

# Identification and Comparison of Patients with Hemophilia A Receiving Prophylactic versus On-Demand Factor VIII Treatment Regimens Using Health Care Claims Data

Jennifer Pocoski, PharmD<sup>1</sup>; Joseph LeCates, PhD<sup>2</sup>; Abhijit Gadkari, PhD<sup>1</sup>; Mei Sheng Duh, ScD, MPH<sup>2</sup>; Francis Vekeman, MA<sup>3</sup>

<sup>1</sup> Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

<sup>2</sup> Analysis Group, Inc., Boston, MA, USA

<sup>3</sup> Groupe d'analyse, Ltée, Montréal, QC, Canada

[ Under Review, *Hematology* ]

**Key Words:** Hemophilia, Factor VIII Modalities, Prophylaxis, On-Demand, Health Care Claims Data, Medicaid

**Corresponding Author:** Francis Vekeman  
Analysis Group, Inc.  
1000 De La Gauchetière Ouest, Bureau 1200  
Montréal, QC, CANADA H3B 4W5  
Tel: 514 394 4442  
Fax: 514 394 4461  
fvekeman@analysisgroup.com

Earlier versions of this research have been previously presented in poster format at the National Hemophilia Foundation's 65th Annual Meeting, Anaheim, CA, USA, October 3–5, 2013; the World Federation of Hemophilia, 2012 World Congress, Paris, France, July 8–12, 2012; and the International Society for Pharmacoeconomics and Outcomes Research, 17th Annual International Meeting, Washington, DC, USA, June 2–6, 2012, as well as in a podium presentation at the International Society for Pharmacoepidemiology, 28th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Barcelona, Spain, August 23–26, 2012.

## Abstract

Health care claims databases have sufficient patient counts to provide real-world evidence comparing prophylactic versus on-demand factor VIII (“FVIII”) treatment for hemophilia A (“HemA”), yet lack treatment regimen information available in specialty pharmacy databases necessary for those comparisons. We used age and FVIII units, data elements available in both data sources, from 3,645 specialty pharmacy patients with HemA, aged  $\geq 2$ , receiving only one regimen, and without bypassing agents, to calibrate a flexible algorithm for predicting treatment regimen in claims data. The algorithm maximizing the product of sensitivity and specificity identified the following age groups and annual FVIII IU thresholds: 2–7 [16,480]; 8–12 [32,770]; 13–16 [66,920]; 17–21 [122,757]; 22+ [204,552]. Annual FVIII use exceeding these thresholds predicted prophylactic treatment. We applied these results to a claims data sample of Medicaid patients with HemA,  $\geq 2$  filled FVIII prescriptions after age 2, continuous coverage  $\geq 6$  months before and  $\geq 12$  months after the eligible FVIII dispensing, and without bypassing agent or desmopressin use. Four hundred forty-eight patients met the eligibility criteria, with 225 (50.2%) identified as receiving prophylactic FVIII treatment. Younger patients were more likely to receive prophylaxis (percent [age group]: 61% [2–7]; 70% [8–12]; 63% [13–16]; 43% [17–21]; 20% [22+], mean (SD) age, prophylaxis: 10.7 (9.8); on-demand: 18.7 (14.3) years old). With average follow-up greater than 5.5 years for both treatment groups, using the algorithm’s results with Medicaid claims allows the opportunity for long-term, real-world comparisons of prophylactic versus on-demand FVIII treatment.

## Introduction

Hemophilia A is a recessive, sex-linked, inherited bleeding disorder caused by a deficiency in a functional clotting factor, factor VIII (FVIII), and affects approximately 20,000 people in the United States [1–3]. Low levels of FVIII delay or prevent wound closure, and bleeding after injury may continue for days or indefinitely [4]. Up to 70% of patients with hemophilia A suffer from a severe form of the disease, being able to produce less than 1% of the normal amount of clotting factor FVIII (< 0.01 IU/mL), and another 15-26% of patients are diagnosed with moderate disease, being able to produce up to 5% of the normal clotting factor level (0.01-0.05 IU/mL). A common problem for patients with hemophilia A from an early age is internal bleeding (hemorrhage) after injury, particularly in the joints [5]. Recurring hemorrhaging in the joints (hemarthrosis) eventually escalates into arthropathy – a crippling joint disease associated with pain, physical and psychosocial impairments, and lowered quality of life [5, 6].

Current treatment of hemophilia A involves infusions of plasma-derived or recombinant FVIII concentrates in order to treat or prevent hemorrhage [1, 7], which may be administered either on-demand (episodic treatment for a bleed), or in a prophylactic regimen. Prophylactic treatment aims to reduce the severity of disease to prevent the long-term risk of joint damage [1, 7]. Primary prophylaxis is frequently recommended for patients under two years of age, before the first bleed or development of joint damage [8]. Secondary prophylaxis, more common in older patients, is meant to slow the development of hemophilic arthropathy [9]. Based on the patient's age, weight, and prognosis, the prophylactic dose and frequency are chosen to meet a patient's needs [1, 7, 10]. Treatment pattern surveys show that patients on a prophylactic regimen are likely to receive more units of FVIII over a time period compared to those receiving an on-demand regimen [11]. Because hemophilia is rare and treatment is customized, FVIII is often dispensed from specialty pharmacies, where patient and treatment information is collected.

