Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1796 – ADAMTS13 testing for the diagnosis of thrombotic thrombocytopenic purpura (TTP)

Applicant:	**The Royal College of Pathologists of Australasia (RCPA)**
Date of MSAC consideration	**1 April 2026**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of ADAMTS13 testing (ADAMTS13 activity testing, anti-ADAMTS13 autoantibodies testing and *ADAMTS13* genetic testing) for the diagnosis of thrombotic thrombocytopenic purpura (TTP) was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health, Disability and Ageing.

Thrombotic microangiopathies (TMAs) are a group of disorders characterised by endothelial injury within the microcirculation. TTP is a rare type of TMA caused by markedly reduced activity of the ADAMTS13 enzyme. This deficiency is usually due to autoantibodies to the ADAMTS13 protein (immune-mediated TTP, iTTP), but it can also result from homozygous or compound heterozygous pathogenic or likely pathogenic variants in the *ADAMTS13* gene (congenital TTP, cTTP). Clinically, TTP typically presents as an abrupt onset illness with relatively non-specific signs and symptoms, yet it has the potential for rapid progression and life-threatening complications. The mainstay treatment for acute episodes is plasma exchange therapy (PEX), which both replenishes ADAMTS13 activity and removes the circulating anti-ADAMTS13 antibodies that mediate TTP in the majority of cases. PEX is supplemented with immune modulation therapy.

The diagnostic purpose of each test is as follows:

- ADAMTS13 activity test – to rapidly identify patients with life-threatening deficiency of ADAMTS13 activity to ensure more targeted use of a complex and invasive treatment (PEX) in patients at-risk (those with TTP) and avoid its use in patients who do not require it (for example those with atypical haemolytic uraemic syndrome (aHUS)).
- anti-ADAMTS13 autoantibody test – to identify a small subset of TTP patients for whom the ADAMTS13 activity deficiency is not antibody-mediated (suspected cTTP) and therefore can safely cease PEX therapy.
- *ADAMTS13* genetic test – to confirm a diagnosis of cTTP to provide more certainty about appropriate treatment and prophylaxis in both the affected individual and first-degree biological relatives of probands.
- The ADAMTS13 activity test can also be used to monitor patients with TTP after the acute phase to identify relapse.

The application includes 3 PICO Sets:

- **PICO Set 1:** patients presenting with symptoms and signs suggestive of TMA and clinical and laboratory features indicating risk for TTP. The 3 ADAMTS13 tests are proposed to be undertaken sequentially to diagnose TTP and then to differentiate iTTP from cTTP; the populations that are tested with the second and third tests are a subset of the starting population.
- **PICO Set 2:** *ADAMTS13* genetic testing in first-degree biological relatives of individuals with confirmed cTTP (probands).
- **PICO Set 3:** monitoring using ADAMTS13 activity testing during the post-acute and chronic phase in patients with a confirmed diagnosis of TTP.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for ADAMTS13 activity, anti-ADAMTS13 autoantibody and *ADAMTS13* genetic testing for the diagnosis of thrombotic thrombocytopenic purpura (TTP) in affected individuals and, where appropriate, targeted *ADAMTS13* genetic testing of first-degree biological relatives. MSAC considered that there was a clinical need for improved diagnosis of this rare disease, which is often fatal if not treated promptly and requires different management depending on whether testing identifies the disease as immune-mediated (iTTP) or congenital (cTTP). In addition, the ability for ADAMTS13 testing to exclude TTP was also informative and can confirm eligibility for medicines listed on the Pharmaceutical Benefits Scheme for the treatment of atypical haemolytic uraemic syndrome. MSAC acknowledged that due to the rarity of TTP there were limitations in the evidence base for ADAMTS13 testing in the diagnostic setting. However, MSAC considered that the available evidence demonstrated that ADAMTS13 testing for diagnosis of TTP had superior clinical effectiveness compared with no testing, and that accurate differentiation of iTTP or cTTP would lead to a change in management and improved health outcomes. MSAC considered that ADAMTS13 testing for diagnosis of TTP was cost-effective and the financial impact to the MBS would be modest but that the proposed fees for ADAMTS13 testing were high. MSAC recommended the fees be reduced to $400 for the ADAMTS13 activity test and $1000 for the *ADAMTS13* genetic test for affected individuals. MSAC requested the department to propose a reduced fee for the anti-ADAMTS13 autoantibody test that aligns with existing MBS items.

MSAC did not support public funding of monitoring ADAMTS13 activity during remission to prevent or reduce recurrence or relapse of TTP. MSAC considered there were critical limitations and gaps in the evidence base for monitoring ADAMTS13 activity in this setting. MSAC concluded that there was insufficient evidence and significant uncertainty regarding the frequency, duration and comparative effectiveness of monitoring ADAMTS13 activity during remission. Accordingly, MSAC considered the estimated utilisation and comparative cost-effectiveness for ADAMTS13 activity testing in the monitoring setting to be highly uncertain and financial impact to be likely underestimated. MSAC considered that any reapplication would need to present sufficient evidence to support the claimed benefits for monitoring ADAMTS13 activity during remission.

Consumer summary
This application from the Royal College of Pathologists of Australasia requested Medicare Benefits Schedule (MBS) listing of ADAMTS13 testing for the diagnosis of thrombotic thrombocytopenic purpura (TTP).

Consumer summary

TTP is a blood disorder in which small clots form in blood vessels throughout the body. These clots can limit or block the flow of blood to organs such as the brain, kidneys or heart. They can also lead to bruising and bleeding under the skin. TTP is very rare, but it is life-threatening if not treated quickly.

TTP occurs when the body does not have the right amount of a protein called ADAMTS13. This is often because the immune system makes antibodies that mistakenly target and attack the ADAMTS13 protein, which stops it from working properly (immune-mediated TTP). In rare cases, the person has a variant in both their copies of the *ADAMTS13* gene, which means their body cannot make ADAMTS13 protein that works properly (congenital TTP).

Three types of ADAMTS13 testing were proposed to diagnose people who have symptoms of TTP. The first, ADAMTS13 activity test, checks if the patient's ADAMTS13 protein is working properly. If the activity is less than 10%, this confirms a patient has TTP. The second test, anti-ADAMTS13 autoantibody test, looks to see if the patient's immune system is producing antibodies that attack the ADAMTS13 protein. This shows whether the patient has immune-mediated TTP. If the second test is negative, the patient then has the third test, *ADAMTS13* genetic testing to see if they have any variants in their *ADAMTS13* gene. This shows whether they have congenital TTP, which is managed differently from immune-mediated TTP. Because congenital TTP can be inherited, the application also included genetic testing of first-degree relatives (parents, children and siblings) when the patient with symptoms is found to have one or more serious genetic variants (called cascade testing). This shows whether they have the same genetic variant(s) for TTP.

MSAC considered that ADAMTS13 testing to diagnose TTP, including differentiating between immune-mediated and congenital TTP, was safe and effective, consistent with best practice guidelines and will improve clinical care for these people. The tests were also good value for money, although MSAC recommended some changes to the proposed fees to bring them in line with other similar items on the MBS.

ADAMTS13 *activity* testing was also proposed for monitoring patients, after they have been diagnosed with TTP, to check if they have responded to treatment and/or to predict if they are at risk of relapse. MSAC considered that there was not enough evidence to show that monitoring improved outcomes for the patient such as reduced relapse. There were not many studies to inform how often the test should be done. MSAC considered the level of uncertainty in this setting was unacceptably high and could not determine if monitoring patients would be good value for money. Therefore, MSAC did not support public funding for ADAMTS13 testing used for monitoring.

MSAC's advice to the Commonwealth Minister for Health, Disability and Ageing

MSAC supported MBS listing of ADAMTS13 (activity, autoantibody and genetic) testing for diagnosis of TTP and genetic testing of family members. MSAC considered ADAMTS13 testing for diagnosis of TTP would improve the clinical care of patients with this rare disease and would be good value for money based on revised fees.

MSAC did not support listing of ADAMTS13 testing for monitoring people with TTP, because there was not enough evidence that this would improve outcomes for patients, or to guide how often patients should be tested.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from the RCPA requested MBS listing of ADAMTS13 testing (including ADAMTS13 activity testing, anti-ADAMTS13 autoantibodies testing and *ADAMTS13* genetic testing) to diagnose TTP. MSAC noted that the 3 tests were used sequentially to first diagnose TTP (activity test), then to differentiate iTTP (autoantibody test) or cTTP (genetic test), and if appropriate, cascade genetic testing of first-degree relatives (PICO set 1 & 2). MSAC also noted the application proposed monitoring ADAMTS13 activity, in patients diagnosed with TTP, to prevent or reduce recurrence, exacerbation and relapse (PICO set 3).

MSAC acknowledged that the diagnostic algorithm and criteria for ADAMTS13 testing to diagnose TTP is well established and already utilised in Australia. Further, the ability for ADAMTS13 testing to exclude TTP was also informative, as this can confirm eligibility to access for medicines listed on the Pharmaceutical Benefits Scheme for the treatment of atypical haemolytic uraemic syndrome (aHUS). MSAC noted that although guidelines also recommended monitoring ADAMTS13 activity to prevent recurrence or relapse, these recommendations are based on expert opinion as the evidence for monitoring is less established.

The applicant was granted a hearing to address queries from MSAC. During the hearing, MSAC heard from the applicant that although cTTP is an ultra-rare disease and only a few individuals would utilise the cascade genetic testing item, identifying that a relative also has a variant in the *ADAMTS13* gene provides highly impactful information. As an example, the applicant highlighted that some patients do not manifest TTP without a trigger and that pregnancy-associated changes in ADAMTS13 activity can trigger TTP onset with potentially disastrous consequences for both the mother and fetus. In this scenario, cascade testing is critical for identifying at-risk relatives and providing appropriate counselling and management during pregnancy. MSAC sought the applicant's views on the lack of evidence for ADAMTS13 testing in the monitoring setting and whether there are any forthcoming trials in this space. The applicant confirmed that, to their knowledge, no studies were underway or planned to expand the evidence base for ADAMTS13 testing for monitoring purposes, and any further information on monitoring would come from registry data. In response to MSAC's queries regarding the proposed fees for the testing items, the applicant acknowledged that the proposed fee for the activity test (item AAAA) was higher than other similar activity tests on the MBS to account for cartridge-based testing costs (using the HemosIL AcuStar machine), which is more costly but provides a faster turnaround time than other methods. The applicant noted that patients in rural and remote areas experience challenges accessing these tests in a timely way because testing is currently centralised, and it was unclear whether laboratories in these areas would expand their services to include ADAMTS13 testing that would be rarely requested given TTP is a rare disease. The applicant also acknowledged that the proposed fee for the genetic test was higher than other similar genetic tests on the MBS, and the proposed fee was informed by correspondence with laboratories in Australia who perform the test.

MSAC noted the consultation feedback received from one organisation (Takeda Pharmaceutical Australia Pty Ltd [Takeda]) and one individual before the ESC meeting, as well as letters of support from 3 professional organisations provided with the application. MSAC noted that the input from Takeda referred to a submission to the Pharmaceutical Benefits Advisory Committee seeking PBS-listing of Adzynma for the treatment of ADAMTS13 deficiency in adults and children with cTTP. MSAC noted that this treatment may require ADAMTS13 testing for both diagnosis of cTTP and monitoring of ADAMTS13 activity to tailor the dose and to screen for potential immunogenicity and inhibitor development.[1] This may provide support for the need for ADAMTS13 activity monitoring, but the application before MSAC did not present or assess the codependency of Adzynma and ADAMTS13 testing, and as such MSAC did not provide any advice in this regard.

Regarding the evidence for the comparative safety and effectiveness of ADAMTS13 testing in the diagnostic setting (PICO sets 1 & 2), MSAC acknowledged that due to the rarity of TTP there were limitations in the evidence base. However, MSAC agreed with ESC that there was no evidence of harm from the testing and that concerns regarding the potential risk for false positives with the Acustar ADAMTS13 activity test would be mitigated by other clinical and laboratory results that would inform patient management. MSAC considered there was reasonable evidence to demonstrate that ADAMTS13 testing for diagnosis of TTP had superior clinical effectiveness compared with no testing, and that accurate differentiation of iTTP or cTTP would lead to a change in management and improved health outcomes.

In the monitoring setting (PICO set 3), MSAC noted the critical limitations and gaps in the evidence base for monitoring ADAMTS13 activity to prevent relapse or recurrence. As such, MSAC agreed with ESC that there was insufficient evidence that monitoring ADAMTS13 during remission would improve health outcomes. MSAC considered there was a high level of uncertainty regarding the frequency and duration of monitoring ADAMTS13 activity during remission.

Regarding the comparative cost-effectiveness of ADAMTS13 testing for diagnosis, MSAC noted that the economic evaluation for ADAMTS13 activity and autoantibody testing indicated that ADAMTS13 testing would be cost saving (-$3,071). This cost-saving increased (to -$3,371) when using a fee of $400 for the ADAMTS13 activity test (instead of the proposed $700 fee) based on a published laboratory fee for urgent ADAMTS13 activity testing. For *ADAMTS13* genetic testing, the economic evaluation resulted in an incremental cost-effectiveness ratio (ICER) of $1,237 per proband for affected individual testing and $1,298 per proband/biallelic sibling for combined affected individual and cascade testing. These ICERs reduced to $1,031 and $1,125 respectively, when using a fee of $1000 for the *ADAMTS13* genetic test for affected individuals (item CCCC), consistent with existing MBS items of similar complexity (instead of the proposed $1200 fee). MSAC considered the ICERs (using the revised fees) acceptable and demonstrated the cost-effectiveness of ADAMTS13 testing in the diagnostic setting.

Regarding the cost-effectiveness of ADAMTS13 testing in the monitoring setting, MSAC noted that critical limitations in the clinical evidence base created an unacceptably high level of uncertainty in the economic evaluation. MSAC considered the estimated incremental cost per additional clinical recurrence avoided over 2 years of $106,710 to be highly uncertain. MSAC

[1] Robichaux T et al. (2026) Recombinant ADAMTS13: An Enzyme Replacement Therapy for the Management of Congenital Thrombotic Thrombocytopenic Purpura. J Adv Pract Oncol. 2026 Jan 9:1-7. doi: 10.6004/jadpro.2026.17.7.5.

noted that one-way and two-way sensitivity analyses, varying the frequency of testing, cost of PEX and number of days on PEX, further highlighted that the estimated ICER was highly uncertain.

MSAC noted that the estimated financial impact of MBS listings for ADAMTS13 testing for diagnosis, including cascade testing, (PICO sets 1 and 2) was ~$250,000 per year and would be lower (~$170,000 per year) using the revised fees for the ADAMTS13 activity ($400) and *ADAMTS13* genetic ($1000) tests. MSAC considered the estimates for ADAMTS13 testing for diagnosis to be modest and acceptable. However, MSAC noted that the estimated financial impact of listing ADAMTS13 testing for monitoring on the MBS was significantly higher (~$1million per year) and could be higher than estimated due to the uncertainty regarding the frequency and duration of monitoring.

Regarding the proposed MBS items, MSAC confirmed that the MBS item descriptors should be method-agnostic. Given the lack of evidence for ADAMTS13 testing for monitoring purposes, MSAC recommended that item AAAA should not include monitoring and should specify testing 'for the diagnosis of suspected thrombotic microangiopathy' rather 'investigation of suspected thrombotic microangiopathy', as this would preclude use of testing to investigate relapse (that is, monitoring). MSAC also recommended that item DDDD (cascade testing) should be requested by a specialist or consultant physician (not 'or on behalf of').

Regarding the proposed fees, for item AAAA (ADAMTS13 activity testing), MSAC considered the fee proposed by the applicant ($700) was too high. MSAC recommended a lower fee, $400, in line with published laboratory fee for urgent testing. For item BBBB (autoantibody testing), MSAC considered that the proposed fee of $1,050 was high and requested the department review the fee and proposed a revised fee that aligns with existing similar MBS items. MSAC noted that the department could present the revised fee (and revised financial analysis using the revised fees) to the MSAC Executive. For item CCCC (genetic testing for affected individuals), MSAC recommended the fee should be $1000 (instead of $1,200 as proposed by the applicant), in line with existing MBS items of similar complexity (e.g. MBS item 73304 for germline *BRCA1/2* testing). MSAC considered the proposed fee of $400 for item DDDD (cascade testing) was acceptable. MSAC approved MBS item descriptors are shown in table 1 below.

Overall, MSAC considered that there was a clinical need for improved diagnosis of this rare disease, which is often fatal if not treated promptly and requires different management depending on whether testing identifies the disease as immune-mediated (iTTP) or congenital (cTTP). Further, the available evidence demonstrated that ADAMTS13 testing for diagnosis of TTP had superior clinical effectiveness, was cost-effective and would have a modest financial impact to the MBS using the reduced fees for ADAMTS13 activity and genetic testing recommended by MSAC, and reduction of the anti-ADAMTS13 autoantibody test fee to align with similar existing MBS items. Therefore, MSAC supported MBS listing for ADAMTS13 testing for the diagnosis of TTP.

MSAC did not support public funding for monitoring ADAMTS13 activity during remission (PICO set 3). Due to the critical limitations and gaps in the clinical evidence, MSAC concluded that there was insufficient evidence and significant uncertainty regarding the frequency, duration and comparative effectiveness of monitoring ADAMTS13 activity during remission. This created unacceptably high uncertainty in the estimated cost-effectiveness, utilisation and financial impact. MSAC considered that any reapplication for public funding for monitoring ADAMTS13 activity during remission would need to present sufficient evidence to support the claimed benefits for this indication.

MSAC recommended that the Pharmaceutical Benefits Advisory Committee (PBAC) be informed of MSAC's recommendations for this application, which maybe of relevance in relation to:

- PBS-listed medicines for the treatment of aHUS where ADAMTS13 activity testing is a prerequisite for accessing these treatments.
- PBAC submission by Takeda for Adzynma for the treatment ADAMTS13 deficiency in adults and children with cTTP – which may require ADAMTS13 testing for both diagnosis but also monitoring (to tailor dosing).

