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Cost-effectiveness of rapid vs. in-house vs. send-out ADAMTS13 testing for immune thrombotic thrombocytopenic purpura

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Abstract:
While awaiting confirmatory results, empiric therapy for patients suspected to have immune thrombotic thrombocytopenic purpura (iTTP) provides benefits and also accrues risks and costs. Rapid assays for ADAMTS13 may be able to avoid the cost and risk exposure associated with empiric treatment. We conducted the first cost-effectiveness evaluation of testing strategies with rapid versus traditional ADAMTS13 assays in patients with intermediate to high-risk PLASMIC scores, with and without caplacizumab use. We built a Markov cohort simulation with four clinical base-case analyses: 1) Intermediate-risk PLASMIC score with caplacizumab, 2) Intermediate-risk PLASMIC score without caplacizumab, 3) High-risk PLASMIC score with caplacizumab, 4) High-risk PLASMIC score without caplacizumab. Each of these evaluated three testing strategies: 1) rapid assay (<1-hour turnaround), 2) in-house FRET-based assay (24-hour turnaround), and 3) send-out FRET-based assay (72-hour turnaround). The primary outcome was the incremental net monetary benefit (iNMB) reported over a 3-day time horizon and across accepted willingness-to-pay thresholds in USD per quality-adjusted life-year (QALY). While accruing the same amount of QALYs, the rapid assay strategy saved up to $46,820 (95% CI $41,961-$52,486) per-patient-tested. No parameter variation changed the outcome. In probabilistic sensitivity analyses, the rapid assay strategy was favored in 100% (three base-cases and scenario analyses) and 99% (one base-case and scenario analysis) across 100,000 Monte Carlo iterations within each. Rapid ADAMTS13 testing for patients with intermediate- or high-risk PLASMIC scores yields significant per-patient cost savings, achieved by reducing the costs associated with unnecessary therapeutic plasma exchange and caplacizumab therapy in patients without iTTP.

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Cost-effectiveness of rapid versus in-house versus send-out ADAMTS13 testing for immune thrombotic thrombocytopenic purpura

SHORT TITLE

Cost savings with rapid ADAMTS13 testing

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Data used in this study is from publicly sourced research, and outlined within the manuscript. Should further questions arise, they can be submitted to the corresponding author.

KEY POINTS (maximum: 140 characters each)

1. Rapid ADAMTS13 assay utilization is a cost-saving strategy in the care of patients with intermediate and high PLASMIC scores
2. Cost savings with the rapid ADAMTS13 assay are greatest in the context of empiric treatment with caplacizumab

ABSTRACT (maximum: 250 words)

While awaiting confirmatory results, empiric therapy for patients suspected to have immune thrombotic thrombocytopenic purpura (iTTP) provides benefits and also accrues risks and costs. Rapid assays for ADAMTS13 may be able to avoid the cost and risk exposure associated with empiric treatment. We conducted the first cost-effectiveness evaluation of testing strategies with rapid versus traditional ADAMTS13 assays in patients with intermediate to high-risk PLASMIC scores, with and without caplacizumab use. We built a Markov cohort simulation with four clinical base-case analyses: 1) Intermediate-risk PLASMIC score with caplacizumab, 2) Intermediate-risk PLASMIC score without caplacizumab, 3) High-risk PLASMIC score with caplacizumab, 4) High-risk PLASMIC score without caplacizumab. Each of these evaluated three testing strategies: 1) rapid assay (<1-hour turnaround), 2) in-house FRET-based assay (24-hour turnaround), and 3) send-out FRET-based assay (72-hour turnaround). The primary outcome was the incremental net monetary benefit (iNMB) reported over a 3-day time horizon and across accepted willingness-to-pay thresholds in USD per quality-adjusted life-year (QALY). While accruing the same amount of QALYs, the rapid assay strategy saved up to $46,820 (95% CI $41,961-$52,486) *per-patient-tested*. No parameter variation changed the outcome. In probabilistic sensitivity analyses, the rapid assay strategy was favored in 100% (three base-cases and scenario analyses) and 99% (one base-case and scenario analysis) across 100,000 Monte Carlo iterations within each. Rapid ADAMTS13 testing for patients with intermediate- or high-risk PLASMIC scores yields significant per-patient cost savings, achieved by reducing the costs associated with unnecessary therapeutic plasma exchange and caplacizumab therapy in patients without iTTP.

INTRODUCTION

Immune thrombotic thrombocytopenic purpura (iTTP) is a life-threatening thrombotic microangiopathy requiring immediate treatment to prevent progressive end-organ damage and death.[1] The annual incidence is 3 per million patients, with an approximate median age at presentation of 40 years.[2] Acute iTTP is the result of severe deficiency in the metalloproteinase that cleaves von Willebrand factor (vWF), ADAMTS13, which results in the persistence of large vWF multimers and formation of platelet-rich microthrombi. The diagnosis depends on clinical expertise to adjudicate a prior probability, the diagnostic assay result, and the ability to interpret this results in the context of the prior and known test characteristics. The diagnosis is confirmed by ADAMTS13 activity <10%. However, the turnaround time (TAT) for ADAMTS13 activity testing is several days. Therefore, patients with an intermediate or high pre-test probability of iTTP are often started on empiric treatment while awaiting diagnostic confirmation.[3,4] Various clinical risk scores were developed to identify patients most likely to have iTTP. Two clinical tools employed in practice include the PLASMIC and French scores.[5,6]