Available evidence comparing the impact of prophylactic versus on-demand treatment has largely been limited to clinical trials [12–19]. Although the demonstrated advantage of prophylactic treatment over on-demand treatment has been decreased joint damage, fewer bleeds, and better quality of life [15], the question of when and how patients with hemophilia A should be treated still persists [20]. Real-world, long-term evidence comes mostly from European national studies [21–25], but it has been sporadic and occasionally inconclusive [26].

United States' health care claims databases cover sufficiently large patient populations to offer the opportunity to study rare diseases such as hemophilia A. Information on patient characteristics, treatment patterns, and outcomes can be extracted from existing health care utilization records to describe a real-world population's use of FVIII treatment. In spite of the abundant information available in health care claims databases, their usefulness for FVIII treatment regimen comparisons is limited by their lack of specific information to distinguish between patients receiving prophylactic versus on-demand FVIII therapy.

The aim of this study was to design and calibrate a treatment prediction algorithm using specialty pharmacy claims data that, when applied to health care claims data, allows researchers to identify patients with hemophilia A receiving prophylactic versus on-demand FVIII regimens. The potential for using the algorithm for real-world research was evaluated by applying the algorithm to health care claims from five state Medicaid Programs (US health insurance for individuals with low income and resources).

## **Materials and methods**

### ***Specialty Pharmacy Claims***

The prediction algorithm for classifying prophylactic versus on-demand FVIII regimens for patients with hemophilia A was developed using data from three specialty pharmacies. Specialty

pharmacies offer services for health care providers and insurers for the delivery of pharmaceutical and biologic products that have high acquisition costs, are difficult to manage, and present reimbursement challenges. FVIII preparations are thus commonly dispensed through specialty pharmacies, which provide treatment materials to patients, coordinate utilization assessment, and manage medical and pharmacy benefit plans [27]. Covering periods between 2008 and 2012, the sample of specialty pharmacy databases collectively includes records for more than five thousand patients receiving FVIII. In addition to dispensing records (vial potency, reported in IU/vial, and number of vials), specialty pharmacy records contain selected patient characteristics (gender, age, weight), clinical information (level of hemophilia severity), and prescription dosing details (treatment regimen, dose, frequency) based on physician notes. When regimen was not specified, two reviewers independently compared prescription details from each dispensing record to determine a patient's FVIII regimen. Any differences in the regimen identified were reconciled by a third party referring to the original data.

Patient records from the specialty pharmacy data were included in the algorithm calibration if the patient (1) had at least 1 dispensing of FVIII together with a diagnosis of hemophilia A (ICD-9-CM: 286.0), (2) was male, to exclude cases of von Willebrand disease, and (3) was 2 years of age or older at the first observed dispensing of FVIII infusion (to capture stable treatment). Patient records were excluded if the patient had any dispensing of a bypassing agent, identified by National Drug Codes [NDCs], or if both on-demand and prophylactic regimens were observed for the patient.

### ***Health Care Claims***

Characteristics and treatment regimens of patients with hemophilia A receiving prophylactic versus on-demand FVIII therapy were evaluated after applying the prediction algorithm to health care claims databases from the Florida, Iowa, Kansas, New Jersey, and Missouri

Medicaid programs. These databases cover families and individuals with low income and resources over the period 1997–2012 and encompass approximately 14.8 million covered lives. These multi-year longitudinal health care claims databases include information on patient demographics (age, gender), enrollment history, medical diagnoses received, procedures performed, dates of service, place of service, and payment amounts on medical and pharmacy claims. All data are de-identified, in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Patients were selected from the Medicaid databases if they met the following criteria: (1) had at least 2 (to exclude rule-out diagnoses) ICD-9-CM diagnoses of hemophilia A, (2) had at least 2 filled prescriptions for FVIII after the age of 2, and (3) had continuous Medicaid insurance eligibility for at least 6 months before and 12 months after one FVIII dispensing after the age of 2. Patients were excluded from the study sample if there was evidence of dispensed bypassing agents or desmopressins or if a patient had 2 or more diagnoses for von Willebrand disease (ICD-9-CM: 286.4). Patients receiving bypassing agents or desmopressins were excluded as their dosing patterns are likely to cause the algorithm to misidentify the intended treatment regimen. Dispensing of bypassing agents is an indicator that a patient has developed inhibitors and thus may receive larger amount of FVIII (predictive of prophylactic treatment) even when receiving on-demand therapy. On the other hand, patients using desmopressins have more mild disease severity and thus may receive lower doses of FVIII (predictive of on-demand therapy) even when receiving prophylactic therapy.