Post-MSAC update

The department presented a revised fee of $630 for item BBBB (autoantibody testing) to the MSAC Executive at its May 2026 meeting. The revised fee was based on targeted consultation with key stakeholders and with reference to existing items and publicly available information. The input noted that a quantitative test would be more helpful for clinicians, and that to provide a comprehensive quantitative result it is expected that the test to be performed would include a Bethesda assay followed by a manual Enzyme-Linked Immunosorbent Assay (ELISA). The MSAC Executive noted that while MSAC requested a proposed fee aligned to existing MBS items, using the fees for MBS items 65150 and 65159 as a benchmark may not adequately reflect the full range of clinical scenarios for anti-ADAMTS13 autoantibody testing and that the testing is likely to entail both a Bethesda assay and an ELISA assay. The MSAC Executive noted that reducing the schedule fee from $1,050 to $630 would reduce in-hospital MBS benefits from $787.50 to $472.50 per service and would reduce the estimated financial impact to the MBS by 40% to $37,800 in 2032-33 for 80 tests. Overall, the MSAC Executive supported an MBS schedule fee of $630 for anti-ADAMTS13 autoantibody testing (item BBBB).

Table 1 MSAC supported MBS items for ADAMTS13 (activity, autoantibody, genetic and cascade) testing for diagnosis of TTP.

Category 6 – PATHOLOGY SERVICES
Group P1 Haematology MBS item AAAA Quantitation of ADAMTS13 activity for the diagnosis of suspected thrombotic microangiopathy (TMA). Rule 3 exemption applies
Proposed fee: $400 Benefit: 75% = $300 85% = $340
Group P1 Haematology MBS item BBBB Anti-ADAMTS13 autoantibody testing in patients presenting with suspected thrombotic thrombocytopenic purpura (TTP) where a service described under MBS item AAAA indicated reduced ADAMTS13 activity. Once per episode
Proposed fee: $630 Benefit: 75% = $472.50 85% = $535.50
Group P7 Genetics MBS item CCCC Characterisation of variant(s) in the ADAMTS13 gene in a patient who has symptoms suggestive of congenital thrombotic thrombocytopenic purpura (cTTP) where: (a) testing has indicated reduced ADAMTS13 activity, and (b) testing has indicated an absence of anti-ADAMTS13 antibodies, and (c) requested by a specialist or consultant physician Available once per lifetime

Proposed fee: $1,000 Benefit: 75% = $750 85% = $895.50
Group P7 Genetics MBS item DDDD Characterisation of variant(s) in the ADAMTS13 gene in a patient who: (a) is a first-degree biological relative of a patient with cTTP found to have pathogenic or likely pathogenic variants in the ADAMTS13 gene (b) has not previously received a service to which item CCCC applies requested by a specialist or consultant physician. Available once per lifetime
Proposed fee: $400 Benefit: 75% = $300 85% = $340

4. Background

MSAC has not previously considered ADAMTS13 testing for the diagnosis of TTP, either as a stand-alone application to MSAC or as part of a co-dependent application to PBAC and MSAC.

The Pharmaceutical Benefits Advisory Committee (PBAC), however, has assessed a few relevant medicines: eculizumab for aHUS (March 2014, recommended), caplacizumab for TTP (July 2020, not recommended) and ravulizumab for aHUS (July 2023, recommended). In its consideration of eculizumab in March 2014, the PBAC considered that:

> "there are a number of uncertainties regarding the diagnosis of aHUS, including the role of genetic testing, the positive and negative predictive values for the tests for ADAMTS-13 and STEC (Shiga toxigenic *Escherichia coli*), and whether the spectrum of disease is different between the thresholds for ADAMTS-13 activity of >5% and >10%" (p3 of Public Summary Document for eculizumab, March 2014 PBAC meeting).

To initiate eculizumab treatment for aHUS, the current PBS restrictions require that a patient must have ADAMTS-13 activity of greater than or equal to 10% on a blood sample taken prior to plasma exchange or infusion; or, if ADAMTS-13 activity was not collected prior to plasma exchange or infusion, patient must have platelet counts of greater than $30x10^9$/L and a serum creatinine of greater than 150 mol/L.

5. Prerequisites to implementation of any funding advice

According to the applicant, ADAMTS13 testing does not need to be included in the Australian Register of Therapeutic Goods (ARTG). Testing would be delivered only by approved practising pathologists with appropriate scope of practice in National Association of Testing Authorities (NATA) Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered medical practitioners (non-pathologists) in line with other tests in the MBS Pathology Table.

6. Proposal for public funding

Four new MBS items for ADAMTS13 testing are proposed (Table 2). In contrast to the MBS items proposed in the application, these items:

- integrate ADAMTS13 activity quantitation for both diagnostic and monitoring purposes into a single item;

- broaden the indication for ADAMTS13 activity testing to include suspected TMA, thereby encompassing patients with aHUS who may be eligible for therapies listed on the Pharmaceutical Benefits Scheme (PBS);
- restrict the use of monitoring to patients with TTP.

The item descriptors in Table 2 incorporate amendments advised by ESC. However, ESC also noted that MSAC may wish to consider:

- separating diagnostic testing from remission monitoring testing (item AAAA)
- removing 'on behalf of' a specialist or consultant physician (item DDDD).

MSAC recommended removing 'monitoring' from item AAAA and removing 'on behalf of' a specialist or consultant physician in item DDDD – see section 3 and Table 1.

Table 2 Proposed new MBS items (post ESC consideration)

Category 6 – PATHOLOGY SERVICES
Group P1 Haematology MBS item AAAA (combined with EEEE) Quantitation of ADAMTS13 activity for the investigation of suspected thrombotic microangiopathy (TMA) or monitoring of diagnosed thrombotic thrombocytopenic purpura (TTP) Rule 3 exemption applies
Proposed fee: $700.00 Benefit: 75% = $525.00 85% = ~~$597.60~~ $595.50
Group P1 Haematology MBS item BBBB Anti-ADAMTS13 autoantibody testing in patients presenting with suspected thrombotic thrombocytopenic purpura (TTP) where a service described under MBS item AAAA indicated reduced ADAMTS13 activity Once per episode
Proposed fee: $1,050.00 Benefit: 75% = 787.50 85% = ~~$947.60~~ $945.50
Group P7 Genetics MBS item CCCC Characterisation of variant(s) in the *ADAMTS13* gene in a patient who has symptoms suggestive of congenital thrombotic thrombocytopenic purpura (cTTP) where testing has indicated reduced ADAMTS13 activity and an absence of anti-ADAMTS13 antibodies, requested by a specialist or consultant physician. Available once per lifetime
Proposed fee: $1,200.00 Benefit: 75% = $900.00 85% = ~~$1,097.60~~ $1,095.50
Group P7 Genetics MBS item DDDD Characterisation of variant(s) in the *ADAMTS13* gene in a person who: (a) is a first-degree biological relative of a patient found to have a pathogenic or likely pathogenic variant(s) in the *ADAMTS13* gene (b) has not previously received a service to which item CCCC applies requested by or on behalf of a specialist or consultant physician. Available once per lifetime
Proposed fee: ~~$1,200.00~~ $400.00 Benefit: 75% = ~~$900.00~~ $300.00 85% = ~~$1,097.60~~ $340.00

Source: Table 11 of ratified PICO confirmation for Application 1796.
MBS = Medicare Benefits Schedule.
85% benefit reflects the 1 November 2025 Greatest Permissible Gap (GPG) of $104.50 and therefore differs to the fees in the ratified PICO confirmation. All out-of-hospital Medicare services that have an MBS fee of $697.00 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).
Changes to fees were made by the assessment group following ratification of the PICO confirmation, to reflect updated GPG and post-PASC advice on the fee for item DDDD (see MSAC 1796 PICO, pg 38), these are shown with ~~strikethrough~~ and blue text.

ADAMTS13 test volumes from 3 Australian pathology laboratories were provided by the applicant and show that ADAMTS13 testing is currently in routine use. During an acute episode, patients may present at emergency department or are hospitalised, and testing is undertaken urgently. During remission, testing is conducted on an out-patient basis during routine follow-up. MBS funding may reduce out-of-pocket costs for patients and could shift costs during inpatient episodes from state/territory budgets to the Commonwealth.

The proposed fee of $700 for ADAMTS13 activity testing (proposed item AAAA) is designed to cover the cost implications of the test across the spectrum of clinical scenarios (urgent testing for diagnosis and batched testing for monitoring) while consolidating these into a single MBS item to reduce administrative burden. Although at least one laboratory publicly advertises a lower fee, the applicant contends that this reflects a restricted service; samples must arrive before 1 pm, testing is performed in 2 to 3 weekly batches, and there is no weekend or after-hours service. Consequently, the service does not offer true 'urgent' testing that would warrant higher reimbursement.

Anti-ADAMTS13 autoantibody testing costs (proposed item BBBB) are titre dependent. The average cost per test is clustered around $980–$1,140. The applicant contends that setting a flat fee of $1,050 ensures cost recovery across the full range of clinical scenarios, while avoiding the complexity and inequity of variable patient billing.

For *ADAMTS13* genetic testing of affected individuals (proposed item CCCC), the use of a multi-gene panel such as a TMA panel would require similar services to those provided by the existing MBS items 73354, 73298, and 73296, which have a benefit of $1,200. Existing items for the sequencing of a single gene range from $400 (e.g. items 73411, 73452) to $1,200 (e.g. items 73405, 73454). Therefore, the requested benefit of $1,200 for affected individual testing in PICO Set 1 is at the higher end of similar MBS services for single-gene sequencing.

The applicant noted that laboratories conducting TMA panels estimate costs ranging from $850 to $1,820, depending on the method and size of the panel. The proposed fee of $1,200 is aimed at ensuring national availability of testing, without tying access to a single laboratory's discounted pricing. This range of pricing may include services for the proposed whole exome sequencing (WES) option. As the majority of *ADAMTS13* variants are private and largely single-nucleotide changes or small insertions/deletions located in exons and flanking intronic regions rather than structural variants, sequencing of exons plus intron/exon boundaries (targeted exome sequencing) is usually sufficient for their detection. This can be achieved by single gene sequencing or as part of a next-generation sequencing (NGS) panel. WES is a more expensive service and does not provide additional value to the diagnosis of cTTP.

Cascade testing (proposed item DDDD) can be achieved by polymerase chain reaction (PCR) testing for variants identified in the proband. The revised fee of $400 post-PASC is consistent with similar MBS services for cascade testing (items 73299, 73353, 73363, 73417, 73443, 73462). MBS item Associated Notes PN.0.23, states that testing of biological relatives should only be performed after written informed consent and pre-test genetic counselling, noting further counselling may be necessary after test results are received.

There is scope for use of the proposed MBS item for differential diagnosis of aHUS and cTTP if it is included on an NGS TMA panel, as aHUS patients frequently have reduced ADAMTS13 activity, albeit not less than 10%. Some authors have suggested that where inherited TMAs are suspected, testing for variants in both complement-related genes and the *ADAMTS13* gene should occur at least as a second-line investigation after complement testing, or, where multi-gene panels are available, as part of first-line testing (i.e. within a TMA panel). The applicant's experts noted a TMA panel has utility outside of solely identifying an *ADAMTS13* variant, while acknowledging benefits from such broader utility will not be captured in the clinical or cost-effectiveness analyses conducted for this DCAR.

7. Population

The ratified PICO confirmation specified 3 PICO Sets: PICO Set 1 for diagnosis of TTP, PICO Set 2 for diagnosis in first-degree biological relatives of patients with cTTP, and PICO Set 3 for monitoring.

PICO Set 1

The proposed intervention (ADAMTS13 testing) is additional to the current diagnosis and management of TTP.

The population for PICO Set 1 is patients presenting with symptoms and signs suggestive of TMA,

(i) thrombocytopenia,
(ii) microangiopathic haemolytic anaemia (MAHA) with red cell fragments (schistocytes) and
(iii) clinical and laboratory abnormalities attributable to organ-specific dysfunction.

The population is also defined by a PLASMIC score >4. The PLASMIC scoring system is based on clinical and laboratory criteria. It is a clinical prediction tool primarily used by clinicians in hospital settings to identify patients with a greater likelihood of having TTP. Patients who meet these criteria commence PEX and **ADAMTS13 activity testing**. Blood samples for ADAMTS13 testing are taken prior to the initiation of PEX therapy; however, treatment is not delayed while awaiting the results.

An ADAMTS13 activity level of <10% confirms a diagnosis of TTP and these patients remain on PEX (<10% supports a diagnosis of TTP, although 1% is more typically observed in these patients). An ADAMTS13 activity level ≥10% excludes a diagnosis of TTP and these patients can safely cease PEX. If further testing confirms a diagnosis of aHUS, these patients would be considered for PBS-listed complement inhibitors (eculizumab or ravulizumab) where ADAMTS13 activity ≥10% is a requirement for access.

Patients with confirmed TTP are the population who undergo **anti-ADAMTS13 autoantibody testing** to distinguish those with iTTP (positive autoantibodies) from suspected cTTP (no autoantibodies). This is important because PEX is continued in patients with iTTP to remove anti-ADAMTS13 antibodies and restore enzyme activity, whereas it is discontinued in suspected cTTP, where the pathology is not immune-mediated.

Only those patients with suspected cTTP would be eligible for ***ADAMTS13* genetic testing.** Unlike the earlier ADAMTS13 activity and anti-ADAMTS13 autoantibody tests in the diagnostic pathway, *ADAMTS13* genetic testing occurs once a clinical response has been achieved and where ADAMTS13 activity levels remain persistently low. This contrasts with the earlier tests that occur during an acute episode when patients are hospitalised.

In Australian laboratories, one of the following 3 ADAMTS13 activity assay tests are typically used:

- enzyme-linked immunosorbent assay (ELISA)
- fluorescence resonance energy transfer assay (FRETS-VWF73)
- chemiluminescence immunoassay (CLIA).

The CLIA test is typically performed with HemosIL AcuStar instrumentation[2] and is supplied as a fully automated commercial kit. CLIA testing of ADAMTS13 activity with AcuStar typically has a more rapid turn-around time compared to the ELISA or FRETS-VWF73 tests, which are likely to involve batch runs with other tests in pathology laboratories. In Australia, ADAMTS13 activity testing is performed almost exclusively on the AcuStar platform. MBS funding is not sought for a specific ADAMTS13 activity assay, and ongoing development of commercial tests is anticipated.

The Therapeutic Goods Administration (TGA) issued notifications for HemosIL AcuStar ADAMTS13 activity testing in February 2022 and again in August 2024[3], following findings that AcuStar ADAMTS13 activity testing produced a relatively high rate of false positives around the diagnostic threshold compared to the FRETS-VWF73 test (i.e. returning values <10% when other tests found >10%). For this reason, the diagnostic accuracy of CLIA AcuStar compared to a clinical reference standard of ELISA or FRETS-VWF73 was also considered in the assessment.

PICO Set 2

PICO Set 2 is for *ADAMTS13* genetic testing in the first-degree biological relatives of probands (i.e. those affected individuals who have been found to have a relevant pathogenic or likely pathogenic genetic variants). PASC confirmed siblings are the most relevant population for cascade testing. cTTP disease onset can occur from childhood (including neonatal presentation) through to later decades. Triggering events for acute episodes include pregnancy, bacterial and viral infections, neoplasia, autoimmune disorders, and exposure to certain drugs.

PICO Set 3

The population for PICO Set 3 is patients with a confirmed diagnosis of TTP (iTTP, cTTP). Monitoring ADAMTS13 activity is proposed to occur at varying frequencies as patients move from an acute episode to remission. Monitoring is intended to prevent or reduce recurrence, exacerbation and relapse. These have been defined as:

- Recurrence – new decrease in the platelet count that necessitates the re-initiation of PEX after normalisation of the platelet count had occurred.
- Exacerbation – a recurrence that occurs within 30 days after the last PEX.
- Relapse – a recurrence that occurs more than 30 days after cessation of PEX.

Because of the increased availability of ADAMTS13 activity measurement, and the range of new and emerging therapies for TTP (rituximab, caplacizumab[4], and recombinant ADAMTS13[5]), an international working group developed updated consensus definitions for iTTP outcomes (Cuker et al. 2021). The original definitions were based on platelet count and lactate dehydrogenase levels while the revised definitions incorporate ADAMTS13 activity levels and make a distinction between ADAMTS13 remission/ relapse (ADAMTS activity <20%) and clinical remission/ relapse (platelet count to $<150 \times 10^9$/L). The authors state 'by distinguishing between clinical and ADAMTS13 remission and relapse, our definitions acknowledge the primacy of ADAMTS13 activity as a predictor of clinical exacerbation and clinical relapse and as a means of guiding

[2] The ACL AcuStar automated system (Werfen) uses a HemosIL kit to assay ADAMTS13 activity.
[3] TGA Recall Reference RC-2024-RN-00633-1; 12 August 2024.
[4] Caplacizumab is TGA registered (ARTG 318058) but not approved by PBAC.
[5] Recombinant ADAMTS13 is undergoing TGA evaluation.

therapeutic decisions'. However, they also acknowledge that the definitions have yet to be prospectively validated.

8. Comparator

In all PICO Sets, the comparator is no ADAMTS13 testing and standard investigative and medical management. None of the 3 intervention tests are proposed as replacements to currently available investigative technology and therefore they are additional tests in the clinical management of TTP.

Currently there are many tests that should be conducted when a patient presents with suspected TTP. While these are necessary, they are not sufficient to establish a definitive diagnosis of TTP. These standard tests (e.g. low platelets, blood film examination, markers of haemolysis, etc.) would be routinely done in public hospitals where there is suspicion of TTP.

Cascade testing of first-degree biological relatives is not currently offered but clinical assessment may be used if symptoms are present.

Monitoring is currently undertaken using clinical history and laboratory testing of platelet counts to identify acute flares. ADAMTS13 activity testing is additional to, and not a replacement for, laboratory testing of platelet counts.

9. Summary of public consultation input

Consultation input was welcomed from:

1796 – ADAMTS13 testing for the diagnosis of thrombotic thrombocytopenic purpura (TTP)	No. of Inputs Received
Organisations (1)	
I am providing input on behalf of a medical, health, or other (non-consumer) organisation. For example, input on behalf of a group of clinicians, research organisation, professional college, or from an organisation that produces a similar service or technology.	1
Health Professionals (1)	
I am a health professional or health academic working in the area.	1
Grand Total	**2**

MSAC received consultation input from the following organisation:

- Takeda Pharmaceutical Australia Pty Ltd (Takeda)

Level of support for public funding

The input from Takeda was strongly supportive of Medicare Benefits Schedule (MBS) listing of ADAMTS13 testing for the diagnosis of thrombotic thrombocytopenic purpura (TTP). The consultation input from a health professional supported the need for ADAMTS13 testing, but raised concerns with the proposed MBS funding for a pathology service that would predominantly be provided in hospitals in the public system.