Current testing for ADAMTS13 activity includes the fluorescence resonance energy transfer (FRET) based assay and chromogenic ELISA based assay.[7] Concerningly, results can take days due to assay complexity, need for in house trained technicians, and test batching.[7,8] Additionally, many hospitals send out their testing to a reference laboratory, which further increases the duration of time until results are available. Two prior studies examined the utilization of various assays in iTTP and their cost-effectiveness. One found that utilizing PLASMIC score in addition to in-house testing was cost-effective, while the other noted a shorter TAT of 1 day to be cost-effective.[9,10]. However, despite these cost-effectiveness analyses showing that a turnaround time of 1 day would be optimal, the assays remain the same, thus diagnostic delays are common. To help overcome these delays, newer assays focused on rapid turnaround time have been developed. For example, the rapid HemosIL AcuStar ADAMTS13 activity assay is a fully automated, chemiluminescent assay with an analytic TAT of less than one-hour, which has demonstrated high concordance with chromogenic ELISA and FRET-based assays.[11-15] The rapid assay requires less resources in person-time in contrast to other assays (i.e., Immucor, recently acquired by Werfen), that require multiple hour assay run times with technician requirement for monitoring and adjustment.

To our knowledge, no cost effectiveness analysis has evaluated the utility of the new rapid assay with turnaround time < 1 hour, in addition to varied PLASMIC scores at intermediate and high risk to see which assay would be the most cost effective. Additionally, the cost-effectiveness of a rapid diagnostic

strategy in the context of caplacizumab use for both intermediate- and high-probability PLASMIC scores, as compared to without caplacizumab, is not known. We sought to fill these gaps by determining the cost-effectiveness of a rapid assay compared to an in-house test with a 24-hour TAT and a send-out test with a 72 hour TAT for the strategies of 1) intermediate (PLASMIC 5) versus high (PLASMIC 6-7)-probability PLASMIC scores, and 2) patients treated empirically with therapeutic plasma exchange (TPE) with or without caplacizumab. We sought to determine if the rapid assay would be worth investing in, should it present cost-savings due to the rapid turnaround time. Our hypothesis was that the use of a rapid assay as part of a diagnostic and management strategy would be cost-effective, as compared to traditional turnaround time test strategies.

METHODS

Model Overview:

We built a Markov cohort model to determine the cost-effectiveness of three different ADAMTS13 assay testing strategies utilized in the care of adult patients with intermediate (PLASMIC score =5) and high (PLASMIC score 6-7) pretest probability for iTTP. Our model evaluated inpatient costs associated with suspected iTTP. Our model examined three testing strategies: 1) rapid turnaround (<1 hour), 2) 24-hour in-house, FRET-based evaluation, and 3) 72-hour send-out, FRET-based evaluation. For in-house and send-out diagnostic strategies, the patient proceeds with empiric treatment with TPE +/- caplacizumab until assay results return, at 24 hours and 72 hours, respectively (Figure 1). The study population were those patients presenting to a hospital with thrombotic microangiopathy and concern for iTTP. For the 24-hour in-house and the 72-hour send-out strategies, the shortest turnaround time was used to have each assay option accrue the least amount of therapy-related cost while waiting for results. Utilizing the lowest bound of turnaround time allowed us to estimate the most conservative potential benefit of a rapid testing strategy, favoring the null hypothesis. For the rapid assay testing strategy, a patient is started on treatment only if the diagnosis is confirmed and not started on treatment if iTTP diagnosis is ruled out. For the in-house and send-out assay testing strategies, the patient is empirically started on treatment while awaiting assay results. For patients in whom iTTP is ruled out upon receipt of ADAMTS13 activity level, empiric therapy is discontinued. Age- and sex-adjusted background mortality were employed. Rituximab was not utilized in this model as it is typically initiated once confirmatory results of severe ADAMTS13 deficiency are available. This model characteristic additionally also favors the null hypothesis (i.e., if rituximab were to be used empirically, then further costs and risks would

accrue with in-house and send-out testing, as compared to the rapid testing strategy). We constructed our model using TreeAge Pro Healthcare 2023 (TreeAge Software). The CHEERS (Consolidated Health Economic Evaluation Reporting Standards) reporting guideline was implemented where applicable.

Model assumptions:

The analytic time horizon was set at 3 days to analyze the impact of waiting up to 72 hours for assay results (i.e., in the send-out testing strategy). We assumed all patients with an appropriately applied and calculated PLASMIC score of 5 for intermediate-risk (or 6-7 for high-risk) were hospitalized in the intensive care unit,[16] rather than the general medicine floor, for the first 3 days of empiric treatment for an incident diagnosis. We assumed that the rapid assays, given concordance in prior studies, had similar diagnostic accuracy to current FRET based assays. [11-15] As a conservative assumption to favor the null hypothesis, we also assumed that earlier adjudication of the diagnosis (i.e., with rapid testing) does not improve iTTP-related mortality or morbidity for patients over the 3-day time horizon.

