adenovirus serotypes contain the hexon protein that is detected by AdenoPlus. The test takes around 10 minutes to return a result. According to the instructions for use, the test is recommended for use within 7 days of the person developing a red eye with signs and symptoms of infectious conjunctivitis. AdenoPlus has a detection limit of 6 ng/ml adenovirus hexon protein.

All the necessary components of the AdenoPlus test are contained in a single test kit. This includes a sterile sample collector with sampling fleece attached to the tip, a test cassette and a buffer vial. The sampling fleece is made of Dacron, which may cause allergic reactions for some people. If both eyes are affected by conjunctivitis, the test should be done using tear samples from the most recently affected eye. To do the test, tear fluid is collected from the person's inferior palpebral fornix conjunctiva (the area between the lower eyelid and the eyeball). This is exposed by pulling the lower eyelid downwards. The sampling fleece is dabbed across the conjunctiva 6 to 8 times in total, and is then rested against the conjunctiva for an additional 5 seconds. If the person experiences discomfort during the sampling procedure, a topical anaesthetic can be used, and the sample collected 5 minutes after applying the anaesthetic. The anaesthetic does not interfere with the test results.

The protective cap is then removed from the test cassette, revealing a sample transfer window and an absorbent tip. The sample collector is placed on the test cassette with the sampling fleece tip inserted into the sample transfer window, and the 2 components are then clipped together. To run the test, the absorbent tip of the test cassette is immersed into the buffer vial for at least 20 seconds. Once the absorbent tip is removed from the buffer vial, the protective cap is replaced on the test cassette and the test placed horizontally on a flat surface for at least 10 minutes. The test cassette also contains a result window. A purple fluid wave will move across the background of the result window while the test is running. Once the background of the result window is white and 10 minutes have elapsed, the test can be read.

The results of the test are indicated by 2 lines: a blue control line and a red result line, which appear in the result window in their respective zones (the control zone and the result zone). The blue control line indicates that the test result is valid. A red line in the result zone indicates a positive result – the presence of adenovirus antigens in the tear fluid. A red line that is faint or uneven in colour or incomplete over the width of the test

strip may happen because of an uneven distribution of eye fluid in the sampling fleece, but this should also be interpreted as a positive result. A single blue control line with no red result line indicates that the test has worked but the result is negative, that is, adenovirus antigens are not present in the tear fluid or are below the 6 ng/ml detection limit of the test. If a blue control line does not appear, the test result may be invalid. In this case, the absorbent tip should be re-immersed in the buffer vial for an additional 10 seconds. If a blue line still does not appear after 10 minutes, the test should be discarded and the person retested using a new AdenoPlus test kit. If a further test is needed, additional samples from the same eye may have fewer adenoviral antigens, so if both eyes are equally affected, the second sample should be collected from the other eye. In patients with only one eye affected, the sample collection may be repeated 30 minutes later. The test cassette should be used within 1 hour of opening, and the test run within 24 hours of taking a sample and assembling the test. The result should be read within 12 hours of completing the test.

Setting and intended use

The AdenoPlus test is intended for use by healthcare professionals to help in the rapid differential diagnosis of acute conjunctivitis in people of any age, to reduce the unnecessary prescribing of antibiotics for viral infections. It is designed for use in any healthcare setting where people with eye conditions present, such as primary care, urgent care services or secondary care ophthalmology services.

Current NHS options

A diagnosis of conjunctivitis is usually made by GPs by assessing symptoms and examining the eyes. People should be referred to an ophthalmology clinic if they have reduced vision or if they do not respond to treatment. People who wear contact lenses may need to be referred to an optometrist to check the cornea for keratitis (NHS Oxfordshire 2010). Further tests (such as a swab test) may be needed if the conjunctivitis is persistent, does not respond to treatment or to help decide what treatment to use (NICE clinical knowledge summary on infective conjunctivitis). The swab from the affected eye is sent to a laboratory to determine the cause of the conjunctivitis. Cell culture with immunofluorescence detection is considered reliable but may take 1 to 2 weeks; polymerase chain reaction (PCR) assays can identify adenovirus, enterovirus, herpes simplex virus or herpes zoster virus in less time (Public Health England 2014).