Perceived Advantages

The consultation input noted that TTP is a serious medical condition with a high mortality rate (approximately 90%) if untreated or not identified early. Testing would reduce the time to diagnosis and any prospective treatments.

Perceived Disadvantages

The consultation input did not identify any disadvantages of ADAMTS13 testing.

Support for Implementation and Issues

Input from a health professional stated that TTP is a serious condition that is usually managed in large metropolitan hospitals and predominately in the public system. The input highlighted that public patients in public hospitals would not be eligible for MBS funding for their pathology services. The input considered that for non-urgent testing, such as *ADAMTS13* genetic testing that was relatively low in volume and required specific expertise, it would be more cost effective to have one reference laboratory in Australia for this service, rather than multiple private and public laboratories providing the service.

10. Characteristics of the evidence base

Although PICO Set 1 included all 3 tests, PASC agreed to a refined assessment approach for *ADAMTS13* genetic testing in both affected individuals (PICO Set 1) and first-degree biological relatives (PICO Set 2). For this reason, genetic testing was considered separately to ADAMTS13 activity testing and anti-ADAMTS13 autoantibody testing for diagnosis.

The key features of the included evidence for PICO Set 1 (ADAMTS13 activity testing and anti-ADAMTS13 autoantibody testing) are summarised in Table 3. No direct from test to health outcomes evidence was identified. However, ADAMTS13 testing is required to exclude a diagnosis of TTP before patients can access treatment for aHUS through the PBS.

Seven studies were included that assessed the test accuracy of ADAMTS13 activity testing against the reference standard of clinical diagnosis (Dimopoulos et al. 2022; Martin et al. 2021; Page et al. 2017; Bendapudi et al. 2015; Barrows et al. 2014; Garizio et al. 2012; Groot et al. 2006). Two of these studies also assessed the test accuracy of anti-ADAMTS13 autoantibody testing against the reference standard of clinical diagnosis (Martin et al. 2021; Barrows et al. 2014). Due to the limited evidence base for the test accuracy of anti-ADAMTS13 autoantibody testing, studies reporting diagnostic yield were also included for this test (Mancini et al. 2022; Dos Santos et al. 2021; Martin et al. 2021; Page et al. 2017; Mariotte et al. 2016; Barrows et al. 2014; Kremer Hovinga et al. 2010).

Three studies were included that assessed the test accuracy of ADAMTS13 activity using the CLIA AcuStar assay compared to the clinical utility standard of FRETS-VWF73 or ELISA (Singh et al. 2023; Dimopoulos et al. 2022; Falcinelli et al. 2021). These were supplemented by 7 additional studies that were in mixed (diagnostic and monitoring) populations (Beranger et al. 2021; Favaloro et al. 2021a; Stratmann et al. 2020) and/or used a case-control design (Favresse et al. 2018; Irsara et al. 2023; Pascual et al. 2021; Valsecchi et al. 2019). A recent systematic review of rapid ADAMTS13 activity testing compared to standard ADAMTS13 activity testing (Deshpande et al. 2025) included an additional 5 studies that were either unpublished or conference abstracts; these were excluded in accordance with MSAC guidelines.

No studies met the inclusion criteria for assessing change in management following the introduction of ADAMTS13 testing compared to no ADAMTS13 testing. Three studies met the inclusion criteria for assessing change in management following the introduction of rapid

ADAMTS13 activity testing compared to standard ADAMTS13 activity testing (Connell et al. 2016; Martin et al. 2016; Yoshii et al. 2017).

Table 3 Key features of the included evidence for PICO Set 1 (ADAMTS13 activity testing and anti-ADAMTS13 autoantibody testing for diagnosis)

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Accuracy and performance of ADAMTS13 activity test (cross-sectional accuracy)	Cross-sectional diagnostic accuracy studies of index test compared to reference standard.	☒ k = 7 n = 1,184	QUADAS-2: most critical risk of bias across all studies is the inclusion of the index test in the reference standard
Accuracy and performance of CLIA AcuStar assay (cross-sectional accuracy)	Cross-sectional diagnostic accuracy studies of index test compared to clinical utility standard. Additional studies in either mixed diagnostic and monitoring populations and/or case-control designs.	Cross-sectional ☒ k = 3 n = 290 Additional studies ☒ k = 7 n = 1,785	QUADAS-2: low or unclear risk of bias in all domains (cross-sectional studies only). Not assessed for additional studies.
Accuracy and performance of anti-ADAMTS13 autoantibody test (cross-sectional accuracy and diagnostic yield)	Cross-sectional diagnostic accuracy studies of index test compared to reference standard. Additional studies of diagnostic yield.	Diagnostic accuracy ☒ k = 2 n = 46 Diagnostic yield ☒ k = 7 n = 1,066	QUADAS-2: not repeated (studies assessed for ADAMTS13 activity testing). Diagnostic yield studies not assessed.
Change in patient management	No studies met inclusion criteria for ADAMTS13 testing compared to no ADAMTS13 testing. 3 comparative cohorts with historical controls compared rapid ADAMTS13 activity testing with standard ADAMTS13 activity testing.	☒ k = 3 n = 339	SIGN checklist for cohort studies: acceptable quality (2 studies) and low quality (1 study)
Health outcomes	No studies met inclusion criteria for direct evidence. One systematic review (summarising 2 RCTs) and one registry study (4 publications) provide information on effectiveness and safety of PEX. Two evidence-based clinical practice guidelines provide information on effectiveness and safety of other therapies for TTP and aHUS.	Systematic review ☒ k = 2 n = 142 Registry ☒ k = 1 n = 3,42	Not done

aHUS = atypical haemolytic uraemic syndrome; CLIA = chemiluminescence immunoassay; PEX = plasma exchange therapy; PICO = Population, Intervention, Comparator, Outcomes; k = number of studies; n = number of patients; QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies tool for comparison of an index test with a reference standard; RCT = randomised controlled trial; SIGN = Scottish Intercollegiate Guidelines Network; TTP = thrombotic thrombocytopenic purpura.

The key features of the included evidence for PICO Set 1 (diagnostic *ADAMTS13* genetic testing) are presented in Table 4. A pragmatic approach to the assessment of *ADAMTS13* genetic testing was accepted by PASC. Three studies were included that reported diagnostic yield (Alwan et al. 2019; Fujimura et al. 2010; Mariotte et al. 2016). These were supplemented by case series, case reports and registry studies in a narrative assessment of patient management (Ferrari et al. 2019; Hamroun et al. 2023; Kim et al. 2016; Rashid et al. 2020; Tarasco et al. 2021) and outcomes (Alwan et al. 2019; Hamroun et al. 2023; Tarasco et al. 2021).

Table 4 Key features of included evidence for *ADAMTS13* genetic testing of affected individuals (PICO Set 1)

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Diagnostic yield of *ADAMTS13* genetic testing in affected individuals	Cross-sectional studies of patient registries.	**Diagnostic yield** ☒ k = 3 n = 159	Institute of Health Economics (IHE) Quality Appraisal of Case Series Studies Checklist: most critical risk of bias across all studies is the criteria used to define patients with suspected cTTP.
Change in patient management	No evidence identified (and not required for this expedited approach). Illustrative studies: case series, case reports and cross-sectional study of patient registry.	☐ k = 0 n = 0 **Illustrative studies** ☒ k = 5 n = 98	Not done as studies did not meet inclusion criteria and are supplemental to expedited approach.
Health outcomes	No evidence identified (and not required for this expedited approach). Illustrative studies: case series and cross-sectional study of patient registries.	☐ k= 0 n = 0 **Illustrative studies** ☒ k = 3 n = 167	Not done as studies did not meet inclusion criteria and are supplemental to expedited approach.

cTTP = congenital thrombotic thrombocytopenic purpura; k =number of studies; n = number of patients; PICO = Population, Intervention, Comparator, Outcomes.

The key features of the included evidence for PICO Set 2 (*ADAMTS13* genetic testing in first-degree biological relatives) are presented in Table 5. No studies reported diagnostic yield in relatives, so this was discussed narratively using case reports and registry studies (Bennett et al. 2014; Kim et al. 2016; Tarasco et al. 2021.) as was change of management (Kim et al. 2016).

Table 5 Key features of included evidence for *ADAMTS13* genetic testing of first-degree biological relatives (PICO Set 2)

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Diagnostic yield of *ADAMTS13* genetic testing in first-degree biological relatives	No evidence identified for diagnostic yield. Illustrative studies: case reports and cross-sectional study of patient registry.	☐ k = 0 n = 0 **Illustrative studies** ☒ k = 3 n = 99	Not done as studies did not meet inclusion criteria and are supplemental to expedited approach.
Change in patient management	No evidence identified (and not required for this expedited approach).	☐ k = 0 n = 0 **Illustrative studies** ☒ k = 1 n = 2	Not done as study did not meet inclusion criteria and are supplemental to expedited approach.
Health outcomes	No evidence identified (and not required for this expedited approach).	☐ k = 0 n = 0	N/A

k = number of studies; n = number of patients; N/A = not applicable; PICO = Population, Intervention, Comparator, Outcomes.

The key features of the included evidence for PICO Set 3 (ADAMTS13 activity testing for monitoring) are presented in Table 6. Two studies (3 publications) reported direct test to health outcomes evidence; one reported the outcomes of using pre-emptive rituximab treatment in patients with low ADAMTS13 activity (Jestin et al. 2018; Hie et al. 2014) but did not report outcomes for patients with normal ADAMTS13 activity and therefore did not fully capture the

effectiveness of monitoring. The other study was in pregnant women and was very small (Hamroun et al. 2013; n=13).

Ten studies met the inclusion criteria for assessing the incremental longitudinal accuracy of ADAMTS13 activity testing compared to current clinical practice (Dutt et al. 2021; Schieppati et al. 2020; Scully et al. 2019; Sui et al. 2019; Upreti et al. 2019; Page et al. 2016; Ferrari et al. 2014; Bettoni et al. 2012; Peyvandi et al. 2008; Ferrari et al. 2007).

Three descriptive observational studies were included in the linked evidence approach for change in patient management (Völker et al. 2020; Doyle et al. 2023; Knovich et al. 2012) and evidence-based clinical practice guidelines informed a narrative discussion of patient health outcomes.

Table 6 Key features of the included evidence for PICO Set 3 (ADAMTS13 activity testing for monitoring)

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Direct test to health outcomes evidence	Comparative cohorts with historic controls.	☒ k = 2 n = 128	Low level evidence. Risk of bias not formally assessed.
Prognostic evidence (longitudinal accuracy)	Single-arm cohort studies reporting predictive outcomes of ADAMTS13 during treatment or remission.	☒ k = 10 n = 865	QUAPAS: studies at high risk in flow and timing and analysis domains due to retrospective designs.
Change in patient management	Descriptive observational studies.	☒ k = 3 n = 531	Not assessed due to low level evidence.
Health outcomes	Evidence-based clinical practice guidelines were used to inform likely health outcomes.	☐ k = 0 n = 0	N/A

k = number of studies; N/A = not applicable; n = number of patients; PICO = Population, Intervention, Comparator, Outcomes; QUAPAS = Quality Assessment of Prognostic Accuracy Studies.

Although TTP is a rare condition, there was a large volume of evidence but these were predominantly retrospective studies from registries overseas. However, interpretation of the evidence base was complicated by changing diagnostic criteria informed by the evolving understanding of the biological mechanisms of the condition. Newer evidence defined TTP by the absence of ADAMTS13 activity, thereby incorporating the index text in the reference standard, whereas older evidence tended to include a range of secondary TMAs within the TTP diagnosis (e.g. drug-associated TMA).

11. Comparative safety

No comparative studies met the inclusion criteria and reported safety outcomes. ADAMTS13 testing (all tests) require a standard venepuncture blood test that is unlikely to cause direct harm to the patient. There are no direct harms from laboratory testing.

All tests, in all PICO Sets, are proposed to guide treatment decisions and therefore to alter patient management.

In PICO Set 1 (diagnosis), ADAMTS13 testing is proposed to improve patient safety by reducing unnecessary exposure to PEX, particularly in cases where ADAMTS13 activity testing excludes a diagnosis of TTP. However, the potential for false-positive or false-negative diagnosis introduces a risk of clinical harm. Such inaccuracies may lead to the initiation of inappropriate treatment or the omission or delay of necessary therapeutic interventions.

A false-positive ADAMTS13 activity test could lead to a diagnosis of TTP that is subsequently not supported clinically. In this case, patients would continue to receive PEX unnecessarily and potentially would have delayed appropriate treatment. False-positive findings tend to occur in patients who have severe systemic disorders, commonly infections and/or sepsis. Delayed diagnosis in these patients is expected to be harmful; however, the ADAMTS13 activity results are not interpreted in isolation and failure to respond to PEX, negative anti-ADAMTS13 autoantibody findings, or other clinical findings may all lead to an appropriate diagnosis despite reduced ADAMTS13 activity.

False-negative ADAMTS13 activity results were also reported. Most affected patients had activity levels within the equivocal range (10–30%) and tested positive for anti-ADAMTS13 autoantibodies. This finding suggests that subsequent anti-ADAMTS13 autoantibody testing is a critical component of the diagnostic pathway and should not be restricted to patients with ADAMTS13 activity levels <10% but should be performed in all patients with reduced or equivocal ADAMTS13 activity, particularly when there is a high pre-test probability of TTP.

Overall, the risk of harm associated with ADAMTS13 testing is considered low, as the testing proposed is not performed in isolation but as part of a broader panel of investigations that are undertaken during acute TMA presentations. The introduction and appropriate use of ADAMTS13 activity testing is likely to improve the targeting of therapy, due to its high sensitivity and specificity. Moreover, false-positive or false-negative results are likely to be identified through correlation with clinical information provided by other concurrent or subsequent tests.

For PICO Set 2, *ADAMTS13* genetic testing in first-degree biological relatives is expected to be safer than no intervention, given there are effective treatments for cTTP. Identification of cTTP in an asymptomatic sibling enables appropriate and timely therapy, whether prophylactic or during an acute presentation. Furthermore, the value of knowing is expected to be high for relatives who receive a negative diagnosis, providing freedom from anxiety.

For PICO Set 3, ADAMTS13 activity testing during remission is for the purpose of initiating treatment earlier (pre-emptively) to reduce the risk of an acute clinical relapse. Rituximab is the standard therapeutic agent used in this context and, while generally well tolerated, is associated with adverse events. The potential for treatment-related harm in asymptomatic individuals must be carefully weighed against the risk of relapse, which carries significant safety concerns, including morbidity and mortality from the acute episode itself and the risk of adverse events associated with PEX treatment. The overall safety of ADAMTS13 activity testing and management of this indication compared with symptomatic management remains uncertain.

ADAMTS13 activity testing is also used for monitoring during and immediately following an acute iTTP episode, enabling treatment regimens (such as immunotherapy) to be tailored according to therapeutic response. This is likely to improve safety by reducing unnecessary exposure to treatment in patients who have achieved a response, or by extending treatment in cases where the risk of exacerbation or relapse is high.

12. Comparative effectiveness

PICO Set 1: ADAMTS13 activity and anti-ADAMTS13 autoantibody testing for diagnosis

Test accuracy

The diagnostic accuracy of ADAMTS13 activity testing compared to the final clinical diagnosis was reported in 7 studies and is presented in Figure 1. Sensitivity and specificity were very high across all studies (range 0.83 to 1.00 and 0.94 to 1.00 respectively) and tended to be higher in

more recent studies. This may reflect changes in the clinical classification of TTP that now aligns diagnosis more closely with ADAMTS13 levels.

Discordant results were tabulated. All patients with false-positive findings had severe systemic disorders, most commonly infections and/or sepsis. Patients with false-negative findings were more variable; 4 of 12 reported cases had an ADAMTS13 activity level <20% (a value that may be considered indeterminate and warrant anti-ADAMTS13 autoantibody testing). Two patients in Page et al. (2017) had high levels of ADAMTS13 activity and were diagnosed with iTTP during subsequent relapses.

Study	TP	FP	FN	TN	Test threshold	Test	Sensitivity (95% CI)	Specificity (95% CI)
Dimopoulos, 2022	27	2	1	182	10%	FRETS-VWF73	0.96 [0.82, 1.00]	0.99 [0.96, 1.00]
Martin, 2021	35	0	0	65	10%	ELISA	1.00 [0.90, 1.00]	1.00 [0.94, 1.00]
Page, 2017	75	3	5	280	10%	FRETS-VWF73	0.94 [0.86, 0.98]	0.99 [0.97, 1.00]
Bendapudi, 2015	68	0	2	184	10%	FRETS-VWF73	0.97 [0.90, 1.00]	1.00 [0.98, 1.00]
Barrows, 2014	10	1	0	141	20%	FRETS-VWF73	1.00 [0.69, 1.00]	0.99 [0.96, 1.00]
Garizio, 2012	5	1	1	17	20%	FRETS-VWF73	0.83 [0.36, 1.00]	0.94 [0.73, 1.00]
Groot, 2006	24	1	3	51	10%	FRETS-VWF73	0.89 [0.71, 0.98]	0.98 [0.90, 1.00]

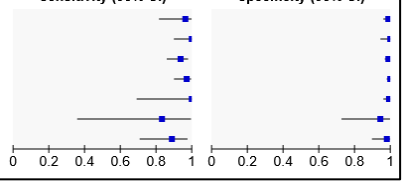

Figure 1 Forest plot of diagnostic accuracy data comparing ADAMTS13 activity testing (FRETS-VWF73 or ELISA) against final clinical diagnosis

CI = confidence interval; ELISA = enzyme-linked immunosorbent assay; FN = false negative; FP = false positive; FRETS = fluorescence resonance energy transfer assay; TN = true negative; TP = true positive.

The diagnostic accuracy of automated ADAMTS13 activity (CLIA AcuStar) testing compared to the clinical utility standard (ELISA or FRETS-VWF73) was reported in 3 studies and is presented in Figure 2. The accuracy of CLIA AcuStar was almost perfect in 2 studies. The one false-positive result reported in Dimopoulos et al. (2022) was clinically classified as TTP and had a FRETS-VWF73 activity of 10%. Therefore, compared to the reference standard, CLIA AcuStar performed better than FRETS-VWF73 in this study.