Model input parameters:

For transition probabilities, our model was informed by extensive literature published on clinical risk score characteristics, informed by the derivation and validation cohorts for the PLASMIC score (Table 1). All probabilities were converted to daily rates before converting back to probabilities, using the recommended transformation formula: p = 1-exp^(-r*t), where p = probability, r = rate, and t = time.[17] During each daily cycle, patients may experience adverse events from therapeutic plasma exchange (TPE), including transfusion-related lung injury (TRALI), anaphylaxis, transfusion associated circulatory overload (TACO), central line thrombosis, and central line infection; while for caplacizumab these additionally include bleeding risk. The daily bleed rate was determined by tabulating the number of major bleed events across all real-world studies reporting major bleeding by the International Society on Thrombosis and Haemostasis (ISTH) criteria and dividing by a full per-person-treatment-exposure period of caplacizumab use of 35 days, corresponding to the median duration of caplacizumab use in clinical trials. Although this approach may underestimate the daily bleed rate (i.e., any bleed event that happened is assumed to have accrued 35 risk-exposure days), it was a necessity due to the lack of reporting of person-risk exposure time. In this context, we preferred to underestimate (rather than overestimate) these risks to again favor the null hypothesis. In addition, since these daily bleed probabilities were expected to be very small, we did not expect them to affect model results (i.e., which of the three strategies is the cost-effective strategy). Nevertheless, in addition to testing all parameters

(i.e., bleeding risk and beyond) with +/-50% extensive ranges in sensitivity analyses, we also conducted a set of scenario analyses where we nullified *all bleeding risk* for all four base cases to see if bleeding related to caplacizumab had any effect in changing model results (i.e., which strategy was the cost-effective strategy).

Health utilities were informed by literature on critically ill adults hospitalized in the medical intensive care unit, originally derived with validated EQ-5D methodology.[18,19] Costs were estimated in 2023 US dollars, with inflation to 2023 costs using the medical component of the consumer price index.[20] Medication cost (i.e., caplacizumab) was obtained from the Centers for Medicare and Medicaid Services (CMS).[21] For the cost of TPE, we used an average of the cost of 1 TPE session reported across all 3 studies reporting in the US context, which included both technical and professional costs.[10,22,23] Baseline cost of hospitalization and treatment-related complication management were obtained from CMS Medicare Severity Diagnosis Related Groups (MS-DRGs) as follows in all treatment strategies: applying MS-DRG #810 for iTTP managed without complications, MS-DRG #809 for complications that include any of TACO, TRALI, anaphylaxis, non-intracranial hemorrhage major bleed, central line complication (i.e., infection or thrombosis), MS-DRG#808 for the complication of intracranial hemorrhage (Table 1).[24] The MS-DRG codes for a major hematologic diagnosis were also specified to favor the null hypothesis, with only intracranial hemorrhage qualifying for the most expensive hospitalization category that accounts for a major complication. The cost of an ICU bed was sourced from our institution's cost reporting.[25] For assay costs, the rapid HemosIL assay was sourced from the Instrumentation Laboratory,[22] while in house and send-out assays were sourced from prior literature utilizing the cost from institutional reported and projected costs.[9] All model parameters were subjected to extensive sensitivity analyses to elucidate whether any model parameters changed the final result in all base-cases (i.e., which strategy is the cost-effective strategy).

Cost effectiveness analysis:

Four base-case analyses were examined, all with TPE anchoring treatment as follows: 1) PLASMIC 5 with caplacizumab, 2) PLASMIC 5 without caplacizumab, 3) PLASMIC 6-7 with caplacizumab, 4) PLASMIC 6-7 without caplacizumab. For completeness, the model was also applied to a PLASMIC score of 0-4 in which patients were not started on empiric TPE or caplacizumab. The primary outcome was the incremental cost-effectiveness ratio (ICER) for each base-case, unless the intervention was cost-saving, in which case the incremental net monetary benefits (iNMBs) were reported since ICERs should not be reported in the cost-saving (i.e., "dominated") context. The iNMB is a reformulation of the ICER to present the same

concept of value as an ICER and is calculated as the difference between two individual NMBs (hence it is termed 'incremental'), with each strategy having an NMB calculated. The individual strategy NMB is calculated for each strategy as a product of effectiveness (quality-adjusted life years; QALYs) and the willingness-to-pay ($/QALY)—whose product is cost in $ units—and is then subtracted by the total cost of each testing strategy also in $ units, to result in a monetary value that captures a health strategy's value in $ units. The iNMB is then calculated as the difference (i.e., "incremental") between individual strategy NMBs. To minimize emphasis on any one willingness-to-pay point estimate, most recently derived to be $104,000/QALY [95% uncertainty interval $51,000-$209,000/QALY) in the US context,[26] we utilized the full range of accepted willingness-to-pay thresholds in the United States, reporting model outputs across WTPs of $50,000/QALY, $100,000/QALY, and $150,000/QALY.

Sensitivity and scenario analyses:

To determine how sensitive our results were to all the individual and collective parameter uncertainties, we performed extensive deterministic and probabilistic sensitivity analyses, varying all input parameter estimates +/-50% (Table 1). We performed probabilistic sensitivity analysis (PSA) across >100,000 Monte Carlo simulations using (β)-PERT distributions for transition probabilities and utilities, and (γ) distributions for costs. In addition, in scenario analyses for each base case we nullified the possibility of any bleeding events with caplacizumab to prove that the small (i.e., daily) probability of bleeding does not affect the model's result (i.e., of which strategy is the cost-effective strategy).

