Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Disclaimer: These policies are clinical editing payment decisions for Blue Cross of Blue Shield of Michigan and do not apply to Blue Care Network of Michigan.***

# Measurement of Thromboxane Metabolites for ASA Resistance

| | |
|---|---|
| Policy Number: AHS – G2107 – Measurement of Thromboxane Metabolites for ASA Resistance | Prior Policy Name and Number, as applicable: |
| Original Effective Date: 6/01/2022<br>Current Effective Date: 6/01/2022 | |

## I. Policy Description

Thromboxane A2 (TXA2) is a metabolite that causes platelet activation in the cyclooxygenase metabolic pathway (Abrams, 2021). Aspirin (ASA) is an acetylated salicylate and is classified as a nonsteroidal anti-inflammatory medication. Aspirin is intended to inhibit cyclooxygenase-1 (COX-1), which then inhibits generation of TXA2, producing the desired antithrombotic effect. Aspirin resistance is the inability of aspirin to decrease platelet production of thromboxane A2 leading to platelet activation and aggregation. (Abramson, 2021).

## II. Related Policies

| Policy Number | Policy Title |
|---|---|
| AHS-G2050 | Cardiovascular Disease Risk Assessment |

## III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request

*The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.*

1. The measurement of thromboxane metabolites in urine (e.g. AspirinWorks) to evaluate aspirin resistance **DOES NOT MEET COVERAGE CRITERIA** for all indications.

## IV. Scientific Background

Aspirin acts primarily by interfering with the biosynthesis of cyclic prostanoids, including thromboxane (Abrams, 2021). It irreversibly inhibits COX-1, resulting in an antithrombotic

effect due to a decrease in production of thromboxane. Low doses of aspirin (typically 75 to 81 mg/day) have antiplatelet properties (Abramson, 2021) and are indicated for the primary and secondary prevention of cardiovascular disease. However, aspirin has been noted to occasionally fail to provide any significant benefit in patients with cardiovascular disease. Several possible explanations can account for this phenomenon, such as genetic variability or pharmacological interactions with other drugs, but nonadherence tends to be the most likely cause of nonresponse (Zehnder, Tantry, & Gurbel, 2019).

Numerous studies show that aspirin resistance affects 15% to 25% of individuals (Alberts, 2010). A systematic review and meta-analysis on aspirin resistance indicated that patients who are resistant to aspirin are at a greater risk (odds ratio [OR]: 3.85) of clinically important cardiovascular morbidity than patients who are sensitive to aspirin (Krasopoulos, Brister, Beattie, & Buchanan, 2008). The effect of aspirin administration varies considerably among patients at high risk for cardiovascular events. Gum and colleagues found insufficient inhibition of platelet aggregation by aspirin in 6 to 24% of patients with stable coronary artery disease (Gum et al., 2001) while other estimates range from 5 to 60% (Martin & Talbert, 2005).

Many biochemical tests and several commercially available products have been developed to detect aspirin resistance. Tests used in research laboratories include aggregometry, tests based on activation-dependent changes in platelet surface, and tests based on activation-dependent release from platelets. Point-of-care tests include PFA-100, IMPACT, and VerifyNow, which can detect platelet dysfunction that may be due to aspirin effect (Paniccia, Priora, Liotta, & Abbate, 2015). Other tests include Multiplate® analyzer, a multiple electrode aggregometry test (Gillet et al., 2016) and Plateworks assay, a rapid platelet function screening test (Helena_Laboratories, 2021).

It has been proposed that aspirin resistance can also be detected by thromboxane metabolites in urine. Aspirin inhibits platelet activation through the permanent inactivation of the cyclooxygenase (COX) activity of prostaglandin H synthase-1 (COX-1), and consequently inhibits the biosynthesis of thromboxane A2(TXA2), a platelet agonist (Abramson, 2021). The urinary concentrations of the metabolite 11-dehydrothromboxane B2 (11 dhTx$B_2$) is proposed to indicate the level of TXA2 generation (Smock & Rodgers, 2010).