The Singh et al. (2023) study reported 5 false positives with CLIA AcuStar leading to lower specificity. The 5 false positives appear to have been reported in 4 patients (i.e. 1 patient provided 2 diagnostic samples). Three of these patients had sepsis and none had anti-ADAMTS13 autoantibody results above the reference range.

The prevalence of TTP in Singh et al. (2023) was 41%, higher than the other included studies, which ranged from 7% to 35% with a median of 24%. It was also one of the smallest included studies (32 samples). The higher prevalence may translate to a higher number of samples likely to be misclassified, and a smaller study size may have contributed to greater variability in the findings. Both factors could explain the considerably lower specificity of this study compared with all other included studies. Nevertheless, the study highlights that AcuStar has the potential to return results that differ from FRETS-VWF73 and is the basis for the TGA notifications for AcuStar ADAMTS13 activity testing in February 2022 and again in August 2024[6].

Study	TP	FP	FN	TN	Clinical utility standard	Sensitivity (95% CI)	Specificity (95% CI)
Dimopoulos, 2022	29	1	0	182	FRETS VW73	1.00 [0.88, 1.00]	0.99 [0.97, 1.00]
Falcinelli, 2021	13	0	0	33	ELISA	1.00 [0.75, 1.00]	1.00 [0.89, 1.00]
Singh, 2023	13	5	0	14	FRETS VW73	1.00 [0.75, 1.00]	0.74 [0.49, 0.91]

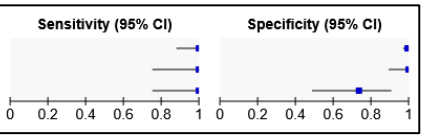

Figure 2 Forest plot of diagnostic accuracy data comparing automated ADAMTS13 activity testing (CLIA AcuStar) against the clinical utility standard (FRETS-VWF73 or ELISA)

CI = confidence interval; CLIA = chemiluminescence immunoassay; ELISA = enzyme-linked immunosorbent assay; FN = false negative; FP = false positive; FRETS = fluorescence resonance energy transfer assay; TN = true negative; TP = true positive.

[6] TGA Recall Reference RC-2024-RN-00633-1; 12 August 2024.

There is a broader body of evidence for the test performance of CLIA AcuStar compared to ELISA or FRETS-VWF73 when the population is not restricted to diagnosis and case-control designs are included. This is expected to increase the diagnostic accuracy of the index test; however, it was included as supplementary evidence. Under these broader inclusion criteria, the sensitivity of CLIA AcuStar compared to FRETS-VWF73 ranged across 7 studies from 0.93 to 1.00 and the specificity ranged from 0.74 to 1.00. Compared to ELISA, the sensitivity ranged across 5 studies from 0.89 to 1.00 and the specificity ranged from 0.94 to 1.00.

The diagnostic accuracy of anti-ADAMTS13 autoantibody testing was reported in 2 studies (Figure 3). Both were retrospective cohorts spanning 5 or more years; however, the total number of included patients was small due to TTP being a rare condition. No false positives were identified, leading to perfect specificity, albeit with very wide confidence intervals. One false negative was reported; the patient had an indeterminant anti-ADAMTS13 autoantibody level. Of the 12 true negatives, 3 patients were diagnosed as cTTP and one had an ADAMTS13 activity of 10% and concurrent sepsis. The remaining 8 true negatives had ADAMTS13 activity levels >10% and <30%.

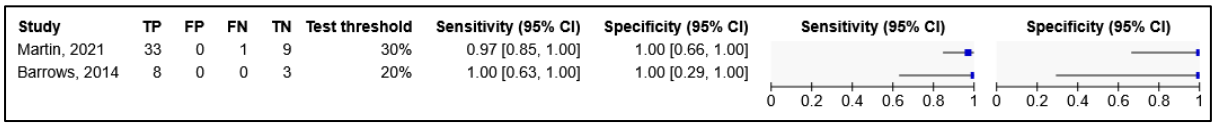

Figure 3 Forest plot of diagnostic accuracy data comparing anti-ADAMTS13 autoantibody testing against final clinical diagnosis

CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive.

Change in management

No studies met the inclusion criteria for change of management following the introduction of ADAMTS13 testing compared to no ADAMTS13 testing. ADAMTS13 testing forms an integral component of the diagnostic criteria for TTP and is widely adopted in routine clinical practice.

Three studies met the inclusion criteria for assessing change in management following the introduction of rapid ADAMTS13 activity testing compared to standard ADAMTS13 activity testing (mean difference of 60 hours for test turn around). The studies varied in their clinical algorithm and patient populations.

Martin et al. (2016) included 14 patients and is therefore underpowered for key outcomes. The study by Yoshii et al. (2017) only included patients with confirmed TTP and therefore does not capture the broader clinical utility of ADAMTS13 testing, which is avoiding unnecessary PEX in patients without TTP. Results from Connell et al. (2016) are summarised in Table 7. The study reported fewer patients initiating PEX and fewer procedures per patient where rapid ADAMTS13 activity testing was used. There was no difference in mortality. The findings support the clinical assertion that earlier ADAMTS13 activity testing reduces PEX utilisation when TTP is excluded.

Table 7 Change to PEX management and mortality comparing rapid ADAMTS13 activity testing and standard ADAMTS13 activity testing (Connell et al. 2016)

Outcome	Rapid ADAMTS13 activity testing	Standard ADAMTS13 activity testing	Absolute difference [95% CI]	Relative difference [95% CI]
Number of patients who received PEX, n/N (%)	12/28 (43%)	32/32 (100%)	-0.57 [-0.76, -0.39]	0.44 [0.29, 0.67]
Mean number of PEX procedures mean ± SD (range)	5.3 ± NR (0–35)	14.1 ± NR (1–38)	-8.8 (NR)[a]	-
30-day mortality, n/N (%)	6/28 (21.4%)[b]	7/32 (21.9%)	-	-

CI = confidence interval; NR = not reported; PEX = plasma exchange therapy; SD = standard deviation.
a. Study reported statistically significant difference (p=0.0008) using an interrupted time series regression analysis that included weight and haematocrit as variables as these determine plasma dose.
b. Difference was not statistically significant, p=0.9659.

Health outcomes

In a large registry of 342 TMA patients treated with PEX from 1996 to 2014, 7 deaths were attributed to catheter-related PEX complications (McClain et al. 2014). The most common nonfatal major complications were systemic infections (37 patients) and thrombosis (24 patients). Overall, 23% of patients experienced a major PEX-related complication. Therefore, reducing the duration of unnecessary PEX (i.e. in patients without TTP) is expected to reduce harm.

Guidelines are consistent in recommendations for the treatment of TTP and these differ to those recommended for non-TTP TMAs. Earlier and more accurate diagnosis is expected to have clinical benefit through earlier initiation of appropriate treatment.

Clinical claim

The clinical claims for ADAMTS13 activity testing and anti-ADAMTS13 autoantibody testing in the diagnosis of TTP are summarised in Table 8. The tests result in superior safety and effectiveness in the diagnosis of TTP among patients presenting with TMA and a high clinical suspicion of TTP.

Table 8 Synthesis of the evidence and evidence gaps for diagnostic ADAMTS13 activity testing and anti-ADAMTS13 autoantibody testing (PICO Set 1)

Evidence component of the assessment	Interpretation and key uncertainties
Test accuracy	**ADAMTS13 activity testing** demonstrates high sensitivity and specificity compared to clinical diagnosis without ADAMTS13 activity testing (*moderate certainty*). **Anti-ADAMTS13 autoantibody testing** demonstrates high sensitivity and specificity compared to clinical diagnosis without anti-ADAMTS13 autoantibody testing (*very low certainty*). **Combined testing** with ADAMTS13 activity and anti-ADAMTS13 autoantibody assays provides higher diagnostic accuracy than either test alone, as the antibody can identify cases with false-negative ADAMTS13 activity results. **CLIA AcuStar** demonstrates high accuracy and concordance with clinical utility standards (ELISA or FRETS VWF73), although occasional discrepancies occur, mostly in patients with systemic conditions and/or a low clinical suspicion of TTP.
Change in management	Rapid ADAMTS13 testing is associated with reduced PEX utilisation and/or shorter treatment duration without an increase in mortality (*low level evidence*). Requirement for ADAMTS13 activity testing to access PBS-funded therapies (eculizumab and ravulizumab) for aHUS.
Health outcomes	PEX is effective in the treatment of iTTP but not complement-mediated aHUS, for which eculizumab or ravulizumab is the recommended therapy, or cTTP where plasma infusion is sufficient. PEX is associated with major complications in approximately 23% of patients with TMA, most commonly related to catheter use. Targeted therapies for iTTP include corticosteroids, rituximab and caplacizumab. Accurate differentiation between iTTP, cTTP and aHUS is expected to lead to more appropriate use of therapies for these conditions, particularly reducing uptake of PEX where it is not clinically indicated.
Safety of the test	No evidence of harm associated with ADAMTS13 activity or anti-ADAMTS13 autoantibody testing was identified.
Safety of the treatment	Use of ADAMTS13 testing may improve safety by reducing inappropriate PEX and ensuring patients receive the most appropriate therapy. Potential harms exist for patients with a low clinical suspicion of TTP who receive false-positive results, which could delay treatment for underlying systemic conditions (e.g. sepsis).
Overall assessment of the evidence	***Superior** for both safety and effectiveness*

CLIA = chemiluminescence immunoassay; cTTP = congenital TTP; ELISA = enzyme-linked immunosorbent assay; FRETS-VWF73 = ADAMTS13 fluorescence resonance energy transfer assay; HUS = haemolytic uraemic syndrome; iTTP = immune-mediated TTP; PBS = Pharmaceutical Benefits Scheme; PEX = plasma exchange therapy; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura.

PICO Set 1 & 2: *ADAMTS13* genetic testing

Comparative effectiveness is not relevant for the genetic tests as the PICO confirmation specified a refined assessment approach that estimates diagnostic yield for use in a cost per diagnosis analysis.

- PICO Set 1 – diagnostic yield in affected individuals with suspected cTTP
- PICO Set 2 – diagnostic yield among first-degree biological relatives of probands.

Genetic testing of affected individuals – PICO Set 1

Three registry studies were used to estimate diagnostic yield in affected individuals (Alwan et al. 2019; Fujimura et al. 2010; Mariotte et al. 2016). A diagnostic yield of 97% was derived from the study considered most applicable in terms of suspected cTTP cohort definition (Fujimura et al. 2010), and this was used for the economic evaluation of cost per diagnosis. Diagnostic yield may be as high as 100% where the suspected cTTP cohort is more stringently defined, and may be as low as 72% where the testing includes relatives of probands.

Genetic testing of first-degree biological relatives – PICO Set 2

No studies were identified that reported data relevant to diagnostic yield for genetic testing in first-degree biological relatives or relatives. A diagnostic yield of 25% was inferred, based on a Mendelian inheritance pattern for an autosomal recessive disorder, noting any bias in sibling selection for testing arising from the presence of non-overt symptoms will increase the diagnostic yield. This value was used for the economic evaluation of cost per diagnosis.

Clinical claim

The clinical claims for *ADAMTS13* genetic testing are summarised in Table 9 (affected individuals) and Table 10 (cascade testing in first-degree biological relatives). Compared with no genetic testing, *ADAMTS13* genetic testing in affected individuals with suspected cTTP is superior with respect to safety and effectiveness. *ADAMTS13* genetic testing in first-degree biological relatives of identified cTTP probands is also superior to no testing with respect to safety and clinical effectiveness.

Table 9 Synthesis of the evidence and evidence gaps for *ADAMTS13* genetic testing of affected individuals (PICO Set 1)

Evidence component of the assessment	Interpretation and key uncertainties
Diagnostic yield	No studies specifically designed to determine the diagnostic yield of genetic testing in the PICO population were identified. The best available evidence suggests a high diagnostic yield for *ADAMTS13* genetic testing in affected individuals *(very low certainty)*, although the reported estimates may overstate the diagnostic yield in the intended population due to a likely overrepresentation of probands in the test cohorts. Genetic testing for *ADAMTS13* variants in affected individuals, when used to confirm suspected cTTP, demonstrates a diagnostic yield of approximately 97%, with a reported range of 72% to 100%.
Change in management	According to clinical practice guidelines, in the absence of genetic testing, patients with suspected cTTP are managed based on their response to treatment, and some may receive prophylaxis. In some circumstances, *ADAMTS13* genetic testing in affected individuals may lead to a change in management by enabling timely and appropriate treatment of future acute episodes or supporting access to prophylactic therapy *(low level evidence)*. Genetic testing can provide diagnostic certainty, which is important in the context of decision-making about lifelong prophylaxis.
Health outcomes	The best available evidence *(low level)* indicates that access to prophylaxis reduces morbidity (non-overt symptoms, stroke, ischaemic organ damage) and the incidence of acute episodes during pregnancy. Australian and international clinical practice guidelines support the use of prophylaxis in patients with suspected cTTP. As a result, the incremental diagnostic value of *ADAMTS13* genetic testing may be limited for many affected individuals. However, where a proband has first-degree biological relatives, the genetic test may offer greater incremental diagnostic value. This is particularly relevant for cascade testing, which can inform early diagnosis and management in at-risk family members.
Safety of the test	No evidence of direct harms associated with *ADAMTS13* genetic testing in affected individuals was identified.
Safety of the treatment	Use of *ADAMTS13* genetic testing in affected individuals may improve treatment safety by supporting the appropriate use of prophylaxis, which can reduce morbidity and mortality associated with cTTP.
Value of knowing	A confirmed genetic diagnosis can provide reassurance to patients, particularly in relation to decisions about initiating prophylaxis. It also supports timely access to appropriate therapy during acute episodes, regardless of the clinical setting.
Overall assessment of the evidence	***Superior*** *for both safety and effectiveness.* This assessment is based on single-arm observational studies and clinical practice guidelines.

cTTP = congenital thrombotic thrombocytopenic purpura.

Table 10 Synthesis of the evidence and evidence gaps for *ADAMTS13* cascade testing (PICO Set 2)

Evidence component of the assessment	Interpretation and key uncertainties
Diagnostic yield	No studies evaluating the diagnostic yield of cascade testing for *ADAMTS13* variants were identified. One single-family study confirmed the expected 25% yield of biallelic siblings, consistent with Mendelian inheritance patterns of an autosomal recessive condition. While this represents a conservative estimate, selective testing of symptomatic relatives may increase the yield of cTTP diagnoses. A negative result in cascade testing provides value through diagnostic certainty, particularly in ruling out disease in at-risk relatives. In this context, the diagnostic yield can be considered 100%.
Change in management	No studies specifically evaluating change in management resulting from cascade testing were identified. Limited descriptive evidence was found in case reports. A confirmed cTTP diagnosis through *ADAMTS13* genetic testing can support timely and appropriate therapy in the event of an acute attack and can inform strategies for prophylaxis where necessary. The incremental diagnostic value of a positive cTTP diagnosis in relatives prior to disease onset may be greater than in probands, as relatives do not have response-to-treatment information to guide management. Early identification enables prompt access to appropriate treatment at disease onset and consideration of primary prophylaxis.
Health outcomes	No studies evaluating change in management from cascade testing were identified, and only limited descriptive evidence was found in case reports. Additionally, no studies were found assessing the use of pre-emptive prophylaxis upon diagnosis prior to symptom onset in relatives. The best available evidence *(low level)*, derived from affected individual testing, also applies to relatives with confirmed cTTP. It indicates that access to prophylaxis can reduce morbidity (non-overt symptoms, stroke, ischaemic organ damage) and the incidence of acute episodes during pregnancy.
Value of knowing	The absence of a genetic diagnosis can provide significant reassurance to individuals, alleviating concerns about potential disease onset and its associated risks, including morbidity and mortality. A diagnosis of a genetic condition can support informed decision-making regarding prophylaxis and ensure timely access to appropriate therapy during acute episodes, contributing to a sense of preparedness and control.
Safety of the test	No evidence of direct harms associated with *ADAMTS13* genetic testing in biological relatives was identified.
Safety of the treatment	Use of *ADAMTS13* genetic testing in biological relatives may improve treatment safety by supporting the appropriate use of prophylaxis, which can reduce morbidity and mortality associated with cTTP.
Overall assessment of the evidence	***Superior** for both safety and effectiveness.* This assessment is based on observational studies, including case reports and clinical practice guidelines.

cTTP = congenital thrombotic thrombocytopenic purpura.

PICO Set 3: ADAMTS13 activity testing for monitoring

Direct test to health outcomes evidence

One study (2 publications) partially met the inclusion criteria for assessing the direct health outcomes of monitoring during remission. The study (Jestin et al. 2018; Hie et al. 2014) included patients with a decline in ADAMTS13 activity levels (<10%) during clinical and haematological remission and compared those who received pre-emptive rituximab (92 patients) against those who did not receive pre-emptive treatment (23 patients). The comparison group comprised patients treated either in an earlier time period (8 patients) or at a centre that did not manage patients with pre-emptive rituximab (10 patients).

Although pre-emptive administration of rituximab is a clinically applicable treatment strategy, the study evaluated its effectiveness exclusively in patients who tested positive for ADAMTS13 activity <10%. Consequently, it does not assess the broader clinical utility of monitoring all patients during remission and initiating treatment selectively based on test results.

The relapse rate in rituximab treated patients was lower than in the comparator group. In Kaplan-Meier analysis, the Log Rank test for relapse free survival was statistically significant in favour of the intervention (p<0.001). Outcomes in the test-negative population could be inferred from the earlier publication of a smaller sample (Hie et al. 2014). This publication reported that 185/233 (79.4%) of patients were test negative (ADAMTS13 activity ≥10%) and not treated with rituximab. Of these patients, 20.5% relapsed over a median follow-up of 24 months (Figure 4). This relapse rate is higher than that observed in test-positive patients (ADAMTS13 activity <10%) who received rituximab, and lower than test-positive patients who did not receive rituximab. However, these comparisons should be interpreted cautiously due to differences in the duration of follow-up.