RESULTS

Base-case:

The estimated cost, QALYs and iNMB with 95% credible intervals across all 3 testing strategies are reported in Table 2. Across all four base-case analyses, the rapid testing strategy with rapid assay was cost *saving* (i.e., better than cost-effective) while accruing the same amount of QALYs (Table 2). The savings with rapid assay use versus send-out testing with a 72-hour TAT *per-patient-tested* ranged from $3,260 (95% CI [$739-$8,190]) (PLASMIC 6-7, without caplacizumab) to $46,820 (95% CI [$41,960-$52,490]) (PLASMIC 5, with caplacizumab); and from $940 (95% CI [$90-$2,630]) to $20,710 (95% CI [$19,050-$22,630]) versus in-house testing with a 24-hour TAT. When looking specifically at a PLASMIC score of 0-4 the costs of the strategies were directly related to assay cost variation with results demonstrating: rapid $8,510, in-house $8,400, and send-out $8,540. Notably, even when looking at the

most modest per person benefit base-case (i.e., rapid vs in-house testing, without caplacizumab use), proportionally weighted across the population of patients in PLASMIC derivation and validation cohorts, the per-person savings for rapid testing in a cohort of patients with thrombotic microangiopathy would be approximately $1300 savings per patient tested (regardless of PLASMIC score).

Sensitivity analyses:

The top five parameters that all models were most sensitive to were: caplacizumab cost, TPE cost, probability of having iTTP, and cost of ADAMTS13 assays (2 assays were parameters per sensitivity analysis) (Figure 2). The only parameter variation in broad sensitivity analyses that could steer the cost-effective strategy away from the rapid testing strategy occurred when the probability of iTTP with a PLASMIC 6-7 was at least 99.7% (for send-out versus rapid) and at least 97.1% (for in-house versus rapid). These probabilities are implausibly high compared with published cohorts and are not relevant to clinical practice.[5] Nevertheless, despite *including* these broad ranges in probabilistic sensitivity analyses and across all willingness-to-pay thresholds, the rapid assay was favored in 100% of iterations in the context of an intermediate-risk PLASMIC score (with and without caplacizumab), and 99.94% and 98.81% in the context of a high-risk PLASMIC score with and without caplacizumab use, respectively (Table 3). We additionally report probabilistic sensitivity analysis outputs as iNMB distributions for each strategy as compared to rapid testing for all intermediate and high-risk PLASMIC scores empirically treated with TPE, with and without caplacizumab use, generating all eight distributions (Figure 3). An iNMB greater than $0 denotes cost-effectiveness of rapid testing versus the comparator strategy, which is visualized on the x-axis in all instances (Figure 3).

Scenario analyses:

For the scenario analysis the risk of caplacizumab-related bleeding (and its associated cost) was nullified to examine the impact on each strategy. There was no significant difference in the analysis output when bleeding costs were removed: the cost-savings from the rapid assay testing strategy remained nearly identical to base case scenarios including the cost of bleeding. For the intermediate-risk PLASMIC score with caplacizumab scenario, savings were $46,810 (95% CI [$41,950-$52,480]) for rapid vs send-out and $20,700 (95% CI [$19,040-$22,620]) for rapid vs in-house. For those with a high-risk PLASMIC score with caplacizumab, savings associated with rapid vs send-out and rapid vs in-house were $9,530 (95% CI [$2,210-$22,540]) and $4,100 (95% CI [$830-$9,970]), respectively. The conclusion in all scenario

analyses remained the same: the rapid assay testing strategy is a cost-saving or cost-effective strategy in the same proportion of iterations as in the base-case analyses (Table 3).

Discussion

This study extends the literature and is the first to evaluate the potential cost-savings associated with turnaround times of rapid (<1 hour), in-house (24 hours), and send-out (72 hours) ADAMTS13 testing in patients with intermediate and high PLASMIC scores, with and without caplacizumab use. First, regardless of the PLASMIC score, a rapid turnaround time diagnostic strategy was the most cost-effective strategy. In fact, it is cost-saving. Second, whether or not caplacizumab is used, the rapid assay remains a cost saving option compared to traditional turnaround times, with more savings when caplacizumab is used. These results are achieved because the rapid testing strategy reduces costs of unnecessary TPE and caplacizumab therapy in patients without iTTP. The highest cost savings occur in those individuals with intermediate-risk PLASMIC scores who are initiated on TPE and caplacizumab while awaiting traditional confirmatory results. When comparing the cost of the send-out versus the rapid testing strategy with intermediate- and high-risk PLASMIC score, the cost savings are $46,820 and $9,529 for *every* patient tested and empirically treated. These data highlight that the rapid assay testing strategy is a cost-saving strategy, irrespective of PLASMIC score (i.e., intermediate or high-risk) and is greatest with caplacizumab use. The per-person cost savings are greater when caplacizumab is used empirically versus when it is not, due to medication cost averted with the rapid testing strategy. Prior studies did not examine rapid testing, intermediate versus high-risk PLASMIC score, nor utilization of caplacizumab.[9,10]

These results have several broader applications. The Oklahoma registry noted that there is a large gap between those with suspected TTP and those confirmed to have severe ADAMTS13 deficiency, (11.29 versus 1.74 per one million people annually).[27] Given that patients present across a variety of institutions (i.e., academic, urban, and rural) with variability in available resources, rapid ADAMTS13 testing would help expedite diagnosis in all cases. The small portion of suspected TMAs that are iTTP, as well as diagnostic uncertainties present in diagnosis, allows the rapid—and technically simpler—assay to be crucial in expediting the care for individuals with suspected iTTP. At American centers with extensive clinical iTTP experience, there is an inability to consistently perform same-day testing leading to diagnostic delays and cost expenditures with empiric treatment initiation.[28-30] The rapid HemosIL assay lowers the barrier to rapid test availability given that there is not an intensive technical component and