NICE is not aware of any other CE-marked devices with a similar function to the AdenoPlus

test.

Costs and use of the technology

AdenoPlus costs £150 (excluding VAT) for a box of 10 tests. There are no additional consumables or maintenance requirements. Both the AdenoPlus test cassette and the buffer are stable until the expiry dates marked on their outer packaging and containers. The shelf life is 2 years.

Likely place in therapy

AdenoPlus would be used as an alternative to existing laboratory tests to identify the type of infection in people with infectious conjunctivitis.

Specialist commentator comments

Two specialist commentators stated that AdenoPlus is fairly easy and quick to use at the point of care. However, 2 of the specialist commentators noted that the process of swabbing might be difficult, particularly in people with sore or severely inflamed eyes, and is likely to be impractical in children.

One specialist commentator mentioned that AdenoPlus is cheaper than the current gold standard PCR test (if swab and laboratory costs are taken into account), although PCR is not commonly used because the results are not available in time to guide first-line management. One specialist commentator stated that the current management options for conjunctivitis are either no treatment or treating with antibiotics (usually chloramphenicol eye drops) and that both options are cheaper than using AdenoPlus (about £1.50 compared with £15). One specialist commentator noted that the need for steroid treatment for the acute condition or for adenoviral keratitis, which may occur as a complication of certain serotypes of the virus, is based on the symptoms of the patient. They added that although it is reassuring to know that the patient definitely has adenovirus, it is not necessary for ongoing management.

One specialist commentator stated that using AdenoPlus in an acute setting or GP practice is cost and time effective. Another specialist commentator stated that they do not consider AdenoPlus to be clinically necessary and that it does not offer sufficient utility to warrant its routine use in infectious conjunctivitis. They did note that it would be 'nice to

have', particularly in primary care settings without access to a slit lamp, and for atypical cases, such as those where only one eye is affected. The specialist commentator stated that, assuming the conjunctivitis is viral, no harm would come to the person by not doing any tests, giving no antibiotics and waiting for a few days. They also said that this strategy would not cause side effects related to antibiotic usage and would also minimise expense. The specialist commentator noted that even if they have a positive test using AdenoPlus, patients also need to be checked by a healthcare professional with a slit lamp if they have a lot of pain, blurred vision or sensitivity to bright lights (photophobia) because they might need topical steroid treatment.

One specialist commentator stated that AdenoPlus was cheaper than the current gold standard PCR test, which is not commonly used because the results are not available to guide first-line management. They noted that although PCR can detect atypical cases of chlamydia conjunctivitis as well as other viruses such as herpes simplex virus and varicella-zoster virus, which all have specific treatments, they considered PCR to be a waste of resources unless chlamydia was the likely cause. The specialist commentator raised a concern that AdenoPlus could give false reassurance in people with both adenovirus and chlamydia. This might lead to under-treatment of chlamydia, which has far greater potential complications for the person and their sexual partner.

Two specialist commentators stated that antibiotics are often prescribed because people find their symptoms distressing, although most cases of conjunctivitis seen by GPs are mild conditions that may get better with no treatment, and are likely to be of viral origin. Two specialist commentators suggested that it would be more cost effective to target public health messages (for example, in school and nursery health education and policies) to reduce the pressure on GPs to prescribe antibiotics for conjunctivitis. One specialist commentator noted that there are currently no real-world data to support the idea that antibiotic prescribing would decrease by using AdenoPlus. The commentator stated that it would be useful to see more studies on AdenoPlus to confirm if regular use of the test reduces the numbers of people requesting antibiotics from GPs, as well as reducing the number of antibiotic prescriptions.