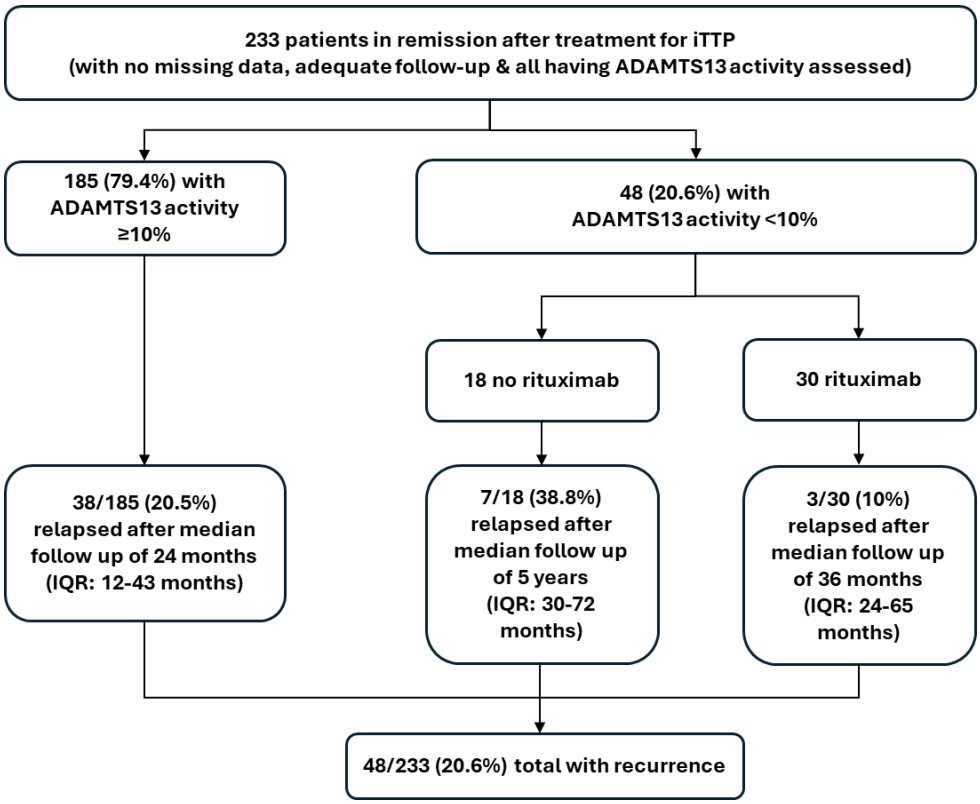

Figure 4 Outcomes in test-positive (ADAMTS13 activity <10%) and test-negative (ADAMTS13 activity ≥10%) patients in Hie et al. (2014)

iTTP = immune-mediated thrombotic thrombocytopenic purpura; IQR = interquartile range.
This data was used for the economic analysis.

One study met the inclusion criteria for assessing the direct health outcomes of ADAMTS13 activity monitoring during pregnancy compared to no ADAMTS13 activity monitoring (i.e. clinical management based on platelet count and symptoms) (Hamroun et al. 2023). This small study included pregnant women with iTTP (n=6) and cTTP (n=7), comparing outcomes between index pregnancies (during which ADAMTS13 activity was not monitored) and subsequent pregnancies that were monitored. Maternal and perinatal outcomes were improved in monitored pregnancies. However, the results are not specific to ADAMTS13 activity monitoring as the index and comparator pregnancies differed more broadly ADAMTS13 activity was not monitored frequently during pregnancy, and no treatment changes were reported to have been made in response to reduced ADAMTS13 levels.

Longitudinal accuracy

Eight studies reported data that could be extracted into a 2-by-2 table to generate positive and negative predictive values. The most common outcome was relapse. The prevalence of relapse varied from 4% to 33% with the variation largely attributable to the variable length of follow-up. In most cases, the measurement of ADAMTS13 activity was early in remission, even where follow-up was extensive.

For studies with shorter follow-up (1 to 18 months; Scully et al. 2019; Dutt et al. 2021; Ferrari et al. 2007), ADAMTS13 activity testing at initial remission had a very high negative predictive value, suggesting that ADAMTS13 activity above the diagnostic threshold has good predictive value for identifying patients at low risk of relapse. However, the positive predictive value of ADAMTS13 activity was low, indicating that although almost all relapses were in this group, ADAMTS13 activity below the diagnostic threshold is a poor predictor of relapse (Table 11). Two of these studies (Scully et al. 2019; Dutt et al. 2021) reported exacerbations separately to relapses with very similar findings in terms of (low) positive and (high) negative predictive value for both outcomes.

Table 11 Longitudinal accuracy of ADAMTS13 activity testing during treatment or early remission for predicting relapse (up to 18 months)

Study ID	Outcome	Cut-off	Time of testing	Outcome in test positive n/N	Outcome in test negative n/N	PPV (95% CI)	NPV (95% CI)	Prevalence (%)	Follow-up
Scully, 2019	Relapse	<10%	At the end of treatment (caplacizumab or placebo)	9/29	0/91	0.31 (017, 0.49)	1.00 (0.96, 1.00)	8%	28 d post-treatment
Dutt, 2021	Relapse	<10%	At completion of PEX	3/37	0/39	0.08 (0.03, 0.21)	1.00 (0.91, 1.00)	4%	80 d (IQR 59, 166)
Ferrari, 2007	Relapse	<5%	At initial remission	5/13	1/19	0.38 (0.18, 0.64)	0.95 (0.75, 0.99)	19%	18 mo

CI = confidence interval; d = days; mo = months; IQR = interquartile range; NPV = negative predictive value; PEX = plasma exchange therapy; PPV = positive predictive value.

Three studies followed patients for longer than 18 months (Peyvandi et al. 2008; Bettoni et al. 2012; Schieppati et al. 2020). The informativeness of ADAMTS13 activity measured at initial relapse or an unspecified timepoint over this period remains uncertain, as ADAMTS13 activity levels may change over time (hence the proposal for repeated monitoring). Nevertheless, relapse rates, although higher overall compared to studies with shorter follow-up, remained higher in test-positive than test-negative patients. However, the negative predictive value declined (range

0.75 to 0.79), and the positive predictive value increased (range 0.38 to 0.47) suggesting limited value for ADAMTS13 activity at remission for predicting relapse over this longer time frame.

Evidence from studies evaluating ADAMTS13 activity monitoring during acute iTTP episodes suggest that the test is responsive to treatment. Two studies reported median ADAMTS13 activity values over the course of acute treatment (Dutt et al. 2021; Sui et al. 2019). Although the timing of measurements differed, the overall pattern of increasing ADAMTS13 activity supports the responsiveness of the test to treatment. Similarly, patients in remission with low ADAMTS13 activity treated with rituximab demonstrate an ADAMTS13 response.

There are less data regarding the detectability of long-term change. Page et al. (2016) presented serial ADAMTS13 activity measurements during remission of 8 patients selected to illustrate different patterns. They reported that 17 of 57 (30%) patients had a remission ADAMTS13 activity <10% and 10 of these patients relapsed. Two patients who relapsed had spontaneous recovery of remission ADAMTS13 activity to 55% and 96% for 2 years before they relapsed. For the 7 patients who did not relapse, median follow-up after remission ADAMTS13 activity <10% was 5.8 years (range 4.5 to 12.1), with some patients exhibiting severe ADAMTS13 deficiency without relapse for many years. No patients whose ADAMTS13 activity was always ≥60% relapsed. The authors concluded that their findings were consistent with previous observations that iTTP and cTTP patients may have prolonged periods of severe ADAMTS13 activity deficiency without an acute episode and they noted that the clinical course of individual patients is unpredictable.

One study reported on stroke in iTTP patients during remission (Upreti et al. 2019). Stroke was associated with below normal levels of ADAMTS13 activity (≤70%) (p=0.007). This raises the possibility that low levels of ADAMTS13 activity are associated with health effects beyond risk of relapse and the treatment to raise the levels may lead to additional health benefits not captured in the DCAR.

Change in management

Three studies met the inclusion criteria for assessing change in management following ADAMTS13 activity monitoring; the studies were descriptive observational studies and provide a very low level of evidence.

One study considered the use of ADAMTS13 activity monitoring for treatment decisions in the acute and post-acute phase (Völker et al. 2020). Caplacizumab was stopped before day 30 in 35 instances in 31 patients (if it was stopped and resumed later due to exacerbation or relapse, time to normalisation was measured again). Treatment was stopped based on a platelet-guided approach in 20 of these instances, of which 9 (45%) experienced disease exacerbation. In 15 instances, treatment was stopped based on ADAMTS13 activity; none of these patients experienced exacerbation or relapse during the follow-up.

Two studies considered the use of ADAMTS13 activity for monitoring during long-term remission (Doyle et al. 2023; Knovich et al. 2012).

Doyle et al. (2023) included 443 patients from the UK TTP registry (30 sites) with more than 3 years of follow-up. ADAMTS13 relapses were treated with pre-emptive rituximab when activity levels were <20% but higher thresholds may have been used if there was clinical concern. To investigate the effect of modern TTP management (plasma exchange, steroids, and rituximab), the type of relapse for each patient was compared in those presenting up to 2012 (n=217) with those presenting after 2012 (n=226). There was a statistically significant reduction in patients having at least one episode of clinical relapse from 49 (23%) diagnosed before 2012 compared with 25 (11%) diagnosed after 2012. Conversely, there was an increase in ADAMTS13 relapses from 17 (8%) in the earlier time period in comparison with 37 (16%) in the later period

(p=0.0004). The authors attributed this to increased surveillance, including targeted monitoring and pre-emptive treatment. However, they did not report whether follow-up duration or other characteristics differed between the two cohorts.

Knovich et al. (2012) describe routine monitoring at their institution and report that since it became available, 28 patients have been treated for TTP and one relapsed. In contrast, the relapse rate was approximately 30% in the 20 years before monitoring. The authors stated that serial ADAMTS13 measurements led to a modification of immune modulation treatment in 16 (57%) patients and an earlier cessation of PEX (rather than a taper) in the remaining 12 patients.

Health outcomes

No additional studies were included for the linked evidence of health outcomes. Treatments for acute iTTP are also applicable for exacerbations and relapse. Evidence-based guidelines recommend the use of rituximab where ADAMTS13 activity is low (<20 IU/dL in current British Society of Haematology guidelines; ADAMTS13 activity level not specified in International Society on Thrombosis and Haemostasis guidelines).

Clinical claim

The clinical claims for ADAMTS13 activity testing to monitor disease during acute episodes and remission are summarised in Table 12. During acute iTTP and early remission, monitoring with ADAMTS13 activity testing is superior for both safety and effectiveness. There is insufficient evidence to determine the safety and effectiveness of ADAMTS13 activity monitoring during late remission.

Table 12 Synthesis of the evidence and evidence gaps for ADAMTS13 activity testing for monitoring (PICO Set 3)

Evidence component of the assessment	Interpretation and key uncertainties
Direct evidence	**Monitoring in remission:** No direct evidence on whether relapse-free survival is improved in patients in remission who are monitored with ADAMTS13 activity testing compared to those monitored with clinical symptoms and platelet count. Median relapse free survival is improved in patients who are treated with rituximab where ADAMTS13 activity levels are <10% (*low level evidence).*
Test accuracy	**Monitoring in acute iTTP and early remission:** ADAMTS13 activity ≥10% strongly predicts remission during the first 12–18 months (high NPV); exacerbations and relapses occur most commonly where ADAMTS13 activity is <10% but the predictive value is low (low NPV) *(low level evidence).* **Monitoring in remission (iTTP):** ADAMTS13 activity is associated with relapse but there is individual variation and the data are insufficient to draw conclusions on its predictive value. Reduced ADAMTS13 activity may be associated with a higher risk of stroke *(very low level evidence).*
Change in management	**Monitoring in acute iTTP and early remission:** ADAMTS13 activity testing results in treatment changes including reduced duration of PEX and caplacizumab, changes to immunosuppressive therapies and extended duration of caplacizumab *(low level evidence).* **Monitoring in remission (iTTP):** ADAMTS13 activity testing results in treatment changes, mostly use of rituximab *(low level evidence).*
Health outcomes	Treatments for TTP relapse are the same as for an initial acute episode and are effective.
Safety of the test	No evidence of harm associated with ADAMTS13 activity testing was identified.
Safety of the treatment	**Monitoring in acute iTTP and early remission:** Use of ADAMTS13 activity monitoring during treatment may improve safety by reducing exposure to unnecessary treatments (PEX and caplacizumab). ADAMTS13 activity testing may reduce the risk of exacerbations and re-initiation of these treatments by extending the initial course of treatment where the response has been poor. **Monitoring in remission (iTTP):** The safety of treatment with rituximab in response to low ADAMTS13 activity in remission is uncertain. For an individual patient, it would need to be balanced against the risk of iTTP relapse and the individual patient's clinical history and preferences.
Overall assessment of the evidence	***Superior*** *for both safety and effectiveness for acute iTTP and early remission.* *Rituximab treatment of patients with low ADAMTS13 activity levels is* ***superior*** *to no rituximab treatment for the outcome of relapse.* *There is* ***insufficient evidence*** *to determine the safety and effectiveness of ADAMTS13 activity monitoring during remission.*

iTTP = immune-mediated TTP; NPV = negative predictive value; PEX = plasma exchange therapy; PPV = positive predictive value; TTP = thrombotic thrombocytopenic purpura.

13. Economic evaluation

PICO Set 1: ADAMTS13 activity and anti-ADAMTS13 autoantibody testing for diagnosis

An economic evaluation was conducted comparing 2 scenarios: one in which rapid ADAMTS13 activity testing is available to support the diagnosis of TTP, and one in which it is not.

The evaluation was conducted for patients with TMA where there was a clinical suspicion of TTP, including a PLASMIC score >4, who were initiated on treatment with PEX.

Given the substantial resource use associated with PEX, it was considered likely that the proposed strategy (incorporating rapid assay testing for ADAMTS13 activity) could be a dominant approach, offering both improved clinical outcomes and lower overall costs compared to the alternative approach that omits testing. On this basis, a direct cost comparison (cost-minimisation analysis) was undertaken.

Table 13 summarises the key features of the economic evaluation.

Table 13 Summary of the economic evaluation: rapid ADAMTS13 for diagnosis

Component	Description
Perspective	Australian health care system perspective
Population	Patients clinically suspected of having TTP, including a PLASMIC score > 4[a]
Prior evaluation	PLASMIC score > 4[a]
Intervention	Rapid assay testing for ADAMTS13 activity in addition to standard investigations and observation of clinical response to PEX
Comparator	Standard investigations and observation of clinical response to PEX
Type of analysis	Cost comparison (cost-minimisation analysis)
Outcomes	Time to confirmation or exclusion of a diagnosis of TTP
Time horizon	3 days (average time to confirmation or exclusion of a diagnosis of TTP in the absence of rapid assay testing for ADAMTS13 activity)
Computational method	Cohort expected value decision analysis
Generation of the base case	Trial-based (Dimopoulos et al. 2022)
Health states	Model is a decision analysis. Terminal states in the model reflect either a confirmed diagnosis of TTP or exclusion of TTP diagnosis
Cycle length	Not applicable
Transition probabilities	Prevalence of TTP in patients undergoing testing with rapid assay of ADAMTS13 activity, sourced from Table 1 of Dimopoulos et al. (2022) Sensitivity and specificity of rapid assay testing of ADAMTS13 activity to inform diagnosis of TTP, sourced from Dimopoulos et al. (2022) Assumptions are made that: (i) results from the rapid assay testing are available within 1 day, and (ii) the time to confirmation/exclusion of a diagnosis in the absence of testing is 3 days (based on observed response to PEX)
Discount rate	Not applicable given the 3-day time horizon examined
Software	TreeAge Pro

PEX = plasma exchange therapy; TTP = thrombotic thrombocytopenic purpura.
a. PLASMIC score is a clinical prediction score that considers the following 7 clinical and laboratory features: Platelet count <30 x 10^9/L; haemoLysis (elevated lactate dehydrogenase or low haptoglobin); no Active cancer; no history of Solid organ or stem cell transplant; Mean corpuscular volume < 90 femtolitres; International normalized ratio < 1.5; Creatinine <2 mg/dL.

Figure 5 presents the decision tree structure used to conduct the first step of the economic evaluation. The decision tree includes the following nodes:

- a decision node (shown with a blue square) representing initiation of PEX either with or without rapid assay testing of ADAMTS13 activity
- chance nodes (shown with green circles) representing the result from testing (positive/negative)
- the classification of the result (true/false)
- clinical response to PEX treatment after 3 days (improvement/deterioration).

The assumption that, in the absence of rapid assay testing for ADAMTS13 activity, a diagnosis of TTP would be confirmed or excluded after 3 days of empiric PEX is based on interview findings validating this assumption, as reported by White et al. (2022).

Table 14 summarises the disaggregated (by resource) and the aggregated costs in the scenarios being compared in patients with a PLASMIC score >4 and a clinical suspicion of TTP who are initiated on treatment with PEX. This analysis includes the cost of anti-ADAMTS13 autoantibody testing, which is performed after a TTP diagnosis is confirmed via rapid ADAMTS13 activity assay, to differentiate between cTTP and iTTP.

Table 14 Health care resource items: disaggregated summary of cost impacts in the economic evaluation

Type of resource item	Unit cost	Proportion in scenario where rapid ADAMTS activity testing is available	Costs in scenario where rapid ADAMTS activity testing is available	Proportion in scenario where ADAMTS activity testing is not available	Costs in scenario where ADAMTS activity testing is not available	Incremental costs
Rapid assay of ADAMTS13 activity	$700	100%	$700	0%	$0	$700
Anti-ADAMTS13 autoantibody testing	$1,050	18.71%[a]	$196.49	0%	$0	$196.49
PEX	$2,440.65[b] per day	18.71% x 3 days[c] 81.29% x 1 day	$3,354.08	100% x 3 days[c]	$7,321.95	−$3,967.87
Additional testing in false negatives	$1,900[d]	0%	$0[e]	0%	$0	$0
Total costs	**-**	**-**	**$4,250.57**	**-**	**$7,321.95**	**−$3,071.38**

PEX = plasma exchange therapy; PPV = positive predictive value.
a. PPV derived from sensitivity, specificity and prevalence reported in Dimopoulous et al. (2022).
b. Derived from the cost weight for AR-DRG I66A - Inflammatory Musculoskeletal Disorders, Major Complexity (which covers ICD-10 code M31.1, under which patients with TTP are classified) divided by average length of stay of patients hospitalised under this AR-DRG.
c. Assumption that in the absence of rapid testing, a diagnosis of TTP would be confirmed or excluded after 3 days of empiric PEX based on White et al. (2022).
d. $700 for a repeat rapid ADAMTS13 activity test plus $1,200 for ADAMTS13 activity testing with a reference assay (ELISA).
e. Although costs of $1,900 (retesting with both rapid and standard ADAMTS13 activity tests) would apply to the proportion of patients found to have false-negative test results, there are no false negatives, given sensitivity is reported to be 100%.