297 easier technical methodology, a practical limitation of FRET-based assays at both urban and rural
298 centers.[15] The rapid results would allow a more rapid diagnostic adjudication of iTTP (i.e., versus not iTTP
299 in the thrombotic microangiopathy context), supporting the potential for an improved yield in the rapid
300 transfer of individuals with confirmed iTTP to centers capable of TPE and further reducing time requiring
301 simple plasma infusion, which is inferior.[31] The rapid turnaround time would also help exclude iTTP and
302 consider alternative thrombotic microangiopathies with alternative therapies sooner. One additional
303 benefit of rapid testing may lie in the care of elderly patients who often present atypically and where
304 diagnostic uncertainty can lead to treatment delays.[32] Thus, institutions should consider investing in a
305 rapid assay option to help with cost-savings and rapid triage of patients with suspected iTTP.
306
307 This study has several strengths. First, we analyzed the cost-effectiveness of diagnostic testing strategy
308 with and without caplacizumab use, with our findings supporting the cost-saving nature regardless of
309 caplcacizumab utilization (and greater cost savings when caplacizumab is utilized versus not). Second, we
310 performed scenario analyses to nullify the cost related to bleeding that may arise on caplacizumab to
311 ensure that this was not significantly impacting the cost-saving results observed. With the scenario
312 analyses we observed no significant changes in cost-savings, further supporting that cost-savings
313 observed with the rapid assay are not related to bleeding, but to the cost of unnecessary caplacizumab
314 and TPE. Third, our model structure was designed to favor the null hypothesis by analyzing the shortest
315 turnaround time for the in-house and send-out test strategies, thus minimizing the accrual of additional
316 cost (and risk) that would occur while awaiting results. Fourth, these findings are relevant to any rapid
317 assay that is produced, with similar cost-savings unless that theoretical rapid assay is logarithmically
318 more expensive. This can be directly calculated from our findings. Fifth, this cost-effectiveness analysis is
319 independent of industry influence.[33]
320
321 This study also has limitations. First, rituximab is used as part of the initial therapy in iTTP, and it was not
322 included as a cost in our study.[34] We decided to not include it as rituximab is often not given in clinical
323 practice unless and until severe ADAMTS 13 deficiency is confirmed. [35,36] It should also be noted that the
324 additional cost (and risk) associated with empiric rituximab infusion would serve as additional cost (and
325 risk) to be averted with the rapid testing strategy. This would in turn only strengthen our finding that the
326 rapid turnaround testing strategy is the cost-effective strategy. Additionally, there will be initial cost in
327 acquiring the assay to perform this rapid, fully automated testing. While the upfront cost of purchasing
328 assay equipment was not accounted for in our model—we also did not include the initial cost of the

equipment for in-house testing—the incremental net monetary benefit specific to each institution can be easily calculated by subtracting the quotient resulting from dividing the purchase price by the expected number of patients tested and empirically treated at the same institution over the course of the equipment's warranty. In addition, we used TAT of 24 and 72 hours for the in-house and send-out testing options, respectively. However, there are often delays beyond this timeline. Longer TATs with in-house and send-out testing would expose patients to more time facing risks of TPE and/or caplacizumab as well as their associated cost, which would in turn only strengthen our result. In fact, we see this effect in the iNMB comparisons of rapid versus in-house (1 day difference) and rapid versus send-out (3-day difference) with greater iNMB in the case of the latter than the former. Additionally, the PLASMIC score cannot be applied to pediatric patients or individuals who are pregnant, limiting the generalizability of our findings to these cohorts. However, should similar scores be developed for these populations, models could be structured to evaluate assay TAT based on the pre-test probability of scoring systems for iTTP in those contexts. The impact of the pre-test probability of iTTP on the negative predictive value of ADAMTS13 testing should also be considered, with a lower negative predictive value when prevalence is higher.

In summary, we performed the first cost-effectiveness analysis evaluating the utilization of a rapid testing strategy compared with in-house and send out testing strategies for the diagnostic adjudication of iTTP, in the context of both intermediate and high PLASMIC scores, and with and without empiric caplacizumab initiation. The rapid ADAMTS13 activity assay demonstrated cost-savings in the care of both intermediate and high-risk PLASMIC score patients, with or without use of caplacizumab. These results are consistent across extensive sensitivity and scenario analyses. The implication of this study is that the utilization of rapid testing will result in overall per-person cost savings, rather than expenditures, for hospitals and healthcare systems. This result occurs because of speedier determination of who needs treatment for iTTP and who does not. Institutions should consider investing in the cost-saving option of a rapid turnaround assay.

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AUTHOR CONTRIBUTIONS

C. A. and G.G. conceived the analysis. All authors wrote and edited the manuscript.

CONFLICTS OF INTEREST

In the past 3 years, HMK has received expenses and/or personal fees from UnitedHealth, Element Science, Eyedentifeye, and F-Prime. He is a co-founder of Refactor Health and HugoHealth and is associated with contracts, through Yale New Haven Hospital, from the Centers for Medicare & Medicaid Services, and through Yale University, from the Food and Drug Administration, Johnson & Johnson, Google, and Pfizer. AC has served as a consultant for MingSight, Sanofi, and Synergy and has received authorship royalties from UpToDate

Data Sharing Statement: Emails to the corresponding author, Dr. George Goshua, george.goshua@yale.edu

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Table 1. Base case input parameters and their probability distributions for probabilistic sensitivity analysis.