The AspirinWorks Test Kit is an enzyme-linked immunoassay test that can be used to determine levels of 11 dhTxB2 in human urine (Geske, Guyer, & Ens, 2008). The AspirinWorks Test Kit was compared to the Accumetrics VerifyNow Aspirin Assay as the predicate device. The manual AspirinWorks Test Kit measures urinary 11 dhTxB2, a metabolite of TxA2, a direct inducer of platelet aggregation while the automated Accumetrics VerifyNow Aspirin Assay is a turbidimetric-based optical detection system, which measures platelet-induced aggregation in whole blood. Both analyze aspirin's effect through the reduction of TxA2 production or the resulting inhibition of platelet aggregation (FDA, 2015).

A major limitation of this test is that while serum TxB2 comes primarily from platelets, urinary 11dhTxB2 is not a specific measure of platelet thromboxane formation. Urine 11dhTxB2 reflects systemic thromboxane formation, and up to 30% or more can derive from extra-platelet sources, including monocytes, macrophages, atherosclerotic plaque, and other tissues that contain nucleated cells capable of regenerating functional COX-1, or that contain COX-2 (Smock & Rodgers, 2010).

*Clinical Validity and Utility*

The FDA noted that results from two different clinical studies established a cutoff for aspirin effect at ≤1500 pg 11d hTxB2/mg creatinine. Further analysis revealed that 180/204 (88.2%) of samples from individuals not taking aspirin were above the cut-off value. Analysis of samples from individuals taking various doses of aspirin revealed that 7/163 (4.3%) of 81 mg/day aspirin users indicated a lack of aspirin effect (greater than 1500 pg 1 ldhTxB2/mg creatinine) and 4/38 (10.5%) of the 325 mg/day aspirin users indicated a lack of aspirin effect. In total, 11/201 (5.5%) of all aspirin users tested indicated a lack of aspirin effect (FDA, 2007).

Lordkipanidze et al. (2007) compared the results obtained from six major platelet function tests in the "assessment of the prevalence of aspirin resistance in patients with stable coronary artery disease." 201 patients receiving 80 mg of aspirin were evaluated. Two of the tests used to measure platelet aggregation were VerifyNow and urinary 11-dehydro-thromboxane B(2) concentrations. Prevalence of aspirin resistance for VerifyNow was measured to be 6.7% and 22.9% for urinary 11-dehydro-thromboxane B(2) concentrations. The prevalence of aspirin resistance varied according to the assay used. Results from these tests showed "poor correlation and agreement between themselves." The authors concluded that "platelet function tests are not equally effective in measuring aspirin's anti-platelet effect and correlate poorly amongst themselves and that the clinical usefulness of the different assays to classify correctly patients as aspirin resistant remains undetermined" (Lordkipanidze et al., 2007).

Dretzke et al. (2015) examined "whether or not insufficient platelet function inhibition by aspirin ('aspirin resistance'), as defined using platelet function tests (PFTs), is linked to the occurrence of adverse clinical outcomes, and further, whether or not patients at risk of future adverse clinical events can be identified through PFTs." The authors reviewed 108 studies, with 58 on patients on aspirin monotherapy, and found that some PFTs may have prognostic utility. However, the authors noted that many of the studies found contained significant "methodological and clinical heterogeneity". No cost-effectiveness studies were found.

Wang et al. (2018) evaluated the association between stable urine metabolites of thromboxane (TxA2-M), prostacyclin (PGI2-M), levels of cellular adhesion molecules, chemokines, C-reactive protein, and the incidence of major adverse cardiovascular events (MACE). 120 patients with stable atherosclerotic cardiovascular disease on aspirin therapy were examined. The authors found that urinary TxA2-M levels were "significantly" correlated with circulating

P-selectin and E-selectin levels, and associated with higher risk of MACE. The authors concluded that "these results provide insight into the contribution of TxA2 biosynthesis to ASCVD progression in humans, and suggest that patients with elevated TxA2-M levels may be predisposed to advanced platelet and endothelial activation and higher risk of adverse cardiovascular outcomes" (Wang et al., 2018).