Table 15 Revise health care resource items: disaggregated summary of cost impacts in the economic evaluation – using MSAC supported fees

Type of resource item	Unit cost	Proportion in scenario where rapid ADAMTS activity testing is available	Costs in scenario where rapid ADAMTS activity testing is available	Proportion in scenario where ADAMTS activity testing is not available	Costs in scenario where ADAMTS activity testing is not available	Incremental costs
Rapid assay of ADAMTS13 activity	$0	100%	$0	0%	$0	$400
Anti-ADAMTS13 autoantibody testing	$1,050	18.71%[a]	$196.49	0%	$0	$196.49
PEX	$2,440.65[b] per day	18.71% x 3 days[c] 81.29% x 1 day	$3,354.08	100% x 3 days[c]	$7,321.95	−$3,967.87
Total costs	**-**	**-**	**$4,250.57**	**-**	**$7,321.95**	**−$3,371.38**

PEX = plasma exchange therapy; PPV = positive predictive value.
a. PPV derived from sensitivity, specificity and prevalence reported in Dimopoulous et al. (2022).
b. Derived from the cost weight for AR-DRG I66A - Inflammatory Musculoskeletal Disorders, Major Complexity (which covers ICD-10 code M31.1, under which patients with TTP are classified) divided by average length of stay of patients hospitalised under this AR-DRG.
c. Assumption that in the absence of rapid testing, a diagnosis of TTP would be confirmed or excluded after 3 days of empiric PEX based on White et al. (2022).

The scenario where rapid ADAMTS13 testing is available to support the diagnosis of TTP is cost saving by $3,071.38 per person compared to the scenario where it is not available. The savings are primarily due to substantially lower PEX costs in the proposed scenario.

Given the cost savings and the conclusion that use of ADAMTS13 activity testing (followed by anti-ADAMTS13 autoantibody testing in those testing positive for TTP) results in superior effectiveness and superior safety compared with standard investigation and management with no ADAMTS13 tests, the scenario where ADAMTS13 testing is available dominates the scenario where it is not.

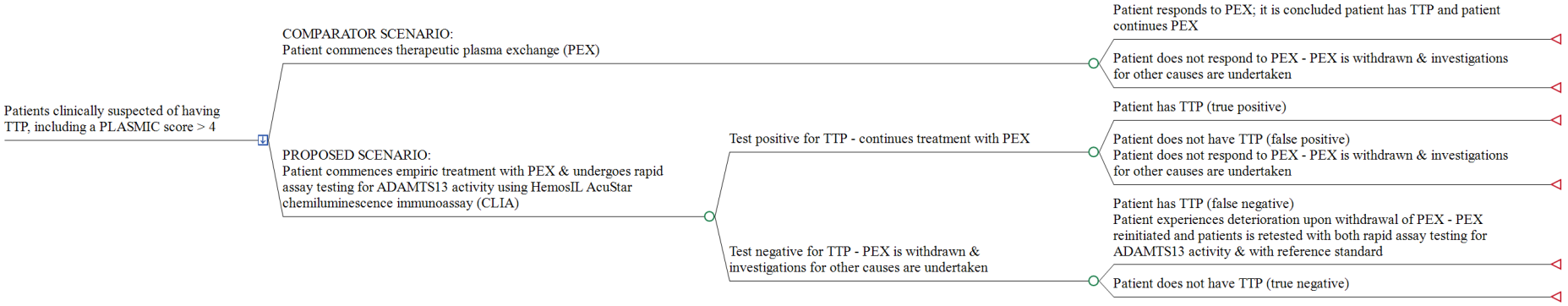

Figure 5 Structure of the decision analysis used to conduct the economic evaluation: rapid ADAMTS13 activity testing followed by anti-ADAMTS13 autoantibody testing for diagnosis

PEX = plasma exchange therapy; TTP = thrombotic thrombocytopenic purpura.

Key drivers of the model are presented in Table 16. The results of the base-case analysis are most sensitive to the turnaround time for results from ADAMTS13 testing and the number of days (on PEX) before a diagnosis of TTP can be made in the absence of ADAMTS13 testing.

Table 16 Key drivers of the model: rapid ADAMTS13 activity testing followed by anti-ADAMTS13 autoantibody testing for diagnosis

Description	Method/Value	Impact **Base case: incremental cost** −$3,071.38
Number of days of empiric PEX (comparator)	Varied from 8 to 2 days	*High; longer duration favours rapid ADAMTS13 activity testing* *Use of 5 days decreased the incremental cost to -$7,039.25*
Time to ADAMTS13 result (days of PEX before result)	Varied from 0 to 3 days	*High; longer duration favours the comparator* *Use of 3 days (same turn around as empiric treatment) increased the incremental cost to $896.49.*

PEX = plasma exchange therapy.

PICO Set 1 & 2: *ADAMTS13* genetic testing

The PICO confirmation specified a refined assessment approach for the genetic tests, with cost per diagnosis (diagnostic yield), rather than cost per health outcome, being the appropriate evaluation method.

Table 17 presents a stepped evaluation of the cost and diagnostic outcomes per suspected cTTP patient who undergoes affected individual testing and ICERs for affected individual testing (step 1) and affected individual testing followed by cascade testing (step 2). Base case values for diagnostic yields are used. The ICER for affected individual testing followed by cascade testing of first-degree biological relatives of probands is $1,298 per positive genotype (proband plus biallelic siblings).

Table 18 presents the revised stepped evaluation using the MSAC supported fee ($1000) for *ADAMTS13* genetic testing for affected individuals (item CCCC). The ICER for affected individual testing followed by cascade testing of first-degree biological relatives of probands is $1,125 per positive genotype (proband plus biallelic siblings).

Table 17 Stepped presentation of ICERs for affected individual testing and combined affected individual and cascade testing, showing costs and outcomes per suspected cTTP patient undergoing affected individual testing

Stepped analysis	Incremental cost	Incremental outcome (base case values)	ICER
Step 1 – affected individuals with suspected cTTP. Incremental cost is cost of genetic testing only.	$1,200	0.97 proband identified per affected individual tested	$1,237 per proband
Step 2 – affected individuals with suspected cTTP and their first-degree biological relatives. Incremental cost is cost of genetic testing per suspected cTTP patient ($1,200) plus cost of cascade testing in 0.8 siblings[a] per proband ($400 x 0.97 x 0.8 = $310). Incremental outcome is diagnostic yield for affected individual testing (0.97) plus cascade testing (0.97 x 0.8 x 0.25 = 0.194).	$1,510	1.164 proband and biallelic siblings identified per affected individual tested	**$1,298** per proband/ biallelic sibling

cTTP = congenital thrombotic thrombocytopenic purpura; ICER = incremental cost-effectiveness ratio.
a Assumption that 0.8 siblings per proband undergo cascade testing is based on Australian family composition data indicating an average of 1.8 children per family (Parliamentary Library, 2021 Census of Population and Housing: Quick Summary, Department of Parliamentary Services, 28 June 2022), noting this includes half siblings and non-biological siblings, so is likely an overestimate.

Table 18 Stepped presentation of ICERs for affected individual testing and combined affected individual and cascade testing, showing costs and outcomes per suspected cTTP patient undergoing affected individual testing – using revised fee supported by MSAC

Stepped analysis	Incremental cost	Incremental outcome (base case values)	ICER
Step 1 – affected individuals with suspected cTTP. Incremental cost is cost of genetic testing only using MSAC-supported fee of $1000.	$1,000	0.97 proband identified per affected individual tested	$1,031 per proband
Step 2 – affected individuals with suspected cTTP and their first-degree biological relatives. Incremental cost is cost of genetic testing per suspected cTTP patient ($1,000) plus cost of cascade testing in 0.8 siblings[a] per proband ($400 x 0.97 x 0.8 = $310). Incremental outcome is diagnostic yield for affected individual testing (0.97) plus cascade testing (0.97 x 0.8 x 0.25 = 0.194).	$1,310	1.164 proband and biallelic siblings identified per affected individual tested	**$1,125** per proband/ biallelic sibling

cTTP = congenital thrombotic thrombocytopenic purpura; ICER = incremental cost-effectiveness ratio.
a Assumption that 0.8 siblings per proband undergo cascade testing is based on Australian family composition data indicating an average of 1.8 children per family (Parliamentary Library, 2021 Census of Population and Housing: Quick Summary, Department of Parliamentary Services, 28 June 2022), noting this includes half siblings and non-biological siblings, so is likely an overestimate.

PICO Set 3: ADAMTS13 activity testing for monitoring

An economic evaluation was conducted comparing: (i) a scenario where patients with iTTP, following clinical response to treatment with PEX for TTP, have their ADAMTS13 activity level routinely monitored for early signs of recurrence; with (ii) a scenario where routine monitoring of

ADAMTS13 activity is not conducted. The evaluation is a decision analysis and results are generated by cohort expected value analysis.

A summary of the key features of economic evaluation is presented in Table 19. The key objective of ADAMTS13 routine monitoring is to avoid clinical recurrence. Monitoring is intended to identify patients who would benefit from pre-emptive rituximab treatment to reduce the likelihood of clinical recurrence. The key difference across management arms is how patients with an ADAMTS13 activity that indicates they are at high risk of deterioration are managed. This drives the incremental differences generated in the economic evaluation. The approach adopted is, by necessity, pragmatic.

Table 19 Summary of economic evaluation: ADAMTS13 activity testing for monitoring (PICO 3)

Component	Description
Perspective	Australian health care system perspective
Population	Patients achieving a clinical response following treatment with PEX for iTTP
Prior testing	Prior confirmation of iTTP with ADAMTS13 activity testing and anti-ADAMTS13 autoantibody tests Confirmation of clinical response to PEX including platelet count recovery (i.e. >150 x 10^9/L for at least 2 days) and decrease in LDH
Intervention	Routine monitoring of ADAMTS13 activity level to identify patients with early signs of clinical recurrence (monitoring is assumed to be conducted weekly for 30 days, every 3 months for 1 year then 3-6 monthly [Masias & Cataland 2018])
Comparator	No routine monitoring of ADAMTS13 activity level following treatment of an iTTP event with PEX; clinical management is based on symptoms and platelet counts
Type of analysis	Cost-effectiveness analysis
Outcomes	Clinical recurrence events avoided
Time horizon	2 years
Computational method	Cohort expected value decision analysis
Generation of the base case	Modelled economic evaluation Clinical inputs were estimated based on data from the French TMA Reference Centre registry (Hie et al. 2014)
Health states	Model is a decision analysis Terminal states reflect either deterioration of a patient to clinical recurrence or no deterioration to clinical recurrence
Cycle length	Not applicable
Transition probabilities	Transitions in the model were estimated based on data reported by Hie et al. (2014) Proportion of patients with an ADAMTS13 activity level <10% (20.6%) was the same in both the comparator and intervention arm; this proportion would be known in the intervention arm but unknown (though still applicable) in the comparator arm Proportion of patients with an ADAMTS13 activity level ≥10% deteriorating to recurrence is the same in both arms given that pre-emptive rituximab is only administered to those with ADAMTS13 activity level <10%; difference in outcomes generated by the economic model is due to use of pre-emptive rituximab only in the proportion of patients with an ADAMTS13 activity level <10%
Discount rate	No discounting applied; the time horizon is short and individual timing of recurrence events is unknown, making the application of discounting for costs and outcomes accruing beyond 1 year uncertain
Software	TreeAge Pro

iTTP = immune-mediated TTP; LDH = lactate dehydrogenase; PEX = plasma exchange therapy; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura.

The structure of the economic model is summarised in Figure 6.

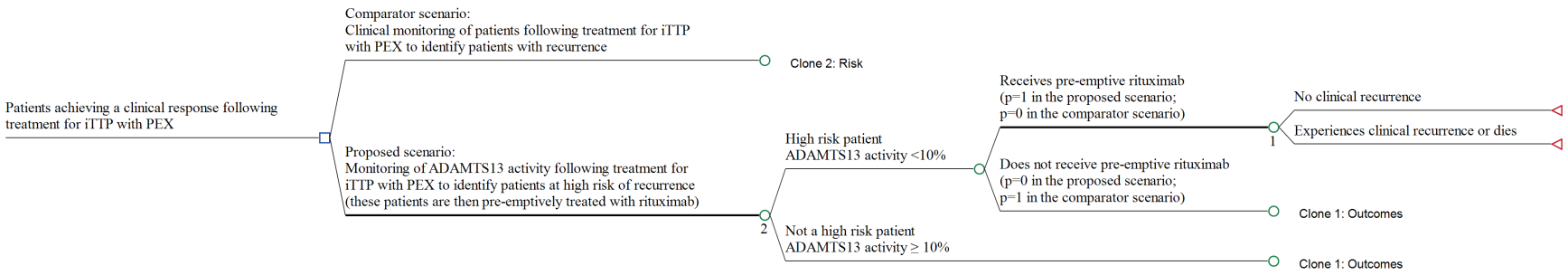

Figure 6 Structure of the decision analysis used to conduct the economic evaluation comparing monitoring of ADAMTS13 activity levels to clinical monitoring without ADAMTS13 activity levels in patients with a clinical response following treatment with PEX for TTP

iTTP = immune-mediated TTP; PEX = plasma exchange therapy; TTP = thrombotic thrombocytopenic purpura.

Table 20 summarises the aggregated and disaggregated base case results of the economic evaluation. Over a 2-year time horizon, monitoring of ADAMTS13 activity results in a cost of $106,710 per additional clinical recurrence avoided compared with the current monitoring approach for patients with iTTP. The key driver of incremental costs (and the high ICER) is the cost of monitoring patients - all patients in the proposed monitoring scenario are tested routinely for ADAMTS13 activity but the benefit is limited to the relatively small proportion of patients with ADAMTS13 activity levels indicating pre-emptive treatment with rituximab is warranted (20.6% of patients).

Table 20 Aggregated and disaggregated base case results of the economic evaluation (PICO 3)

	ADAMTS13 monitoring		**Current monitoring**		**ADAMTS13 monitoring arm**	**Current monitoring arm**	**Increment**
	High-risk (<10%) [A]	**Low-risk (≥10%) [B]**	**High-risk (<10%) [C]**	**Low-risk (≥10%) [D]**	**[E]**	**[F]**	**[G]**
Cost of ADAMTS13 testing	$1,538.20	$5,928.47	$0	$0	$7,466.67	$0	$7,466.67
Cost of pre-emptive rituximab	$249.40	$0	$0	$0	$249.40	$0	$249.40
Cost of hospitalisation	$472.63	$3,741.63	$1,837.99	$3,741.63	$4,214.26	$5,579.63	-$1,365.37
Total costs	**$2,260.23**	**$9,670.10**	**$1,837.99**	**$3,741.63**	**$11,930.33**	**$5,579.63**	**$6,350.70 [H]**
Proportion without clinical recurrence	**0.185**	**0.631**	**0.126**	**0.631**	**0.816**	**0.757**	**0.060 [I]**
Incremental cost per additional clinical recurrence avoided over 2 years							**$106,710 [J]**

E=A+B
F=C+D
G=E-F
J=H/I
Differences compared to when numbers in the table are used for calculations are due to rounding.

Key drivers of the model are presented in Table 21. The model is most sensitive to the assumption of monitoring frequency and to the cost of each ADAMTS13 activity test.

Table 21 Key drivers of the model: ADAMTS13 activity testing for monitoring

Description	Method/Value	Impact Base case: $106,710 per recurrence avoided
Monitoring frequency	Varied according to ISTH Guidelines (Zheng et al. 2025)	*High; lower frequency favours monitoring but impact on effectiveness outcomes (i.e. likely reduced) is not considered*
Number of days of PEX/ hospitalisation	Base case 9.4 days. Varied from 7 to 14.4 days.	*Low; longer duration favours monitoring*
Number of rituximab infusions	Base case 4 infusions. Varied from 2 to 6.	*Low; fewer infusions favours monitoring*
Cost of ADAMTS13 activity testing	Base case $700. Varied down to $105 per test.	*High; lower cost favours monitoring*

ISTH = International Society on Thrombosis and Haemostasis; PEX = plasma exchange therapy.

Results of one-way sensitivity analyses around the frequency of monitoring, number of days of PEX/hospitalization, cost of PESC and cost of ADAMTS13 activity testing are presented in Table 22.

Table 22 One-way sensitivity analyses: ADAMTS13 activity testing for monitoring

Input	Incremental costs	Incremental outcomes	ICER per additional recurrence over 2 years	% change
Base case	**$6,350.70**	**0.060**	**$106,710**	-
ADAMTS13 monitoring frequency: weekly for 30 days, 3 monthly for 1 year then 3-6 monthly [Masias & Cataland 2018]) (total tests: 10.67)				
weekly until ADAMTS13 activity is >50% (assume 1 month), 3 monthly for 3 years, 6 monthly for 2 years then annually (Coppo et al. 2018) (total tests: 12)	$7,284.03	0.060	$122,393	+14.7%
monthly for 3 months, 3 monthly for 1 year then 6-12 monthly (Zheng et al. 2025) (total tests: 8)	$4,484.03	0.060	$75,345	-29.4%
Number of days of hospitalisation for a patient with clinical recurrence (base case = 9.4 days)				
7 days: Median number of days of PEX, placebo arm (Scully et al. 2019)	$6,699.31	0.060	$112,568	+5.5%
14.4 days: Mean number of days of hospitalisation, placebo arm (Scully et al. 2019)	$5,624.44	0.060	$94,507	-11.4%
Cost of PEX per day (base case = $2,440.65)				
$3,346 per day	$5,844.22	0.06	$98,200	-8.0%
$4,500 per day	$5,198.64	0.06	$87,352	-18.1%
Cost of each ADAMTS13 activity test (base case = $700)				
$105 per test	$4.03	0.060	$67.80	-99.9%
$244 per test	$1,486.70	0.060	$24,981	-76.6%
$384 per test	$2,980.03	0.060	$50,073	-53.1%

ICER = incremental cost-effectiveness ratio; PEX - plasma exchange therapy

Results of two-way sensitivity analyses are presented below (Table 23). The clinical risk of recurrence is derived from Hie et al. (2014). Patients in this cohort were monitored 3-monthly during remission (Table 68). Different monitoring frequencies are expected to lead to different clinical outcomes; however, the available clinical evidence was insufficient to identify the most suitable testing interval. The sensitivity analyses on monitoring frequency account for the change in costs associated with more or less frequent ADAMTS13 activity testing, but does not incorporate the clinical consequences (e.g. rate of positive tests, rate of recurrence) or the associated downstream costs such as rituximab treatment or PEX/hospitalisation.