One specialist commentator stated that the AdenoPlus test itself would not reduce the number of working days and school days lost as a result of conjunctivitis, because the test will not affect the course of the condition or the symptoms. However, replacing PCR tests with AdenoPlus could decrease the number of unnecessary GP appointments and days off work or school needed to get the results, reducing health-related anxiety and additional expenses for the person.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women
- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Evidence review

Clinical and technical evidence

Regulatory bodies

A search of the Medicines and Healthcare Products Regulatory Agency website revealed no manufacturer Field Safety Notices or Medical Device Alerts for this device. No reports of adverse events were identified from a search of the US Food and Drug Administration (FDA) database: Manufacturer and User Device Facility Experience (MAUDE).

Clinical evidence

Studies evaluating the Adeno Detector test (the predecessor of AdenoPlus) were excluded from further assessment because it has a higher limit of detection and a partly different design, so limiting the generalisability of findings. This briefing includes 2 prospective diagnostic accuracy studies (Sambursky et al. 2013; Kam et al. 2015) and 1 conference abstract and its respective poster (Tuil et al. 2015a, 2015b), which reported interim analyses of an observational epidemiological study.

The study by Sambursky et al. (2013; presented in tables 1 and 2) was a prospective, multicentre diagnostic accuracy study conducted in 8 private ophthalmology practices and

academic centres in the USA. It compared the sensitivity and specificity of the AdenoPlus test with polymerase chain reaction (PCR) and viral cell culture with confirmatory immunofluorescence assay (CC-IFA), to detect adenovirus in tear fluid from 128 consecutive people presenting with a clinical diagnosis of acute viral conjunctivitis.

Compared with PCR, AdenoPlus showed a sensitivity of 85% (29/34), a specificity of 98% (89/91), a negative predictive value (NPV) of 95% (89/94), and a positive predictive value (PPV) of 94% (29/31). The overall agreement was 94% (118/125).

Compared with CC-IFA, AdenoPlus showed a sensitivity of 90% (28/31), a specificity of 96% (93/97), a NPV of 97% (93/96), a PPV of 88% (28/32), and an overall agreement of 95% (121/128).

Compared with the combination of CC-IFA and PCR, AdenoPlus showed a sensitivity of 93% (27/29) and a specificity of 98% (88/90).

The Kam et al. (2015) study (presented in tables 3 and 4) was a prospective, single-centre diagnostic accuracy study done in a walk-in ophthalmic accident and emergency service in the UK. It assessed the diagnostic accuracy of the AdenoPlus test compared with PCR in 109 consecutive people presenting to the emergency eye unit with a clinical indication of acute adenoviral conjunctivitis.

Using PCR as the reference standard, the sensitivity of the AdenoPlus test in detecting adenovirus was 39.5% (95% confidence interval [CI] 25 to 56) and the specificity was 95.5% (95% CI 87 to 99). The authors report the positive (8.7; 95% CI 2.71 to 27.9) and negative (0.63; 95% CI 0.49 to 0.81) likelihood ratios incorrectly as PPV and NPV. The authors of the briefing have calculated the correct PPV and NPV as 85% (95% CI 62.11 to 96.79) and 70.79% (95% CI 60.19 to 79.95) respectively. No adverse events from doing the AdenoPlus or PCR tests were reported.

The conference abstract (Tuil et al. 2015a) reported an interim analysis of an ongoing observational epidemiology study (ADVISE), which is being done in France, Germany, Spain, Italy and the UK (Duquesroix et al. 2014). The information presented in table 5 was extracted from the conference poster (Tuil et al. 2015b), which includes more detail than the abstract. The investigators assessed the clinical characteristics and incidence of adenovirus conjunctivitis in people who presented with symptoms of acute conjunctivitis. The interim analysis was based on 334 patients from 16 sites in France (all but 1 were hospital ophthalmology departments).

Before using the AdenoPlus test, the investigators believed that the conjunctivitis was of viral origin in 89% of the people. This was confirmed by the AdenoPlus test in only half of these people. AdenoPlus test results were reported (0.6%), for which no further definition was stated. No further information was reported that would allow the calculation of any test accuracy measures.