Result or Transition	Input Parameter	Probability Distribution	Study or Data Source
Probability of iTTP based on PLASMIC (6-7)	0.81	β-PERT (0.41, 1)	Bendapudi et al.[5]
Probability of iTTP based on PLASMIC (5)	0.045	β-PERT (0.023, 0.068)	Bendapudi et al.[5]
Daily mortality in iTTP patients with caplacizumab and TPE (converted to daily using a conservative median per-person treatment period of 35 days)	0.000266	β-PERT (0.00013, 0.00040)	Peyvandi et al. [37]
Daily mortality in non-iTTP patients with TPE	0.00411	β-PERT (0.0021,0.0.0062	Li et al.[38]
Daily probability of ISTH-defined major bleeding with caplacizumab (converted to daily using a conservative median per-person treatment period of 35 days across available real world reports)	.000592	β-PERT (0.000296, 0.000888)	Coppo et al., Dutt et al., and Knobl et al.[29,39,40]
Daily probability of ICH with caplacizumab (converted to daily using a conservative median per-person treatment period of 35 days across available real world reports)	.000423	β-PERT (0.000212, 0.000635)	Dutt et al., and Knobl et al. and Izquierdo et al. [39-41]
Mortality of (ISTH-defined) non-ICH major bleeding	0.00440	β-PERT (0.0022, 0.0066)	Franco et al.[42]
Mortality of ICH	0.00758	β-PERT (0.0038, 0.011)	Franco et al.[42]
Probability of TRALI	0.0000833	β-PERT (0.000042, 0.00013)	Pandey et al.[43]
Probability of TACO	0.000639	β-PERT (0.00032, 0.00096)	Narick et al.[44]
Daily probability of severe anaphylaxis	0.000000606	β-PERT (0.0000003, 0.0000009)	Som et al.[45]
Daily probability of catheter thrombosis	0.0000106	β-PERT (0.0000053, 0.000016)	Som et al.[45]
Daily probability of central line infection	0.0000218	β-PERT (0.000011, 0.000033)	Som et al.[45]
Daily mortality of TRALI	0.00107	β-PERT (0.00054, 0.0016)	Li et al.[46]
Daily mortality of TACO	0.000410	β-PERT (0.0002, 0.006)	Li et al.[46]

Daily mortality of central line infection	0.0568	β-PERT (0.028, 0.085)	Ziegler et al.[47]
Costs			
Caplacizumab dose (11mg)	8,112.62	Fixed	CMS 2023[21,25]
TPE, per session (professional and technical cost)	5573.47	Gamma (36, 154.82)	Average of all 3-US reports: White et al., Connell et al., Goshua et al., Kim et al.[10,22,23,25]
ICU bed per day	1291.3	Gamma (36, 35.87)	Goshua et al.[25]
Rapid testing (HemosIL Acustar ADAMTS13 activity)	546.02	Gamma (36, 15.17)	White et al.[22]
In-house testing	442.51	Gamma (36, 12.29)	Kim et al.[9]
Send-out testing	582.85	Gamma (36, 16.19)	Kim et al.[9]
iTTP hospitalization without complications	6,667.84	Gamma (36, 185.22)	MS-DRG 810[24]
iTTP hospitalization with a complication (non-major)	8,482.30	Gamma (36, 235.62)	MS-DRG 809[24]
iTTP hospitalization with a major complication (i.e., ICH)	15,155.00	Gamma (36, 420.97)	MS-DRG 808[24]

Table 2. Incremental net monetary benefits (iNMB) per patient tested and empirically treated for immune thrombotic thrombocytopenic purpura for 1) rapid (<1 hour) vs send-out (72 hours) and 2) rapid (<1 hour) vs in-house (24 hours) testing, over a 3-day time-horizon. iNMB calculated also for all scenario analyses (last column). All point estimates rounded to maximum 4 significant digits. Legend: QALY = quality-adjusted life-year; TPE = therapeutic plasma exchange; USD = United States Dollar

Testing Strategy Comparison	Cost (USD)	Effectiveness (QALYs)	Base-Case Incremental Net Monetary Benefit (USD) [95% credible interval]	Scenario Incremental Net Monetary Benefit (95% credible interval)
	PLASMIC = 5 (intermediate), TPE <u>with</u> caplacizumab			
Rapid vs Send out	13,310 vs 60,130	0.0051	46,820 [41,960-52,490]	46,810 [41,950-52,480]
Rapid vs In-house	13,310 vs 34,020	0.0051	20,710 [19,050-22,630]	20,700 [19,040-22,620]
	PLASMIC = 5 (intermediate), TPE <u>without</u> caplacizumab			
Rapid vs Send out	11,830 vs 27,770	0.0051	15,930 [11,130-21,530]	15,930 [11,160-21,570]
Rapid vs In-house	11,830 vs 17,050	0.0051	5,220 [3,590-7,100]	5,220 [3,600-7,110]
	PLASMIC = 6 or 7 (high), TPE <u>with</u> caplacizumab			
Rapid vs Send out	50,960 vs 60,220	0.0051	9,530 [2,210-22,540]	9,530 [2,210-22,540]
Rapid vs In-house	50,960 vs 54,790	0.0051	4,100 [830-9,870]	4,100 [830-9,970]
	PLASMIC = 6 or 7 (high), TPE <u>without</u> caplacizumab			
Rapid vs Send out	24,550 vs 21,810	0.0051	3,260 [730-8,190]	3,260 [730-8,190]
Rapid vs In-house	24,550 vs 25,510	0.0051	940 [90-2,630]	940 [90-2,630]