Table 23 Two-way sensitivity analyses: ADAMTS13 activity testing for monitoring

Input	Incremental costs	Incremental outcomes	ICER per additional recurrence over 2 years	% change
Base case ADAMTS13 monitoring frequency: weekly for 30 days, 3 monthly for 1 year then 3-6 monthly [Masias & Cataland 2018]) (12/4.5=2.67) Cost of PEX per day: $2,440.55	**$6,350.70**	**0.060**	**$106,710**	**-**
ADAMTS13 monitoring frequency: weekly until ADAMTS13 activity is >50% (assume 1 month), 3 monthly for 3 years, 6 monthly for 2 years then annually (Coppo et al. 2018) Cost of PEX per day: $3,346	$6,777.56	0.060	$113,883	+6.3%
ADAMTS13 monitoring frequency: weekly until ADAMTS13 activity is >50% (assume 1 month), 3 monthly for 3 years, 6 monthly for 2 years then annually (Coppo et al. 2018) Cost of PEX per day: $4,500	$6,131.98	0.060	$103,035	-3.4%
ADAMTS13 monitoring frequency: monthly for 3 months, 3 monthly for 1 year then 6-12 monthly (Zheng et al. 2025) Cost of PEX per day: $3,346	$3,977.56	0.060	$66,834	-37.4%
ADAMTS13 monitoring frequency: monthly for 3 months, 3 monthly for 1 year then 6-12 monthly (Zheng et al. 2025) Cost of PEX per day: $4,500	$3,331.98	0.060	$55,987	-47.5%

ICER = incremental cost-effectiveness ratio; PEX - plasma exchange therapy

Results of scenario analysis where the ADAMTS13 activity threshold is increased to 20% (base case 10%) for identifying patients at high risk of clinical recurrence/relapse per Cuker et al (2020) consensus guidelines are presented in Table 24. Applying a 20% threshold, rather than 10%, would result in the reclassification of some patients from the lower to the higher risk category. This is likely due to a greater proportion of patients receiving pre-emptive rituximab, resulting in improved outcomes. This is evident by the larger incremental difference in clinical recurrence in the scenario analysis (0.090 clinical recurrence events avoided over 2 years) compared to the base-case analysis (0.060 clinical recurrence events avoided over 2 years). The scenario analysis results likely represent an optimistic, high-benefit bound for the impact of a 20% threshold, and MSAC should interpret the results cautiously, considering potential biases and uncertainties in the conduct of this analysis.

Table 24 Results of the scenario analysis examining the impact of applying an ADAMTS13 activity threshold of 20% (rather than 10%) to identify patients at high risk of clinical recurrence/relapse (i.e. with 'ADAMTS13 recurrence')

	ADAMTS13 monitoring arm	Current monitoring arm	Increment
Total costs	$10,590.75	$4,802.36	$5,788.39
Proportion without clinical recurrence	0.880	0.791	0.090
Incremental cost per additional clinical recurrence avoided over 2 years			**$64,477**

The QALY gain where an acute recurrence is avoided is not known. Acute TTP, whether an initial episode or a relapse, entails a substantial risk of morbidity and mortality. The model also does not consider additional health benefits that may accrue from treating ADAMTS13 relapse; for example, risk of stroke (Upreti et al 2019). Furthermore, ADAMTS13 recurrence can be symptomatic (40% of patients in Doyle et al. 2023, most commonly headaches and fatigue). This could be interpreted as further supporting pre-emptive treatment or alternatively as supporting treatment based on symptoms rather than routine monitoring.

Although a QALY valuation of avoiding a recurrence of TTP did not appear to be reported in the literature, a very rough estimate was derived by making the following (unsubstantiated) assumptions:

- case-fatality rate for acute iTTP episodes is ~5% with modern care
- average age of a patient experiencing an iTTP episode is 50 years
- life expectancy for the average Australian aged 50 years is approximately 35 years.

In this case, it could be estimated that one avoided clinical recurrence will result in 0.05*35 = 1.75 life years saved (on average). Applying a utility weight of about 0.8 to remaining survival, approximately 1.4 QALYs could be gained by monitoring. The ICER for the base case then becomes ~$76,220/QALY gained.

14. Financial/budgetary impacts

An epidemiological approach was taken to estimate the number of ADAMTS13 tests in Australia for the proposed services. This was supplemented by a market-share approach using data supplied by the applicant from 3 Australian pathology laboratories performing ADAMTS13 testing. The epidemiological approach formed the basis of the financial analysis.

Table 25 Epidemiological and market-share estimates of yearly test volume

Data	Value	Output
Population of Australia (2026) ABS Population Projection	27,805,684	-
Epidemiological approach		
Incidence of suspected TTP (per million per year)[a]	12.0	Incident TMA population/ Number of diagnostic ADAMTS13 activity tests: 334
Incidence of acute first-episode TTP (per million per year)[b]	2.17	Incident TTP population: 60 Number of diagnostic anti-ADAMTS13 autoantibody tests (+25%): 75
Incidence of all acute TTP episodes (per million per year)[b]	3.1	Incident acute TTP episodes: 86 Number of ADAMTS13 activity tests for monitoring following acute episode (86 x 8): 690
Prevalence of TTP (per million)[b]	19	Prevalent TTP population: 528 Number of tests during stable remission ([prevalent population – incident acute TTP] x 2.67 tests per year): 1,180
Proportion of TTP that is cTTP	3% (assume 5% are tested)	Prevalent cTTP population: 14 Number of ADAMTS13 affected individual genetic tests (incident TTP [60] x 0.05): 3 Number of ADAMTS13 sibling genetic tests (3 x 0.8): 2
-	-	Total number of ADAMTS13 activity tests (334 + 690 + 1,180): 2,204
Market-share approach[c]		
ADAMTS13 activity tests per million	97.1	Number of tests: 2,699
Anti-ADAMTS13 activity tests per million	69	Number of tests: 166
ADAMTS13 genomic tests per million	6.0	Number of tests: 18

ABS = Australian Bureau of Statistics; cTTP = congenital TTP; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura.
a. Consecutive ADAMTS13 activity tests at centralised laboratory servicing all of Québec, Canada. (Merlen, 2022).
b. Oklahoma TTP-HUS Registry. Consecutive patients identified by request to the Oklahoma Blood Institute for PEX for TTP or HUS (Page, 2017 & Reese, 2013).
c. Test numbers from NSW Health (NSW), PathWest (WA) and Pathology Queensland for a recent financial or calendar year (not specified) and extrapolated to a rate per million and total number per year.
Number of tests has been rounded to whole numbers.

Using epidemiological estimates, the estimated incidence of TMA in Australia is 334 per year, of which the number of acute TTP episodes is 86 (60 of whom are first episode cases). The prevalent TTP population is estimated at 528, and of these 14 are estimated to have cTTP.

PICO Set 1 & 2: ADAMTS13 testing for diagnosis

The financial implications to the MBS resulting from the proposed listing of ADAMTS13 testing on the MBS for diagnosis are summarised in Table 26. No annual growth rate was applied beyond population growth, as it was assumed that current uptake is effectively 100% given the acute and life-threatening nature of the condition. The diagnostic cost to the MBS is relatively modest,

estimated at approximately $250,000 per year, with most of this cost attributed to ADAMTS13 activity testing in patients who will ultimately be excluded from a TTP diagnosis.

ADAMTS13 testing is already undertaken in Australia as demonstrated by the pathology data provided in the application. Therefore, changes to other health technologies, particularly in the diagnosis of TTP, are not anticipated in practice.

Table 26 Net financial implications of PICO Set 1 and 2 ADAMTS13 testing for diagnosis

Parameter	FY 2026-27	FY 2027-28	FY 2028-29	FY 2030-31	FY 2031-32	FY 2032-33
Estimated use and cost of the proposed health technology						
Projected population of Australia [A]	27,805,684	28,201,094	28,581,272	28,946,317	29,294,970	29,628,141
Number of proposed services for ADAMTS13 activity testing [B]	334	338	343	347	352	356
Number of new TTP cases [C]	60	61	62	63	64	64
Number of proposed services for anti-ADAMTS13 autoantibody testing [D]	75	76	78	79	79	80
Number of proposed affected individual genetic testing services [E]	3	3	3	3	3	3
Number of proposed cascade genetic testing services [F]	2	2	2	2	2	2
Cost to the MBS of ADAMTS13 activity testing services (75% benefit) [G]	$175,350	$177,450	$180,075	$182,175	$184,800	$186,900
Cost to the MBS of anti-ADAMTS13 autoantibody testing services (75% benefit) [H]	$59,063	$59,850	$61,425	$62,213	$62,213	$63,000
Cost to the MBS of affected individual genetic testing services (85% benefit) [I]	$3,287	$3,287	$3,287	$3,287	$3,287	$3,287
Total cost to the MBS of PICO 1 – diagnostic testing services [J]	**$237,699**	**$240,587**	**$244,787**	**$247,674**	**$250,299**	**$253,187**
Total cost to the MBS of PICO 2 – cascade genetic testing services [K]	**$680**	**$680**	**$680**	**$680**	**$680**	**$680**

FY = financial year; MBS = Medicare Benefits Schedule; TTP = thrombotic thrombocytopenic purpura.
B = A x incidence of suspected TTP (12/million/year) based on Merlen et al. 2022.
C = A x incidence of acute first-episode TTP per year (2.17/million/year) based on Reese et al. 2013.
D = C + C x 25% to account for use in diagnosis where ADAMTS13 activity is equivocal (25% was an assumption).
E = 5% of C (assumed 5% of TTP patients proceed to genetic testing).
F = E x 0.8 (assumed 0.8 siblings per proband).
G = B x proposed fee for ADAMTS13 activity test (75% benefit, $525).
H = D x proposed fee for anti-ADAMTS autoantibody testing (75% benefit, $788).
I = E x proposed fee for affected individual *ADAMTS13* genetic testing (85% benefit, $1,095.50).
J = G + H + I.
K = F x proposed fee for cascade *ADAMTS13* genetic testing (85% benefit, $340).

The financial impact based on extrapolation of pathology data was higher ($399,602 for diagnostic testing services and $5,100 for cascade genetic testing services in year 2032–33) than the epidemiology estimates (Table 26) due to a greater number of tests. Higher volumes of testing may be driven by testing of patients with related conditions (i.e. diagnostic leakage) and/or the use of tests for purposes beyond initial diagnosis, such as monitoring treatment response.

The application estimated an annual uptake of approximately 50 diagnostic genetic tests, which is much higher than expected given cTTP is an ultra-rare condition. While ADAMTS13 activity testing may be performed as part of a broader TMA panel, genetic testing for TMA or aHUS is not currently listed on the MBS, raising the possibility of diagnostic leakage to patients with related conditions. Nonetheless, even with an increase to 50 tests per year, the financial impact remains modest, estimated at $54,880 annually.

Table 27 Revised net financial implications of PICO Set 1 and 2 ADAMTS13 testing for diagnosis – using MSAC supported fees

Parameter	FY 2026-27	FY 2027-28	FY 2028-29	FY 2030-31	FY 2031-32	FY 2032-33
Estimated use and cost of the proposed health technology						
Projected population of Australia [A]	27,805,684	28,201,094	28,581,272	28,946,317	29,294,970	29,628,141
Number of proposed services for ADAMTS13 activity testing [B]	334	338	343	347	352	356
Number of new TTP cases [C]	60	61	62	63	64	64
Number of proposed services for anti-ADAMTS13 autoantibody testing [D]	75	76	78	79	79	80
Number of proposed affected individual genetic testing services [E]	3	3	3	3	3	3
Number of proposed cascade genetic testing services [F]	2	2	2	2	2	2
Cost to the MBS of ADAMTS13 activity testing services (75% benefit) [G]	$100,200	$101,400	$102,900	$104,100	$105,600	$106,800
Cost to the MBS of anti-ADAMTS13 autoantibody testing services (75% benefit) [H]	$59,063	$59,850	$61,425	$62,213	$62,213	$63,000
Cost to the MBS of affected individual genetic testing services (85% benefit) [I]	$2,687	$2,687	$2,687	$2,687	$2,687	$2,687
Total cost to the MBS of PICO 1 – diagnostic testing services [J]	**$161,949**	**$163,937**	**$167,012**	**$168,999**	**$170,499**	**$172,487**
Total cost to the MBS of PICO 2 – cascade genetic testing services [K]	**$680**	**$680**	**$680**	**$680**	**$680**	**$680**

FY = financial year; MBS = Medicare Benefits Schedule; TTP = thrombotic thrombocytopenic purpura.
B = A x incidence of suspected TTP (12/million/year) based on Merlen et al. 2022.
C = A x incidence of acute first-episode TTP per year (2.17/million/year) based on Reese et al. 2013.
D = C + C x 25% to account for use in diagnosis where ADAMTS13 activity is equivocal (25% was an assumption).
E = 5% of C (assumed 5% of TTP patients proceed to genetic testing).
F = E x 0.8 (assumed 0.8 siblings per proband).
G = B x proposed fee for ADAMTS13 activity test (75% benefit, $300).

H = D x proposed fee for anti-ADAMTS autoantibody testing (75% benefit, $788).
I = E x proposed fee for affected individual *ADAMTS13* genetic testing (85% benefit, $895.5).
J = G + H + I.
K = F x proposed fee for cascade *ADAMTS13* genetic testing (85% benefit, $340).

PICO Set 3: ADAMTS13 activity testing for monitoring

The financial implications to the MBS resulting from the proposed listing of ADAMTS13 activity testing for monitoring on the MBS are summarised in Table 28. The number of tests was based on epidemiological estimates of the number of acute TTP episodes per year, with each episode assumed to require 8 tests for treatment and early monitoring. In addition, prevalent cases of TTP undergoing life-long monitoring were assumed to receive an average of 2.67 tests per year. Based on this, it is estimated there would be around 2,000 tests per year and the cost to the MBS would be up to $1.31 million. The analysis assumed uptake would be 100%; however, monitoring may be undertaken on an individualised basis, particularly for patients who have been in long-term remission.

Monitoring is proposed to help prevent disease exacerbation and relapse, and to tailor the duration of treatment during acute episodes to the individual patient's response. Therefore, monitoring may have financial implications for the PBS, as well as for Commonwealth and state/territory health budgets.

Table 28 Net financial implications of ADAMTS13 activity testing for monitoring

Parameter	FY 2026-27	FY 2027-28	FY 2028-29	FY 2029-30	FY 2031-32	FY 2032-33
Estimated use and cost of the proposed health technology						
Projected population of Australia [A]	27,805,684	28,201,094	28,581,272	28,946,317	29,294,970	29,628,141
Number of acute TTP episodes [B]	86	87	89	90	91	92
Number of ADAMTS13 activity testing services during acute episodes [C]	688	696	712	720	728	736
Number of prevalent TTP cases [D]	528	536	543	550	557	563
Number of ADAMTS13 activity testing services during remission [E]	1,180	1,199	1,212	1,228	1,244	1,258
Cost to the MBS of ADAMTS13 activity testing for acute episode monitoring (80% benefit) [F]	$385,280	$389,760	$398,720	$403,200	$407,680	$412,160
Cost to the MBS of ADAMTS13 activity testing for remission monitoring (85% benefit) [G]	$702,773	$713,903	$721,853	$731,393	$740,933	$748,883
Total cost to the MBS of PICO 3 – testing services for monitoring [H = F + G]	**$1,088,053**	**$1,103,663**	**$1,120,573**	**$1,134,593**	**$1,148,613**	**$1,161,043**

FY = financial year; MBS = Medicare Benefits Schedule; TTP = thrombotic thrombocytopenic purpura.
B = A x incidence of all acute TTP episodes (3.1/million/year based on Page et al. 2017)
C = B x 8 (8 monitoring tests in first year following acute TTP)
D = A x prevalence of TTP (19/million/year based on Page et al. 2017)
E = (D-incidence of acute TTP) x 2.67 (prevalent cases of TTP undergoing life-long monitoring were assumed to receive an average of 2.67 tests per year during stable remission).
F = C x proposed fee for ADAMTS13 activity test (80% benefit, $560).
G = E x proposed fee for ADAMTS13 activity test (85% benefit, $595.50).

15. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- Thrombotic thrombocytopenic purpura (TTP) is a rare condition and diagnostic ADAMTS13 testing is recommended in Australian and international guidelines (although guidelines for monitoring are based on expert opinion). There are a clinical need and a demand for MBS listing of ADAMTS13 diagnostic testing, which is already used in Australia (predominantly in the public hospital setting) for TTP diagnosis and monitoring. In addition, ADAMTS13 testing to exclude TTP is a prerequisite for access to the PBS-listed therapies eculizumab and ravulizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS).
- The evidence, albeit limited, suggests ADAMTS13 diagnostic testing would lead to changes in clinical management that would improve clinical outcomes for patients.
- There are critical limitations/gaps in the evidence base for ADAMTS13 testing for TTP, particularly with respect to the frequency of activity testing for monitoring for disease relapse. Although international guidelines recommend monitoring of ADAMTS13 activity (PICO set 3), there is insufficient evidence and significant uncertainty regarding the frequency, duration and comparative effectiveness of monitoring ADAMTS13 activity during remission.

Economic issues:

- The uncertainty in the clinical evidence flows on to create uncertainty in the economic evaluations. In particular, the uncertainty regarding the frequency, duration and effectiveness of ADAMTS13 activity monitoring creates high uncertainty in the cost-effectiveness analysis for ADAMTS13 activity monitoring (PICO set 3). ESC advised that additional 2-way sensitivity analyses varying the costs of plasma exchange (PEX) and test frequency would be informative for MSAC's consideration.