Recent and ongoing studies

Five ongoing or in-development studies on AdenoPlus for adenoviral conjunctivitis detection were identified in the preparation of this briefing. Four of the ongoing trials are part of the international ADVISE (ADenoVirus Initiative Study in Epidemiology) study with different trial registrations per country (France, Germany, Spain, Italy and the UK). The study has completed recruitment in France (Clinicaltrials.gov identifier: NCT02054234). It is currently recruiting in Spain and Germany (Clinicaltrials.gov identifiers: NCT02254330; NCT02054273) and is not yet recruiting in the UK (Clinicaltrials.gov identifier: NCT02112773). ADVISE trial registration for Italy could not be found. Interim results of the ADVISE study carried out in France are presented in this briefing. The other ongoing US study aims to determine the specificity of AdenoPlus compared with quantitative PCR testing (Clinicaltrials.gov identifier: NCT02472223).

Costs and resource consequences

No published evidence on the resource consequences of the AdenoPlus test was identified. If the AdenoPlus test accurately excludes a bacterial cause of infectious conjunctivitis at its early stages, it has the potential to reduce inappropriate antibiotic use, reduce the number of work days and school days lost, and help to better manage the condition. Using AdenoPlus in primary care, pharmacy and emergency settings could also provide efficiencies to the NHS by reducing the number of unnecessary referrals to ophthalmologic units.

Strengths and limitations of the evidence

Two published diagnostic accuracy studies, and 1 conference abstract and its respective poster were identified.

In the Sambursky et al. (2013) study the patients were recruited consecutively from multiple sites, suggesting that they were likely to be representative of the population

studied. The study was done in the USA, and so the results may not be generalisable to a NHS setting.

In this study, the AdenoPlus test results were compared with those of PCR and of CC-IFA, which seem to be appropriate reference standards because they are commonly used measures for detecting adenovirus. The authors stated that the AdenoPlus test results were analysed by an independent, blinded healthcare professional. It was unclear what the healthcare professional was blinded to when analysing the AdenoPlus test results. The AdenoPlus test result seems objective, with 1 red line and 1 blue line indicating the result as positive, and a single blue line indicating the test as negative. The authors stated that AdenoPlus was done first because this test uses direct sampling, which prohibits splitting a single sample between the reference methods; the second and third samples collected were used for the reference analyses. It was unclear whether the analyses of the PCR and CC-IFA results were done by investigators blinded to the AdenoPlus results.

The Kam et al. (2015) study was done in an emergency eye unit in the UK, indicating that the results are likely to be generalisable to the UK NHS setting. Recruiting consecutive patients into the study minimised potential selection bias. PCR was used as the standard reference test, and either automatically generated or manually entered into the database by qualified biomedical staff blinded to the result of the AdenoPlus test. AdenoPlus test results were analysed by a qualified independent member of clinical staff who had no previous contact with the patients or the clinical notes. Using the blinding methods, the study minimised potential measurement bias. According to the manufacturer's instructions for use, the AdenoPlus test is best done within 7 days of developing a red eye consistent with infectious conjunctivitis, although this study included patients who had an onset of symptoms of up to 2 weeks. This might have contributed to the observed differences in the test accuracy results between this study and that of Sambursky et al. (2013), which included patients presenting within 7 days of developing a red eye. The authors incorrectly report positive and negative likelihood ratios as positive predictive value and negative predictive value in the paper.

In both studies, the AdenoPlus test was done first and then other samples were collected for the reference analyses. As the authors of the Sambursky et al. (2013) study pointed out, this could result in a negative test result for the reference tests because the subsequent samples may contain fewer viruses than the first swab, causing an artificial increase of the AdenoPlus sensitivity.

The manufacturer pointed out that the hospital where the Kam et al. (2015) study took

place did not accept any advice from the manufacturer on training to use the test and this might indicate that inadequate sampling methods were used in the study. The authors state that they trained all specialist nurse practitioners and ophthalmologists in using the AdenoPlus test, but it is unclear if the authors themselves had any training.

In the conference abstract and its respective poster reporting the epidemiology study (Tuil et al. 2015a; Tuil et al. 2015b), 7.2% of the 334 people had protocol deviations at inclusion, mostly for using topical corticosteroids. It is not clear if the same investigators did both the initial assessment and the AdenoPlus test, or if the investigators who carried out the AdenoPlus test were blinded to the initial diagnosis. No relevant data on the diagnostic accuracy of the AdenoPlus test was given in either the conference abstract or the poster.