Table 3. Probabilistic sensitivity analyses of all base-case and scenario* analyses across all accepted willingness-to-pay thresholds in the United States. All parameters varied simultaneously over 100,000 Monte Carlo iterations in each sensitivity analysis. Legend: QALY = quality-adjusted life-year; USD = United States Dollar

Willingness-to-pay threshold (USD/QALY)	**Rapid** Base-case | *Scenario	**In-house** Base-case | *Scenario	**Send-out** Base-case | *Scenario
PLASMIC = 5 (intermediate), TPE with caplacizumab			
50,000	100% | 100%	0% | 0%	0% | 0%
100,000	100% | 100%	0% | 0%	0% | 0%
150,000	100% | 100%	0% | 0%	0% | 0%
PLASMIC = 5 (intermediate), TPE without caplacizumab			
50,000	100% | 100%	0% | 0%	0% | 0%
100,000	100% | 100%	0% | 0%	0% | 0%
150,000	100% | 100%	0% | 0%	0% | 0%
PLASMIC = 6 or 7 (high), TPE with caplacizumab			
50,000	99.94% | 99.94%	0.06% | 0.06%	0% | 0%
100,000	99.94% | 99.94%	0.06% | 0.06%	0% | 0%
150,000	99.94% | 99.94%	0.06% | 0.06%	0% | 0%
PLASMIC = 6 or 7 (high), TPE without caplacizumab			
50,000	98.81% | 98.81%	1.19% | 1.19%	0% | 0%
100,000	98.81% | 98.81%	1.19% | 1.19%	0% | 0%
150,000	98.81% | 98.81%	1.19% | 1.19%	0% | 0%

*Scenario analyses: All bleeding events (and thus cost of managing them) nullified.

Figure Legends

Figure 1. Markov model schematic of the three assay turnaround times (rapid, in-house, and send-out). All patients (PLASMIC = 5 or PLASMIC = 6-7) undergo treatment with TPE +/- caplacizumab. Unlike in the rapid strategy, this treatment is empiric with in-house and send-out testing until 24 and 72 hours, respectively, after which only treatment for patients with confirmed iTTP is continued. Legend: Capla = caplacizumab; iTTP = immune thrombotic thrombocytopenic purpura; TPE = therapeutic plasma exchange.

Figure 2. Tornado diagrams of incremental net monetary benefit for rapid versus send-out and rapid versus in-house diagnostic strategies in the PLASMIC = 5 and PLASMIC = 6-7 clinical contexts, with the utilization of caplacizumab and therapeutic plasma exchange. X-axis is the incremental net monetary benefit for each pairwise strategy comparison. Positive incremental net monetary benefit (i.e., >$0, moving right on the x-axis) favors the rapid strategy. Legend: iTTP = immune thrombotic thrombocytopenic purpura; TPE = therapeutic plasma exchange

Figure 3. Probabilistic distribution (1st to 100th percentile) of incremental net monetary benefit for rapid testing as compared to (1) in-house and (2) send-out testing for each of four base case scenarios: i) PLASMIC = 5, TPE with caplacizumab, ii) PLASMIC = 5, TPE without caplacizumab, iii) PLASMIC = 6-7, TPE with caplacizumab, iv) PLASMIC = 6-7, TPE without caplacizumab. X- and y-axes are aligned to be identical across all 8 distributions. Positive incremental net monetary benefit (i.e., >$0, moving right on the x-axis) favors the rapid strategy.

Figure 1. Markov model schematic of the three assay turnaround times (rapid, in-house, and send-out). All patients (PLASMIC = 5 or PLASMIC = 6-7) undergo treatment with TPE +/- caplacizumab. Unlike in the rapid strategy, this treatment is empiric with in-house and send-out testing until 24 and 72 hours, respectively, after which only treatment for patients with confirmed iTTP is continued. Legend: Capla = caplacizumab; iTTP = immune thrombotic thrombocytopenic purpura; TPE = therapeutic plasma exchange.