Harrison et al. compared 9 platelet function tests to assess responsiveness to three ASA dosing regimens in 24 type 2 diabetes patients randomized to ASA 100 mg/day, 200 mg/day, or 100 mg twice daily for 2 weeks. Of these 9 tests, three were VerifyNow, urinary 11-dehydro-thromboxane B2 (TxB2) and serum TxB2. The investigators evaluated VerifyNow as a "very good" measure, serum TxB2 as a "good" measure, and urinary TxB2 as a "moderate" measure. The authors concluded that "the platelet function tests we assessed were not equally effective in measuring the antiplatelet effect of ASA and correlated poorly amongst themselves, but COX-1-dependent tests performed better than non-COX-1-dependent tests" (Harrison et al., 2018).

Bij de Weg et al. (2020) evaluated the changes in aspirin resistance during and after pregnancy. The study focused on "obstetric high risk women with an indication for aspirin usage during pregnancy to prevent placenta mediated pregnancy complications"; in all, 23 pregnant women were included. Four complementary aspirin resistance tests ("PFA-200, VerifyNow®, Chronolog light transmission aggregometry (Chronolog LTA) and serum thromboxane B2 (TxB2) level measurement") were used to measure aspirin resistance in each trimester of pregnancy, as well as 3 months post-partum. The tests identified aspirin resistance at the following: PFA-200: 30.4%, VerifyNow: 17.4%, Chronolog LTA: 26.1%, and serum TxB2, 23.8% respectively. The authors also identified that aspirin resistance tended to be more frequency during pregnancy compared to after pregnancy. However, the authors also acknowledged that there was "weak" correlation between tests and recommended more research on aspirin resistance as well as obstetric outcome (Bij de Weg et al., 2020).

Ebrahimi et al. (2020) performed a meta-analysis focusing on laboratory-defined aspirin resistance rate in cardiovascular disease patients. 65 studies encompassing 10729 patients were evaluated. The overall prevalence of laboratory-defined aspirin resistance was measured to be 24.7%, with women at slightly higher risk for resistance compared to men (odds ratio = 1.16). The authors also found that higher prevalence of resistance tended to be found in Asia, whereas American studies found the lowest rates of resistance. The authors recommended that providers pay attention to potential aspirin resistance in their patients (Ebrahimi et al., 2020).

Singh et al. (2021) investigated the use of miR-19b-1-5p as a biomarker for aspirin resistance in acute coronary syndrome (ACS) patients as an alternative to in-vitro platelet function tests, which have potential limitations in detection. MiR-19b-1-5p expression was measured in 945 patients with ACS and platelet function was determined by multiplate aggregometry testing. Low miR-19b-1-5p expression was found to be related to aspirin resistance, which agreed with

the sustained platelet aggregation in the presence of aspirin. "Therefore, miR-19b-1-5p could be a suitable marker for aspirin resistance and might predict recurrence of future major adverse cardio-cerebrovascular events in patients with ACS" (Singh et al., 2021).

Piao et al. (2021) compared the performance of the Anysis-200 analyzer and VerifyNow assays to assess platelet inhibition in cardiac disease patients. In relation to VerifyNow, the sensitivity (96.3%) and specificity (90.3%) of Anysis-200 was comparable. The aspirin resistance rate in patients was 20.9% using VerifyNow and 16.5% using Anysis-200. The Cohen's kappa coefficient between the two devices was 0.81, indicating an almost perfect agreement between the two devices. Overall, the Anysis-200 assay "would be used as a point-of-care test to assess aspirin non-responsiveness and abnormal platelet reactivity" (Piao et al., 2021).