The Sambursky et al. (2013) study was supported by the manufacturer and the main author has an affiliation with the manufacturer. The first and last authors of the Tuil et al. (2007b) poster act as consultants for the manufacturer. The manufacturer provided the AdenoPlus test for the Kam et al. (2015) study at no cost.

Overall, the current evidence was based on 2 diagnostic accuracy studies with reasonable methodological quality.

Relevance to NICE guidance programmes

The use of AdenoPlus is not currently planned into any NICE guidance programme.

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Appendix

Data tables

Table 1 Overview of the Sambursky et al. (2013) study

Study component	Description
Objectives/ hypotheses	To compare the sensitivity and specificity of the AdenoPlus test with those of both viral cell culture with confirmatory immunofluorescence assay and polymerase chain reaction in detecting the presence of adenovirus in tear fluid.

Study component	Description
Study design	Prospective diagnostic accuracy study (n=128). Tear samples were collected from 1 affected eye of each patient. The AdenoPlus test results were analysed by an independent, masked healthcare professional. No further information about the mask. It was unclear whether 'masked' means that the person who analysed the AdenoPlus results was blinded to the patient's clinical symptoms and signs. Reference tests used: CC-IFA for AdenoPlus, PCR for AdenoPlus, both CC-IFA and PCR for AdenoPlus, and PCR for cell culture respectively.
Setting	Multicentre study at 8 private ophthalmology practices and academic centres in the USA during June 2009 to June 2011.
Inclusion/ exclusion criteria	The enrolment criteria included onset of symptoms (red eye) within 7 days, a history of spread of infection from 1 eye to the other or recent upper respiratory infection, the presence of follicles or a preauricular node, and symptoms of discharge, eyelash matting, itching, or foreign body sensation. Patients with a corneal ulcer, trauma, allergy to Dacron, or recent medication use were excluded.
Primary outcomes	Sensitivity, specificity, PPV, NPV, and overall agreement.
Statistical methods	Not stated.
Conclusions	AdenoPlus is sensitive and specific for detecting adenoviral conjunctivitis.

Abbreviations: CC-IFA, cell culture with confirmatory immunofluorescence assay; NPV, negative predictive value; n, number of patients; PCR, polymerase chain reaction; PPV, positive predictive value.

Table 2 Summary of results from the Sambursky et al. (2013) study

Patients included	A total of 128 sequential patients with a clinical diagnosis of acute viral conjunctivitis, aged from 5 to 90 years; 76 females (59%) and 52 males (41%).

Outcomes	Of the 128 patients enrolled, the results were positive by either CC-IFA or PCR in 36 patients. Positive results were found in 29 patients by both CC-IFA and PCR. When compared with CC-IFA, AdenoPlus showed a sensitivity of 90% (28/31), a specificity of 96% (93/97), a NPV of 97% (93/96), a PPV of 88% (28/32), and an overall agreement of 95% (121/128). When compared with PCR, AdenoPlus showed a sensitivity of 85% (29/34), a specificity of 98% (89/91), a NPV of 95% (89/94), a PPV of 94% (29/31), and an overall agreement of 94% (118/125). When compared with both CC-IFA and PCR, AdenoPlus showed a sensitivity of 93% (27/29) and specificity of 98% (88/90). When compared with PCR, CC-IFA showed a sensitivity of 85% (29/34), a specificity of 99% (90/91), a NPV of 95% (90/95), a PPV of 97% (29/30), and an overall agreement of 95% (119/125).

Abbreviations: CC-IFA, cell culture with confirmatory immunofluorescence assay; NPV, negative predictive value; n, number of patients; PCR, polymerase chain reaction; PPV, positive predictive value.

Table 3 Overview of the Kam et al. (2015) study

Study component	Description
Objectives/ hypotheses	To estimate the diagnostic accuracy of the AdenoPlus point-of-care adenoviral test compared with PCR in an ophthalmic accident and emergency service.