Financial issues:

- The estimated utilisation of ADAMTS13 testing is uncertain. Estimates using the market-share and epidemiology approaches have significant differences. ESC considered that the applicant should confirm or provide further data on the likely prevalent population for uptake of *ADAMTS13* genetic testing.
- The frequency and duration of monitoring ADAMTS13 activity cannot be predicted and may be higher than estimated. MSAC may wish to consider splitting the proposed MBS item AAAA to create separate MBS items for diagnosis and monitoring, which would provide the ability to review utilisation and limit the frequency of ADAMTS13 activity testing for monitoring during remission (if appropriate).
- The applicant proposed a weighted fee for ADAMTS13 activity testing for diagnosis and monitoring be applied but this weighted fee approach may not be reasonable. MSAC may want to consider a lower fee for monitoring in line with non-urgent testing compared with an acute situation where rapid ADAMTS13 activity testing is required. The department advised there is no Pathology Services Table precedent for fee differentials for urgent specimens.

ESC Discussion

ESC noted that this application from the Royal College of Pathologists of Australasia (RCPA) requested Medicare Benefits Schedule (MBS) listing of ADAMTS13 testing (including ADAMTS13 activity testing, anti-ADAMTS13 autoantibodies testing and *ADAMTS13* genetic testing) to diagnose thrombotic thrombocytopenic purpura (TTP).

ESC noted that thrombotic microangiopathies (TMAs) are a group of disorders characterised by thrombosis and endothelial dysfunction. There are numerous causes of TMA, with TTP being a rare cause (incidence of first TTP episode is 1.47 to 2.67 per million people). TTP presentation can be non-specific and TTP is invariably fatal if not treated promptly. Clinical features and management have been elucidated over decades from observational and registry data. TTP manifests because of very low or absent ADAMTS13 activity (≤10%), due to a patient having either autoantibodies against ADAMTS13 (immune TTP, iTTP) or harbouring a genetic variant that reduces ADAMTS13 production (congenital TTP, cTTP).

ESC noted that ADAMTS13 testing is already performed in Australia[7] and is consistent with international guidelines[8,9]. ESC noted that this is the first time MSAC has considered ADAMTS13 testing in TTP, but noted that the Pharmaceutical Benefits Advisory Committee (PBAC) has discussed ADAMTS13 testing when assessing eculizumab to treat atypical haemolytic uremic syndrome (aHUS) (recommended for listing in March 2014), caplacizumab to treat TTP (not recommended for listing in July 2020) and ravulizumab to treat aHUS (recommended for listing in July 2023). ESC further noted that none of these previous PBAC considerations were for codependent technologies.

ESC noted that consultation input was received from one organisation and one health practitioner prior to this ESC meeting. ESC also noted that letters of support from 3 organisations were submitted with the application. Consultation input from the health practitioner emphasised that TTP is a serious condition that is usually managed by multidisciplinary teams in large metropolitan hospitals and predominantly in the public system. The input suggested that MBS listing for ADAMTS13 testing would disadvantage public pathology providers, and that, especially for the genetic test, it would be more cost-effective to have a single reference laboratory perform all the testing. However, ESC considered that there is a place for ADAMTS13 testing to be available via the MBS, noting it would not be pragmatic for patients to return to a hospital for genetic or monitoring testing, and that a single reference laboratory model would increase the testing turnaround time.

ESC noted the 3 PICO sets for this application:

- PICO set 1 – diagnosis of TTP using ADAMTS13 activity testing, anti-ADAMTS13 autoantibodies testing and *ADAMTS13* genetic testing
- PICO set 2 – cascade (predictive) *ADAMTS13* genetic testing after a proband with cTTP is identified
- PICO set 3 – ADAMTS13 activity monitoring of patients with iTTP.

[7] Fox LC et al 2018 'Consensus opinion on diagnosis and management of thrombotic microangiopathy in Australia and New Zealand', Internal Medicine Journal, 48(6):624–636, doi:10.1111/imj.13804

[8] Scully M et al 2023 'A British Society for Haematology Guideline: Diagnosis and management of thrombotic thrombocytopenic purpura and thrombotic microangiopathies', British Journal of Haematology, 203(4):546–563, doi:10.1111/bjh.19026.

[9] Zheng XL et al 2025 '2025 focused update of the 2020 ISTH guidelines for management of thrombotic thrombocytopenic purpura', Journal of Thrombosis and HaemostasisS1538783625003605, doi:10.1016/j.jtha.2025.06.002.

ESC noted that the MBS item descriptors were method agnostic for ADAMTS13 activity testing. Three methods are commonly used in Australian laboratories: enzyme-linked immunosorbent assay (ELISA), fluorescence resonance energy transfer assay (FRETS-VWF73) and chemiluminescence immunoassay (CLIA). A fully automated CLIA commercial kit using HemosIL AcuStar is the most common method, and ESC considered that this method was more convenient and had a faster turnaround time than the other 2 methods. However, in February 2022 and August 2024, the Therapeutic Goods Administration (TGA) reported that CLIA has a relatively high rate of false positives compared with FRETS-VWF73 (the gold standard). ESC considered that, because the ADAMTS13 activity level is only one component of TTP diagnosis, the false positive risk is unlikely to be clinically significant. Therefore, ESC considered the method-agnostic MBS item descriptor was appropriate.

ESC noted that the descriptor for the proposed MBS item AAAA (ADAMTS13 activity testing) included the non-specific term 'investigation of suspected TMA'. This means the test could be used to confirm TTP (<10% ADAMTS13 activity) but that the test could also be used to determine whether a patient meets eligibility requirements (>10% ADAMTS13 activity) for accessing Pharmaceutical Benefits Scheme (PBS) listed medicines (eculizumb and ravulizumab) for treatment of aHUS. ESC considered that including the PLASMIC score in the MBS descriptor will increase pre-test probability for TTP. However, ESC also acknowledged that a result of >10% ADAMTS13 activity is also informative as exclusion of TTP will guide treatment decisions (including cessation of plasma exchange (PEX)). A result of >10% ADAMTS13 activity can also confirm eligibility to access medicines to treat aHUS, which is a valid and beneficial use for the test that has not been captured in the application.

ESC noted that the fee proposed by the applicant for MBS item AAAA was a weighted fee, that purportedly covered the cost implications for urgent testing for diagnosis and batched testing for monitoring. ESC considered that MSAC may wish to consider separating diagnostic testing (PICO set 1) from remission monitoring (PICO set 3) because a longer turnaround time for the monitoring item is likely to be acceptable to clinicians and may attract a lower MBS fee. The department advised there is no Pathology Services Table precedent for fee differentials for urgent specimens. ESC advised that separate items would also allow review of the predicted versus actual use for monitoring ADAMTS13 activity testing. MSAC may also wish to consider limiting the number of monitoring tests per year that could be claimed. ESC suggested that, following initial occurrence or recurrence, a frequency of 3 times in the first 3 months followed by up to 4 times per year thereafter might be suitable, whilst acknowledging the absence of evidence to support any specific schedule of testing, and also acknowledging that TPP recurrences are episodic and unpredictable.

For the proposed MBS item BBBB (anti-ADAMTS13 autoantibody testing), ESC suggested including MBS item AAAA in the descriptor as the method of detecting reduced ADAMTS13 activity. In addition, ESC supported adding 'once per episode' to the descriptor, as there is the potential for multiple tests to be ordered in the same episode to monitor for a reduction in autoantibodies with immunosuppression.

Regarding the proposed MBS item CCCC (*ADAMTS13* genetic testing), ESC suggested adding 'congenital' to the descriptor. ESC considered that including 'request by specialist/consultant physician' would be consistent with other genetic testing, and that the descriptor should be method agnostic. ESC noted that the restriction "has not previously received a service to which item DDDD applies" could lead to a scenario where an individual may have previously undergone cascade testing for a specific variant and received a negative result, then later on may be precluded from receiving clinically warranted germline testing because of this restriction. ESC considered that this scenario is likely to be rare but that the restriction should be removed to avoid this unintended negative consequence.

For the proposed MBS item DDDD (cascade *ADAMTS13* genetic testing), ESC considered that the item descriptor should be corrected to include relative(s) of a patient found to have a 'pathogenic' variant (i.e. a first-degree biological relative of a patient found to have a *pathogenic or* likely pathogenic variant(s) in the *ADAMTS13* gene). ESC also considered that including the wording 'on behalf of' (a specialist or consultant physician) in the descriptor could lead to increased referral from clinicians who do not usually provide genetic counselling or testing. MSAC may wish to consider removing 'on behalf of'.

ESC noted that, because of the rarity of TTP, the evidence base consisted mainly of cohort studies (with historical comparators) and descriptive studies with uncertain or medium to high risk of bias (selection of known TTP cases). ESC acknowledged the critical limitations with the evidence base as outlined in Table 3, Table 4,Table 5 and Table 6 (in Section 7). However, ESC also acknowledged that higher-quality evidence is unlikely to become available given the rarity of the population being considered.

ESC agreed with the assessment report that there was no evidence of harm from the test. Blood tests have negligible safety issues considering venipuncture is performed for other blood tests. ESC considered that the risk of false positive results with ADAMTS13 activity testing is likely mitigated by other clinical and laboratory results, and that the benefits of testing outweigh the potential risks of false positives when balanced against complications of not testing (prolonged plasma exchange and immunosuppression, or late diagnosis of TTP with complications of TTP).

Regarding comparative effectiveness of ADAMTS13 testing for diagnosis of TTP (PICO set 1) and cascade testing (PICO set 2), ESC noted the evidence on test accuracy for ADAMTS13 activity and anti-ADAMTS13 autoantibody testing demonstrated high sensitivity and specificity but was based on moderate and very low confidence evidence. ESC noted that the evidence indicated that ADAMTS13 testing for diagnosis of TTP led to a change in management (e.g. rapid ADAMTS13 activity testing reduced PEX utilisation) and improvement in health outcomes through accurate differentiation of iTTP, cTTP and aHUS which is expected to lead to more appropriate use of therapies for these conditions. ESC acknowledged the lack of high-quality evidence, but nonetheless considered that the available evidence supported the claim that ADAMTS13 testing for diagnosis of TTP (PICO set 1) and cascade testing of biological siblings (PICO set 2) had superior clinical effectiveness compared with no testing. Tests 1 and 2 (activity and autoantibody testing) are already routinely performed in Australia.

Regarding the comparative effectiveness of monitoring ADAMTS13 activity in patients with iTTP (PICO set 3), ESC emphasised that the evidence consists of low-level evidence with an uncertain to high risk of bias. ESC noted the evidence indicated that monitoring ADAMTS13 activity during acute iTTP could strongly predict remission but the predictive value for exacerbations and relapses was low. ESC acknowledged that the low-quality evidence suggested monitoring ADAMTS13 activity during acute iTTP and early remission was superior to the comparator – monitoring using clinical history and laboratory testing of platelet counts. However, ESC questioned the clinical practicality of the frequency and value of ADAMTS13 activity monitoring during acute episodes. Although consensus guidelines recommended weekly monitoring of ADAMTS13 activity, ESC noted that the turnaround time for ADAMTS13 activity monitoring tests may exceed 7 days in some circumstances. In these cases, ESC considered that lower cost and more rapid testing of platelet count would outweigh ADAMTS13 activity monitoring.

For monitoring after remission, ESC noted the consensus guidelines recommended monitoring ADAMTS13 activity monthly for the first 3 months after remission, then every 6 to 12 months. ESC noted the evidence for monitoring during remission indicated that ADAMTS13 activity is associated with relapse but the data are insufficient to draw conclusions on its predictive value.

ESC noted that the applicant's pre-ESC response acknowledged the evidence base for ADAMTS13 activity monitoring was limited but emphasised that guidelines consistently recommend ADAMTS13 activity monitoring to prevent clinical relapse, which is a high-morbidity, resource-intensive event. The applicant's pre-ESC response also confirmed that ADAMTS13 antibody testing would be used rarely for monitoring. However, ESC highlighted that the guidelines for monitoring are expert opinion recommendations that are not underpinned by systematically reviewed evidence. Further, as the longest follow-up was for 18 months, the value of monitoring for >2 years is unknown. ESC considered that the available evidence was poor quality and there was large uncertainty around the frequency and duration of monitoring. ESC noted that, while ADAMTS13 activity monitoring during acute iTTP and early remission may be superior to no monitoring, there was insufficient evidence for the clinical effectiveness of ADAMTS13 activity monitoring during late remission. However, ESC acknowledged the clinical need for ADAMTS13 activity monitoring to prevent early relapse and reassure patients. ESC accepted that ADAMTS13 activity monitoring is clinically important but that the frequency and duration need to be carefully considered by MSAC and annual limits may be appropriate.

ESC noted that the assessment report presented 3 economic evaluations. A cost-minimisation analysis was presented for ADAMTS13 activity and autoantibody testing for diagnosis (PICO Set 1), with time taken to confirm or exclude a diagnosis of TTP as the main outcome. ESC considered the model structure to be appropriate. In the model, patients who were suspected of having TTP were initiated on plasma exchange therapy (PEX) until testing confirmed they did or did not have TTP. The model assumed a 3-day turnaround time for ADAMTS13 activity testing, which resulted in an overall cost saving (-$3,071) as patients who test negative for TTP are able to safely cease PEX earlier than in the comparator arm (i.e., the use of ADAMTS13 testing reduces unnecessary PEX use). The assessment report valued the cost of PEX ($2,440.65/day) using the Australian Refined Diagnosis Related Groups (AR-DRG) as required by the MSAC Guidelines, but the pre-ESC response stated that the National Blood Authority costs are higher ($1,847 to $3,346/day). ESC noted that using a higher PEX cost would result in greater cost savings.

ESC noted that for *ADAMTS13* genetic testing, the economic evaluation estimated the cost per diagnosis (diagnostic yield) and presented a stepped analysis for affected individual testing (PICO set 1) and combined affected individual and cascade testing (PICO set 1 & 2). For affected individual testing (Step 1), the incremental cost effectiveness ratio (ICER) was $1,237 per proband identified, which ranged from $1,200 to $1,667 in the sensitivity analysis (including genetic counselling). For the combined affected individual and cascade testing (Step 2), the ICER was $1,298 per proband/biallelic sibling identified, ranging from $533 to $2,672 in the sensitivity analyses (including genetic counselling). ESC noted the ICERs for *ADAMTS13* genetic testing appeared to be in the lower range of other incremental cost per diagnostic yield ratios previously considered by MSAC for germline genetic testing.

ESC noted that for ADAMTS13 activity monitoring (PICO set 3), a cost-effectiveness analysis was presented with clinical recurrence events avoided as the outcome. ESC emphasised that the uncertainty in the clinical effectiveness of ADAMTS13 activity monitoring, in particular the frequency and duration of monitoring, flows on to create high uncertainty in the economic evaluation. ESC noted that the incremental cost per additional clinical recurrence avoided over 2 years was $106,710. ESC noted that if the ADAMTS13 activity threshold was increased to 20% (from 10%), this reduced the incremental cost per additional clinical recurrence avoided over 2 years to $64,477. ESC also noted that while the value of avoiding a recurrence of TTP did not appear to be reported in the literature, the assessment report estimated an approximate 1.4 quality adjusted life year (QALY) could be gained from monitoring, using unsubstantiated assumptions on the case fatality rate, average age of patient experiencing iTTP and life expectancy for the average Australian. Using this QALY estimate, a base case ICER of

~$76,220 per QALY gained was estimated, based on a monitoring frequency of weekly for the first month and then every 3 months for 1 year. ESC noted the sensitivity analyses revealed variations in number of days on PEX had a large impact on the incremental costs. In addition, the assessment group's rejoinder estimated that using higher PEX costs (as raised in the applicant's pre-ESC response), reduced the incremental costs to $98,200 and $87,352 per additional clinical recurrence avoided when the PEX cost was increased to $3,346/day and $4,500/day respectively. ESC considered that additional 2-way sensitivity analyses, varying both the cost of PEX and the frequency of testing would be informative for MSAC's consideration.

ESC noted that the financial analysis presented both an epidemiological (base case) and market-share approach. ESC noted that the 2 approaches resulted in different estimates, which indicated that the utilisation estimates were uncertain:

- Approach 1 - Epidemiological data: 2,204 activity tests using epidemiology estimates from Canada applied to the Australian population.
- Approach 2: Market-share data: 2,699 activity tests (22.5% higher) based on pathology data from 3 Australian states extrapolated to the total Australian population.

ESC acknowledged the limitations with the Australian pathology data (Approach 2) but considered that estimates using the market-share data may be more reliable as the base case for MSAC's consideration. ESC also considered that that applicant should confirm or provide further data on the likely prevalent population for uptake of *ADAMTS13* genetic testing.

For the monitoring population, financial impact was based on 8 activity tests in the first year after diagnosis, then 2.67 activity tests for longer-term monitoring in stable TTP remission. However, ESC noted that no sources were available for these test frequency assumptions and suggested that these require further clarification and investigation using sensitivity analyses.

ESC noted that listing ADAMTS13 testing on the MBS would cost $1,326,432 in year 1, increasing to $1,414,909 in year 6. However, there would be cost savings to other health budgets, including to the PBS, so the overall cost to health budgets would be $1,024,733 in year 1, increasing to $1,095,111 in year 6. However, ESC noted calculations from the department suggested that the MBS costs may be higher – possibly $1,724,812 in year 1. ESC reiterated that the financial estimates are uncertain. ESC also noted that the proposed listing may result in cost-shifting from state and territory health budgets to the MBS.

16. Applicant comments on MSAC's Public Summary Document

The RCPA thanks MSAC for its detailed consideration of this complex application and welcomes the Committee's support for ADAMTS13 activity, autoantibody and genetic testing for the diagnosis of TTP and, where appropriate, cascade testing in first-degree biological relatives. We recognise MSAC's concerns regarding uncertainty in the comparative effectiveness, frequency, duration and utilisation of ADAMTS13 activity monitoring, particularly for patients in long-term remission. The RCPA remains committed to finding solutions to address these uncertainties in the context of a rare disease where prospective comparative evidence is unlikely to become available in the near future. ADAMTS13 activity monitoring plays an important role in identifying patients at increased risk of recurrent TTP, informing pre-emptive treatment decisions, and helping to reduce the morbidity, mortality and resource use associated with this condition.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website