## V. Guidelines and Recommendations

**Pan-European, multidisciplinary Task Force for Advanced Bleeding Care in Trauma (Spahn et al., 2019)**

This Task Force includes representatives from six different societies: The European Society for Trauma and Emergency Surgery (ESTES), the European Society of Anaesthesiology (ESA), the European Shock Society (ESS), the European Society for Emergency Medicine (EuSEM), the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA) and the European Society of Intensive Care Medicine (ESICM). Although this guideline focuses on trauma settings, there are some comments on point-of-care (POC) platelet function tests, such as VerifyNow. The Task Force remarks that:

- "The role of POC platelet function devices in guiding haemostatic therapy is not established".
- "Currently, there is no agreement on the optimal assay for platelet function (see R11) and controversy exists as to whether bleeding in the setting of APA [aspirin] use warrants platelet transfusion", although the Task Force acknowledges that "that reliable measures of platelet function would be useful to guide reversal therapies in the setting of the bleeding trauma patient".
- The Task Force also states that due to the "lack of congruency" demonstrated by studies focusing on these platelet function assays, there is a need for future studies to investigate the potential benefit of these platelet function monitoring assays. The Panel remarks that "their [platelet function assays]' role in identifying trauma-induced platelet dysfunction and in guiding haemostatic therapy remains unclear and their use can only be recommended as an adjunct to standard laboratory monitoring".
- Overall, the following recommendation of "We suggest the use of POC platelet function devices as an adjunct to standard laboratory and/or POC coagulation monitoring in patients with suspected platelet dysfunction" was given a grade of "2C",

which was defined as "Very weak recommendation; other alternatives may be equally reasonable" (Spahn et al., 2019).

**International Society on Thrombosis and Haemostasis (Michelson et al., 2005)**

The Working Group on Aspirin Resistance (Michelson et al., 2005) published a position paper which concluded that other than in research trials it is not appropriate to test for aspirin resistance or change therapy based on such tests. There are no published studies which address the clinical effectiveness or data linking aspirin dependent laboratory test to clinical outcomes in patients (Michelson et al., 2005).

**Study Group on Biomarkers in Cardiology of the Acute Cardiovascular Care Association and the Working Group on Thrombosis of the European Society of Cardiology (Aradi et al., 2015)**

This study group was convened to assess the utility of platelet function testing in acute cardiac care for predicting adverse events and guiding antiplatelet therapy. The panel lists recommended assays for assessment of platelet activity during $P2Y_{12}$ inhibitors, which are "the VASP-P® assay, the VerifyNow® device and the Multiplate® analyser". Although VerifyNow is the precursor to AspirinWorks, AspirinWorks itself was not mentioned as a recommended assay (Aradi et al., 2015).

**American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (Douketis et al., 2012) (9th Edition)**

The ACCP states "the clinical significance of [platelet function] assay findings is uncertain, and the assay results have not been shown to predict clinical outcomes" (Douketis et al., 2012).

**The American Society of Anesthesiologists (ASA) (Mahla, Tantry, Schoerghuber, & Gurbel, 2020)**

The ASA released guidelines on platelet function testing in patients on antiplatelet therapy before cardiac surgery. The ASA advises that platelet function testing may be considered to guide decisions on timing of cardiac surgery in patients who have recently received P2Y12 receptor inhibitors or who have ongoing dual antiplatelet therapy. The ASA highlights the advantages and disadvantages of various platelet function assays and notes that the underlying principles between the assays differ therefore, a poor correlation has been reported between the assays. Currently, there is not enough evidence from surgical patients to prefer one test over the other. Among the various methods, the ASA recommends Thromboelastography (TEG5000, TEG6s) with platelet mapping assay or the VerifyNow P2Y12 assay as both are more appropriate in coronary artery surgery patients since it can be performed at bedside (Mahla et al., 2020).

## VI. State and Federal Regulations, as applicable

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g. Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, please visit the applicable state Medicaid website.

VerifyNow-Aspirin Assay, which received 510(k) marketing clearance from the FDA in October 2004, is a qualitative assay to aid in the detection of platelet dysfunction due to aspirin ingestion in citrated whole blood for the point of care or laboratory setting (FDA, 2004).

AspirinWorks received 510(k) marketing clearance from the FDA in May 2007 and is intended to aid in the qualitative detection of aspirin in apparently healthy individuals post ingestion.