Study component	Description
Study design	Cross-sectional, diagnostic accuracy study. AdenoPlus testing was carried out on the more severely affected eye of each patient. PCR analysis was also done on a swab taken from the same eye. AdenoPlus and PCR results were interpreted by personnel masked to the results of the other testing type. Sensitivity and specificity for the AdenoPlus test were calculated using PCR results as the reference standard. The PCR result was automatically generated (including results for herpes simplex and Chlamydia trachomatis), but occasionally manually entered into the database by qualified biomedical staff masked to the result of the AdenoPlus test. AdenoPlus test results were analysed by an independent member of clinical staff (ophthalmologist of at least Specialty Training Year 3 level or specialist ophthalmic nurse practitioner) masked to the PCR results who had no previous contact with the patient or the clinical notes.
Setting	A walk-in ophthalmic A&E in the UK. Year and duration unclear.
Inclusion/ exclusion criteria	Patients presenting to the walk-in ophthalmic A&E, who had a preliminary diagnosis of adenoviral conjunctivitis based on their clinical signs and symptoms, were eligible for entry into this study. The clinical signs and symptoms that elicited suspicion of adenoviral infection were recorded according to a prospectively designed checklist. These patients were seen and recruited by either an experienced specialist ophthalmic nurse practitioner or an ophthalmologist of at least Specialty Trainee Year 3 level. Patients were recruited consecutively, but guidelines were not given as to the threshold of severity at which patients should be included; so, the decision to include a potentially eligible patient was made by the attending clinician. Exclusion: patients who declined AdenoPlus testing; patients aged under 16 years; those who had an onset of symptoms more than 2 weeks before presentation; anyone who had a concurrent corneal ulcer of any form; those who had a history of recent trauma to the eye; and those who had an allergy to Dacron.
Primary outcomes	Sensitivity and specificity.

Study component	Description
Statistical methods	Not stated.
Conclusions	The AdenoPlus test has a high specificity in the diagnosis of adenoviral conjunctivitis, but in this study the authors could not reproduce the high sensitivity that was previously published.

Abbreviations: A&E, accident and emergency department; n, number of patients; PCR, polymerase chain reaction.

Table 4 Summary of results from the Kam et al. (2015) study

Patients included	A total of 109 consecutive patients presenting to an emergency eye unit with a clinical picture of acute adenoviral conjunctivitis and meeting the inclusion criteria of the study. Of these 109 patients, 55 were male (50.5%) and 54 were female (49.5%). The mean age was 40 years (range 16 to 85 years). In terms of severity, 38% of patients had bilateral conjunctivitis, and the median number of symptoms and signs listed by each patient was 6 (IQR 5 to 8).
Outcomes	Using PCR as the reference standard, the sensitivity of the AdenoPlus swab in detecting adenovirus was 39.5% (17/43; 95% CI 25 to 56), specificity was 95.5% (63/66; 95% CI 87 to 99), PPV was 85% (95% CI 62.11 to 96.79), and NPV 70.79% (95% CI 60.19 to 79.95). The authors report the positive (8.7; 95% CI 2.71 to 27.9) and negative (0.63; 95% CI 0.49 to 0.81) likelihood ratios incorrectly as PPV and NPV. No adverse events from doing the AdenoPlus or PCR test were reported.

Abbreviations: CI, confidence interval; IQR, interquartile range; NPV, negative predictive value; n, number of patients; PCR, polymerase chain reaction; PPV, positive predictive value.

Table 5 Summary of the Tuil et al. (2015b) poster

Study component	Description
Objectives/ hypotheses	To assess the clinical characteristics (signs and symptoms) and incidence of adenovirus conjunctivitis in patients who present with signs and symptoms of acute conjunctivitis.

