Suspected Overutilization of Rare Disease Testing: A Case Study of Laboratory Stewardship and *ADAMTS13* Genetic Analysis

With rising healthcare costs and increased availability of genetic testing, test utilization management strategies are essential for delivering accurate, timely diagnoses while concurrently reducing financial liability and unnecessary laboratory testing for patients. In recent years, laboratory stewardship has emerged as a strategy for ensuring high-quality laboratory medicine practices and results with the goal of providing the right test, for the right patient, at the right time (White et al., 2021). Implementing a laboratory stewardship program creates a valuable opportunity for healthcare providers to work collaboratively, take an active role in optimizing the value of laboratory testing, and realize efficiencies for their organization.

In June 2023, Versiti's Hematology Genetics team presented a poster abstract about suspected overutilization of *ADAMTS13* genetic analysis by a single client at the 2023 PLUGS (Patient-centered Laboratory Utilization Guidance Services) Summit, demonstrating our commitment to laboratory stewardship.

Case Study

ADAMTS13 is a plasma protease that cleaves von Willebrand factor (VWF) to prevent the spontaneous interaction of VWF with platelets that can result in microvascular thrombosis. Severe deficiency of ADAMTS13 results in thrombotic thrombocytopenic purpura (TTP), a cause of thrombotic microangiopathy (TMA). TMA, which is characterized by hemolytic anemia, thrombocytopenia and organ dysfunction from microvascular thrombosis, is a serious complication of dysregulated coagulation and complement activation in patients with infections, cancer, autoimmune disorders, pregnancy, organ transplants and other conditions (Chapman et al., 2012).

Autosomal recessive congenital ADAMTS13 deficiency (aka familial/inherited TTP and Upshaw-Schulman syndrome) is caused by biallelic pathogenic variants in the *ADAMTS13* gene, with prevalence estimated at 1.1 per million (Zhao et al., 2021). Our esoteric hematology reference laboratory performs plasma testing for ADAMTS13 activity (to diagnose TTP) and ADAMTS13 inhibitor and antibody (to confirm acquired TTP), as well as genetic analysis of *ADAMTS13* (to identify genetic etiology among patients with known ADAMTS13 deficiency). Genetic analysis of *ADAMTS13* for diagnosis of inherited TTP may be recommended when there is evidence of severe ADAMTS13 deficiency (<10%) by an ADAMTS13 activity assay with no detectable inhibitor or antibody; a normal baseline ADAMTS13 activity rules out inherited TTP/congenital ADAMTS13 deficiency.

As a laboratory stewardship service, our genetic counseling team assesses clinical history provided with incoming genetic test orders and contacts clients when an order change may be beneficial in terms of clinical utility, cost, or turnaround time; orders are only modified