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

## VII. Applicable CPT/HCPCS Procedure Codes

| Code Number | Code Description |
|---|---|
| 82570 | Creatinine; other source |
| 84431 | Thromboxane metabolite(s), including thromboxane if performed, urine |



*Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.*

## VIII. Evidence-based Scientific References

Abrams, C. (2021). Platelet biology. Retrieved from https://www.uptodate.com/contents/platelet-biology?search=Aspirin%20metabolite%20thromboxane&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H10

Abramson, S. (2021). Aspirin: Mechanism of action, major toxicities, and use in rheumatic diseases. Retrieved from https://www.uptodate.com/contents/aspirin-mechanism-of-action-major-toxicities-and-use-in-rheumatic-diseases

Aradi, D., Collet, J. P., Mair, J., Plebani, M., Merkely, B., Jaffe, A. S., . . . Huber, K. (2015). Platelet function testing in acute cardiac care - is there a role for prediction or prevention of stent thrombosis and bleeding? *Thromb Haemost, 113*(2), 221-230. doi:10.1160/th14-05-0449

Bij de Weg, J. M., Abheiden, C. N. H., Fuijkschot, W. W., Harmsze, A. M., de Boer, M. A., Thijs, A., & de Vries, J. I. P. (2020). Resistance of aspirin during and after pregnancy: A longitudinal cohort study. *Pregnancy Hypertens, 19*, 25-30. doi:10.1016/j.preghy.2019.11.008

Douketis, J. D., Spyropoulos, A. C., Spencer, F. A., Mayr, M., Jaffer, A. K., Eckman, M. H., . . . Kunz, R. (2012). Perioperative Management of Antithrombotic Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST, 141*(2), e326S-e350S. doi:10.1378/chest.11-2298

Dretzke, J., Riley, R. D., Lordkipanidze, M., Jowett, S., O'Donnell, J., Ensor, J., . . . Moore, D. (2015). The prognostic utility of tests of platelet function for the detection of 'aspirin resistance' in patients with established cardiovascular or cerebrovascular disease: a systematic review and economic evaluation. *Health Technol Assess, 19*(37), 1-366. doi:10.3310/hta19370

Ebrahimi, P., Farhadi, Z., Behzadifar, M., Shabaninejad, H., Abolghasem Gorji, H., Taheri Mirghaed, M., . . . Sohrabi, R. (2020). Prevalence rate of laboratory defined aspirin resistance in cardiovascular disease patients: A systematic review and meta-analysis. *Caspian J Intern Med, 11*(2), 124-134. doi:10.22088/cjim.11.2.124

FDA. (2004). Accumetrics VerifyNow-Aspirin Assay. Retrieved from https://www.accessdata.fda.gov/cdrh_docs/pdf4/k042423.pdf

FDA. (2007). 510(K-) Summary. Retrieved from https://www.accessdata.fda.gov/cdrh_docs/pdf6/K062025.pdf

FDA. (2015). 510(K-) Summary. Retrieved from https://www.accessdata.fda.gov/cdrh_docs/pdf6/K062025.pdf

Geske, F. J., Guyer, K. E., & Ens, G. (2008). AspirinWorks: a new immunologic diagnostic test for monitoring aspirin effect. *Mol Diagn Ther, 12*(1), 51-54. Retrieved from http://dx.doi.org/

Gillet, B., Ianotto, J. C., Mingant, F., Didier, R., Gilard, M., Ugo, V., . . . Galinat, H. (2016). Multiple Electrode Aggregometry is an adequate method for aspirin response testing in

myeloproliferative neoplasms and differentiates the mechanisms of aspirin resistance. *Thromb Res, 142*, 26-32. doi:10.1016/j.thromres.2016.04.006

Gum, P. A., Kottke-Marchant, K., Poggio, E. D., Gurm, H., Welsh, P. A., Brooks, L., . . . Topol, E. J. (2001). Profile and prevalence of aspirin resistance in patients with cardiovascular disease. *Am J Cardiol, 88*(3), 230-235. doi:10.1016/s0002-9149(01)01631-9

Harrison, P., Bethel, M. A., Kennedy, I., Dinsdale, R., Coleman, R., & Holman, R. R. (2018). Comparison of nine platelet function tests used to determine responses to different aspirin dosages in people with type 2 diabetes. *Platelets*, 1-9. doi:10.1080/09537104.2018.1478402