Study component	Description
Study design	Cross sectional epidemiology study.
Setting	Data from the 334 patients recruited from 16 sites (3 to 60 patients per site) in France (database extraction date not reported). All sites but 1 were hospital ophthalmology departments. Study year and duration unclear.
Inclusion/ exclusion criteria	Before inclusion, patients had to give oral consent. To participate in the study, patients had to present with acute signs and symptoms of conjunctivitis lasting for less than 7 days. The minimum age was 1 year. Exclusion criteria: patients who had already used local antiviral therapies, topical steroids or immuno-modulators; had a history of sensitivity to corn starch, talcum powder or Dacron (sampling fleece components); previous enrolment in the study and direct involvement or family link with the study site.
Primary outcomes	The percentage of AdenoPlus test positives or negatives.
Statistical methods	Not stated.
Patients included	Patients with acute signs and symptoms of conjunctivitis for less than 7 days: 334. Mean age 42 years (range 5 to 89 years). Most (81%) of the 334 patients were 18 to 65 years of age, 13% of the patients were over 65 years of age and 6% were under the age of 18 years. Female: 57%.

Study component	Description
Results	Of the users, 74% rated the ease of doing the AdenoPlus test as good or acceptable and 61% of the patients judged that the test was good or excellent. The percentage of AdenoPlus positive results was 36% (121/334) among the tested patients. Two invalid AdenoPlus test results have been reported (0.6%; no further information about this was provided). In 89% of the 334 patients, the investigators believed the conjunctivitis was of viral origin. The authors stated that 49% of the investigators had their clinical assessment confirmed by the test. No further details were available that would allow clear interpretation of the results reported. Of the 334 patients, 7.2% had protocol deviations at inclusion, mostly for using topical corticosteroids.
Conclusions	More than one-third of patients who presented with signs and symptoms of acute conjunctivitis suspected as being viral were actually diagnosed with adenoviral conjunctivitis using AdenoPlus. The patients testing positive for adenovirus presented more signs and symptoms compared with the other patients, although none of them were definitive signs of the disease. The investigator's initial clinical assessment was not confirmed in half of the patients. In real-life conditions, the AdenoPlus test may be a useful tool in helping early differential diagnosis in patients with conjunctivitis signs and symptoms lasting for 7 days or less.

Search strategy and evidence selection

Search strategy

1. The following databases were searched from start to September 2015 using the keyword "AdenoPlus": Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R); Embase (via OVID); Cochrane Library; CAB Abstracts; Web of Science Science Citation Index.

These citations were sifted to identify any relevant material, using the inclusion criteria in the Evidence selection section.

2. The internet was searched using the above keywords.

3. ClinicalTrials.gov, WHO ICTRP, and Current Controlled Trials were also searched for ongoing trials.

4. Information provided by the manufacturer in supporting this briefing was checked to identify any further information.

5. The manufacturer's website was thoroughly investigated.

6. Information provided by the manufacturer was thoroughly checked for relevant studies.

Evidence selection

The inclusion criteria were as follows:

Population: adults and children presenting to primary care, emergency or ophthalmology settings with signs and symptoms of conjunctivitis.

Intervention: AdenoPlus POC test.

Comparator: viral cell culture (CC) with confirmatory immunofluorescence assay (IFA), or polymerase chain reaction (PCR).

Outcomes:

- sensitivity
- specificity
- positive predictive value
- negative predictive value
- time to diagnosis of adenoviral conjunctivitis

- adverse events.

Study type: published clinical studies. Proof-of-concept, bench-top or basic science studies were excluded. Non-English language studies were excluded.

About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and are not formal NICE guidance.

Development of this briefing

This briefing was developed for NICE by Birmingham and Brunel Consortium. The interim process & methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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Specialist commentators

The following specialist commentators provided comments on a draft of this briefing:

- Stella Hornby, Associate Specialist in Ophthalmology, Oxford University Hospitals NHS Foundation Trust.
- Mark Webb, GP, Bernays and Whitehouse Medical Partnership, Solihull, West Midlands.
- Manoj Parulekar, Consultant Ophthalmic Surgeon, Birmingham Children's Hospital.

Declarations of interest

- Stella Hornby is a partner in Primary Care Ophthalmology, which provides education to GPs, and has received a travel grant from Allergan and honoraria from Allergan and Alcon.

No relevant interests were declared by the additional specialist commentators.

ISBN: 978-1-4731-1583-5