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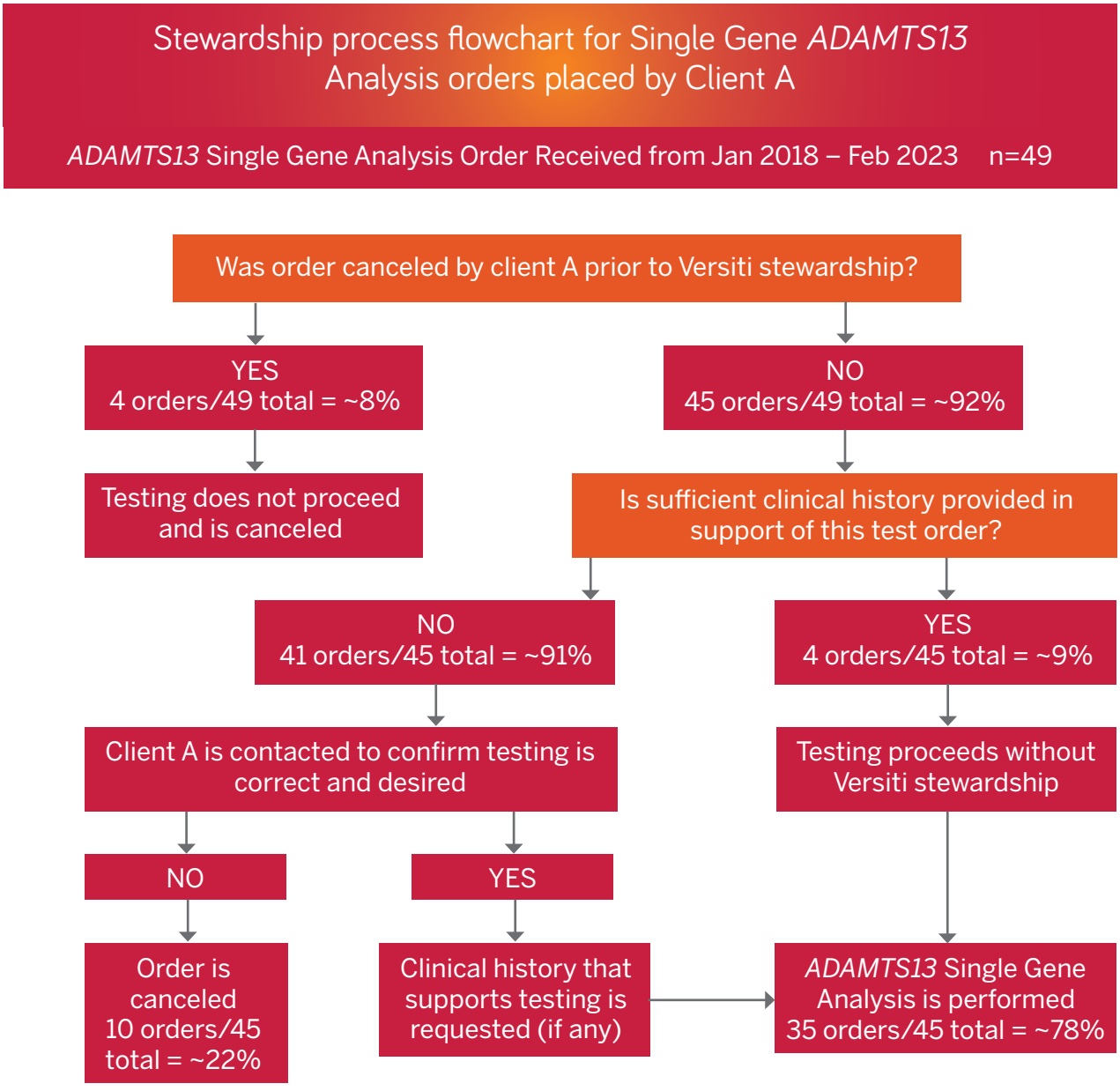
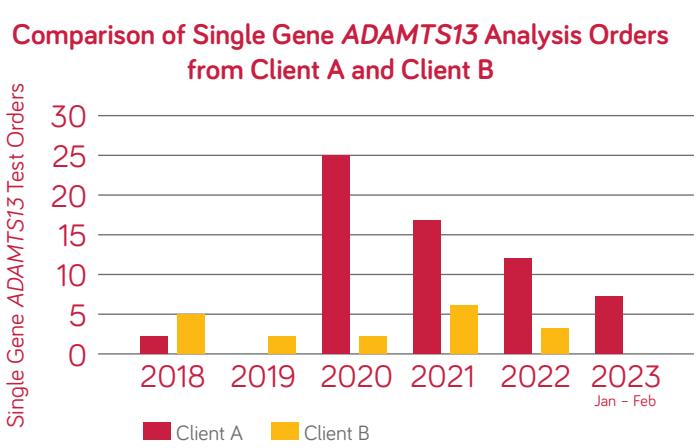
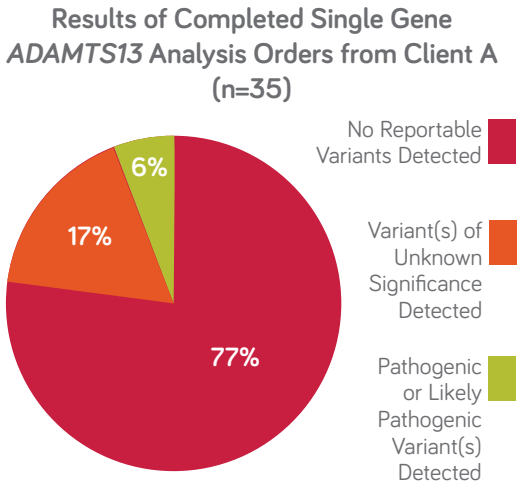
or canceled with explicit instruction from clients. Based on disease frequency of congenital ADAMTS13 deficiency, Versiti's Hematology Genetics team noticed an above average ordering trend for Single Gene *ADAMTS13* Analysis from one specific client ("Client A"). In February 2023, our genetic counselors performed a retrospective review of Single Gene *ADAMTS13* Analysis orders submitted from Client A over the past five years. Using our stewardship process demonstrated in the flow chart below, the 49 orders placed by Client A in the previous five years were individually reviewed for clinical utility.