Helena_Laboratories. (2021). Plateletworks. Retrieved from https://www.helena.com/plateletworks.htm

Krasopoulos, G., Brister, S. J., Beattie, W. S., & Buchanan, M. R. (2008). Aspirin "resistance" and risk of cardiovascular morbidity: systematic review and meta-analysis. *Bmj, 336*(7637), 195-198. doi:10.1136/bmj.39430.529549.BE

Lordkipanidze, M., Pharand, C., Schampaert, E., Turgeon, J., Palisaitis, D. A., & Diodati, J. G. (2007). A comparison of six major platelet function tests to determine the prevalence of aspirin resistance in patients with stable coronary artery disease. *Eur Heart J, 28*(14), 1702-1708. doi:10.1093/eurheartj/ehm226

Mahla, E., Tantry, U. S., Schoerghuber, M., & Gurbel, P. A. (2020). Platelet Function Testing in Patients on Antiplatelet Therapy before Cardiac Surgery. *Anesthesiology, 133*(6), 1263-1276. doi:10.1097/aln.0000000000003541

Martin, C. P., & Talbert, R. L. (2005). Aspirin resistance: an evaluation of current evidence and measurement methods. *Pharmacotherapy, 25*(7), 942-953.

Michelson, A. D., Cattaneo, M., Eikelboom, J. W., Gurbel, P., Kottke-Marchant, K., Kunicki, T. J., . . . Rao, A. K. (2005). Aspirin resistance: position paper of the Working Group on Aspirin Resistance. *J Thromb Haemost, 3*(6), 1309-1311. doi:10.1111/j.1538-7836.2005.01351.x

Paniccia, R., Priora, R., Liotta, A. A., & Abbate, R. (2015). Platelet function tests: a comparative review. *Vasc Health Risk Manag, 11*, 133-148. doi:10.2147/vhrm.S44469

Piao, J., Yoo, C., Kim, S., Whang, Y.-W., Choi, C. U., & Shin, S. (2021). Performance comparison of aspirin assay between anysis and verifynow: Assessment of therapeutic platelet inhibition in patients with cardiac diseases. *Clinical Hemorheology and Microcirculation, Preprint*, 1-8. doi:10.3233/CH-211171

Singh, S., Ronde, M. W. J. d., Creemers, E. E., Made, I. V. d., Meijering, R., Chan, M. Y., . . . Pinto-Sietsma, S. J. (2021). Low miR‐19b‐1‐5p Expression Is Related to Aspirin Resistance and Major Adverse Cardio‐ Cerebrovascular Events in Patients With Acute Coronary Syndrome. *Journal of the American Heart Association, 10*(2), e017120. doi:doi:10.1161/JAHA.120.017120

Smock, K. J., & Rodgers, G. M. (2010). Laboratory evaluation of aspirin responsiveness. *Am J Hematol, 85*(5), 358-360. doi:10.1002/ajh.21674

Spahn, D. R., Bouillon, B., Cerny, V., Duranteau, J., Filipescu, D., Hunt, B. J., . . . Rossaint, R. (2019). The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care, 23*(1), 98. doi:10.1186/s13054-019-2347-3

Wang, N., Vendrov, K. C., Simmons, B. P., Schuck, R. N., Stouffer, G. A., & Lee, C. R. (2018). Urinary 11-dehydro-thromboxane B2 levels are associated with vascular inflammation and prognosis in atherosclerotic cardiovascular disease. *Prostaglandins Other Lipid Mediat, 134*, 24-31. doi:10.1016/j.prostaglandins.2017.11.003

Zehnder, J., Tantry, U., & Gurbel, P. (2019). Nonresponse and resistance to aspirin - UpToDate. In H. Libman & G. Saperia (Eds.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/nonresponse-and-resistance-to-aspirin?source=search_result&search=aspirin%20resistance&selectedTitle=1~12#H2044812

## IX. Revision History

| Effective Date | Summary |
|---|---|
| 06/01/2022 | Initial Policy Implementation |