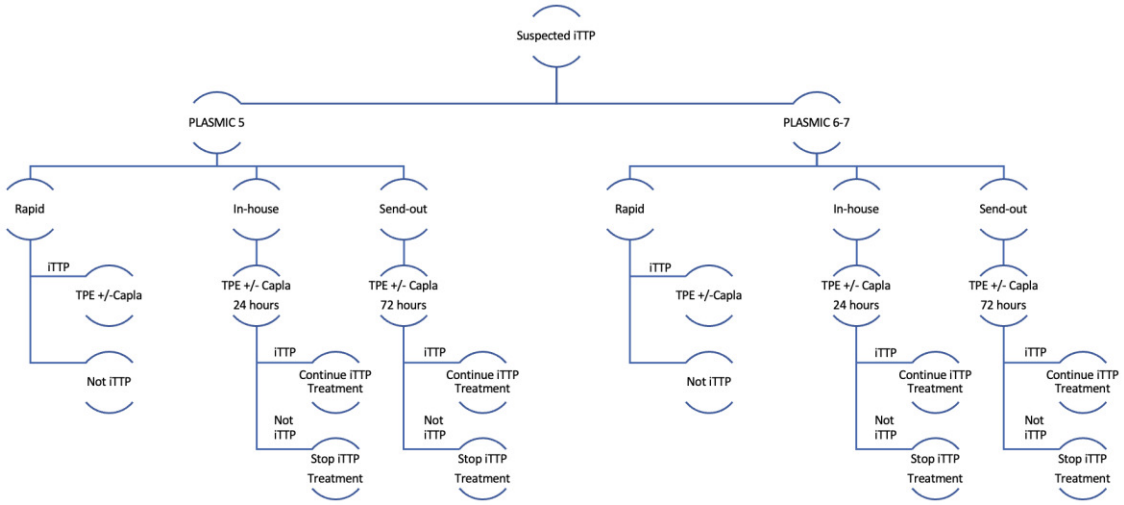

Figure 2. Tornado diagrams of incremental net monetary benefit for rapid versus send-out and rapid versus in-house diagnostic strategies in the PLASMIC = 5 and PLASMIC = 6-7 clinical contexts, with the utilization of caplacizumab and therapeutic plasma exchange. X-axis is the incremental net monetary benefit for each pairwise strategy comparison. Positive incremental net monetary benefit (i.e., >$0, moving right on the x-axis) favors the rapid strategy. Legend: iTTP = immune thrombotic thrombocytopenic purpura; TPE = therapeutic plasma exchange

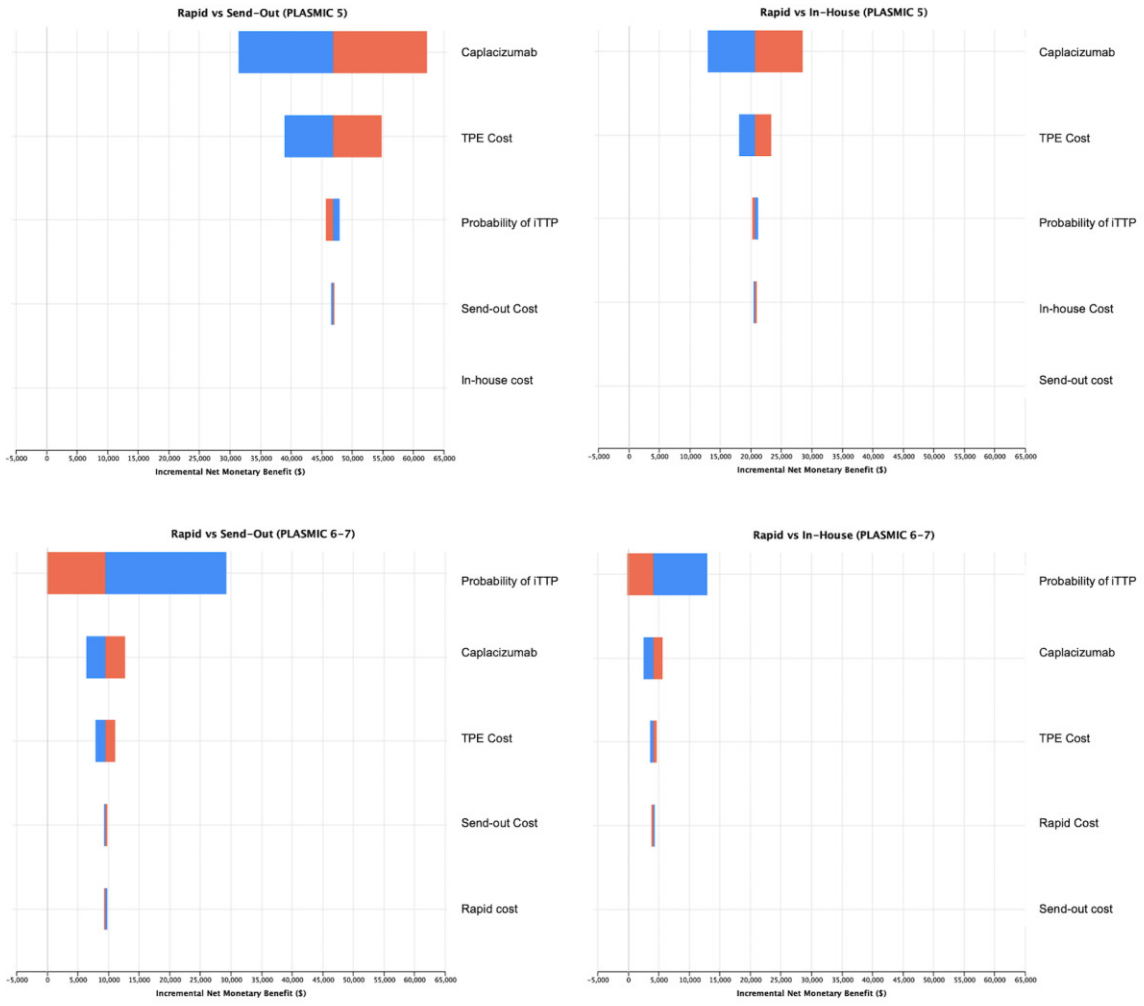

Figure 3

Figure 3. Probabilistic distribution (1st to 100th percentile) of incremental net monetary benefit for rapid testing as compared to (1) in-house and (2) send-out testing for each of four base case scenarios: i) PLASMIC = 5, TPE with caplacizumab, ii) PLASMIC = 5, TPE without caplacizumab, iii) PLASMIC = 6-7, TPE with caplacizumab, iv) PLASMIC = 6-7, TPE without caplacizumab. X- and y-axes are aligned to be identical across all 8 distributions. Positive incremental net monetary benefit (i.e., >$0, moving right on the x-axis) favors the rapid strategy.