Of the 45 cases received from Client A for *ADAMTS13* Gene Analysis, only four orders (9%) were received with sufficient/supportive clinical history for testing. Due to Client A's review of orders and our stewardship practices, 14 cases were deemed to have low clinical utility and were canceled. **This resulted in an estimated cost avoidance of almost $16,000 for Client A.**



A comparison of Single Gene *ADAMTS13* test orders between Client A (our largest client for *ADAMTS13* test orders) and Client B (our second largest client for *ADAMTS13* test orders) was determined.



Of 35 completed orders from Client A, only 4 cases provided sufficient clinical history to support genetic testing for the patient. Of these 35 completed cases, 8 resulted in reportable findings, revealing 6 with variants of unknown significance (~17%), and only 2 cases with pathogenic or likely pathogenic findings (~6%).

The data supported our theory that Single Gene *ADAMTS13* Analysis may be overutilized by Client A's hospital system. Together with Client A, we identified potential contributing factors to the misuse of genetic testing in patients with TMA, including inpatient setting for most patients, lack of familiarity with esoteric testing by non-hematology clinicians, and similarities in the names of the orders in the electronic medical record. With collaborative laboratory stewardship efforts across our referral lab and Client A, a reduction of unnecessary or unintended testing was achieved.

Versiti's Commitment to Laboratory Stewardship

Versiti offers clients a unique approach to genetic diagnosis and disease identification utilizing a multidisciplinary team that includes hematologists, pathologists, genetic counselors and variant scientists with deep, focused expertise in non-malignant hematology. Versiti is proud to offer genetic tests focused on inherited disorders of bleeding, clotting, platelets and neutrophils with careful gene-by-gene selection for clinical validity and utility. With increasing evidence of new gene-disease associations, we continue to curate our clinical genetic testing menu to ensure comprehensive coverage of relevant genetic regions for patients with genetic blood disorders.

An integral component of Versiti's Hematology Genetics Lab is an active laboratory stewardship and utilization guidance program to improve the value of laboratory services for providers and patients. Our multidisciplinary team actively reviews all genetic testing requisitions received, resulting in optimized testing or cost savings in 8.7% of all cases.* We are a proud member of PLUGS, supporting its national mission to increase the value of testing to patients through advocacy of laboratory test stewardship.

To learn more about our Hematology Genetics testing, visit **versiti.org/HG**.

**Versiti data on file.*

Sources:

Chapman, K., Seldon, M., Richards, R. Thrombotic microangiopathies, thrombotic thrombocytopenic purpura, and ADAMTS-13. Semin Thromb Hemost. 2012 Feb;38(1):47-54. doi: 10.1055/s-0031-1300951. Epub 2012 Feb 7. PMID: 22314603.

Smith C., Bajguz D., Palmer E., Perez-Botero J., Dugan S. & Riley J.D. (2023, June 15-16). Overutilization of Rare Disease Testing: An Exploration of ADAMTS13 Genetic Analysis [Poster abstract]. PLUGS Summit, Seattle, WA, United States.

White, T. E., Wong, W. B., Janowiak, D., & Hilborne, L. H. (2021). Strategies for laboratory professionals to drive laboratory stewardship. Practical laboratory medicine, 26, e00249. https://doi.org/10.1016/j.plabm.2021.e00249

Zhao, T., Fan, S., Sun, L. The global carrier frequency and genetic prevalence of Upshaw-Schulman syndrome. BMC Genom Data. 2021 Nov 17;22(1):50. doi: 10.1186/s12863-021-01010-0. PMID: 34789164; PMCID: PMC8600861.

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