The index date for each patient was the date of first FVIII receipt occurring (1) at least 6 months after Medicaid insurance coverage start, and (2) after the patient's second birthday. The follow up period for each patient was defined as the period from the index date to the earliest date between the end of eligibility and end of data availability. By definition of the index date, all follow up is observed for patients age 2 and older. Figure 1 shows the study design scheme.

FIGURE 1  
HERE

### ***Treatment Regimen Prediction Algorithm***

The development of the algorithm was conducted in three steps: (1) identification of the data elements available in both specialty pharmacy and health care claims data, (2) design of the algorithm's prediction scheme, and (3) calibration of the algorithm to maximize treatment prediction accuracy with available information.

First, two data elements available in both specialty pharmacy and claims databases were identified: age and the number of units of FVIII dispensed.

Second, the algorithm's scheme was designed to correctly predict treatment regimens using age at first FVIII dispensing and number of FVIII units dispensed annually. Because the amount of FVIII required increases with a patient's weight as he ages, we grouped patients according to age so that weight and thus the amount of FVIII dispensed for each patient within each group would be similar [1]. Nevertheless, the determination of which ages to group for best model performance is an empirical question. To give the algorithm the flexibility to reflect the real-world use of FVIII for each treatment regimen within each age group, the algorithm included two age-group cut-offs determined within the automated calibration procedure:  $T_1$  between ages 2 and 12, and  $T_2$  greater than 17. Together, these cut-offs created 5 distinct age groups: ages 2 to  $T_1$ ,  $(T_1 + 1)$  to 12, 13 to 16, 17 to  $T_2$ , and  $(T_2 + 1)$  and older. Within each age group, patients with total annual units of FVIII dispensed greater than or equal to the specific threshold were classified as being on a prophylactic regimen; otherwise, they were classified as receiving an on-demand regimen.

In the third step, the ability of each candidate algorithm to accurately identify patients' FVIII regimens in the specialty pharmacy data was assessed. We tested candidate algorithms by comparing their sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). If the sensitivity of the algorithm is high, there is a high probability that patients receiving prophylactic treatment will be classified as such. If the specificity is high, there is a high

probability that patients receiving on-demand treatment will be classified as such. Maximizing sensitivity and specificity involves a trade-off between the two measures: in order to achieve a greater sensitivity, the algorithm must minimize false negatives, thus increasing false positives and decreasing the specificity; conversely, in order to achieve a greater specificity, the algorithm must minimize false positives, thus increasing false negatives and decreasing the sensitivity.

Although sensitivity and specificity are useful measures of algorithm performance when applied to a sample of patients with known treatment regimens, the goal of the current study was to accurately predict FVIII regimen in health care claims data. Positive predictive value and NPV give the degree of confidence we may have in accurate prediction of a regimen when the true regimen is unknown. In general, higher sensitivity and specificity values are associated with higher values of PPV and NPV, but both vary with the population rate of the predicted regimen.

Selection of the final algorithm was based on the maximization of the product of the sensitivity and specificity, thereby balancing improvements in one at the expense of the other. Further, we required PPV and NPV to exceed 0.80 to ensure reliability [28]. Optimization of the algorithm was made by iteratively testing all possible combinations of (1) age group cut-offs  $T_1$  ( $2 < T_1 < 12$ ) and  $T_2$  ( $T_2 > 17$ ), and (2) total annual units of FVIII for each age group.

### ***Identification of Treatment Regimens and Medicaid Patient Characteristics***

To evaluate the potential of using the algorithm in health care claims data, the algorithm was applied to the Medicaid data from Florida, Iowa, Kansas, Missouri, and New Jersey. To determine a patient's treatment regimen, the total units of FVIII dispensed during the 12-month period after the index date was compared to the calibrated algorithm's threshold for the patient's age group. Patients with total annual FVIII units received above the threshold were identified as receiving prophylactic treatment; those below were identified as receiving on-demand treatment.

We report the number and proportion of patients on prophylactic or on-demand treatment as well as the number of years of available follow-up observation for each treatment regimen.

To evaluate whether the algorithm application unintentionally generates sample selection issues, we examined a number of common patient and disease characteristics evaluated in the baseline period. For each treatment regimen cohort, we reported demographic characteristics (age, geographic location), the distribution of patients by index year, relevant comorbidities (HIV, hepatitis C, osteoporosis, arthritis, liver fibrosis/cirrhosis, ischemic heart disease, myocardial infarction, hypertension, hypercholesterolemia, stroke) [29–31], and concomitant medications received.

### *Statistical Analysis*

Patient characteristics were compared among treatment regimen cohorts using Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables. Statistical significance was reached for analysis results with a two-sided alpha-level below 0.05. All statistical analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC).

## **Results**

### *Specialty Pharmacy Data Sample Selection*

A total of 3,645 patients met the sample selection criteria from the specialty pharmacy databases (Table 1). Within the sample, 46.1% of patients were on prophylactic FVIII treatment and 53.9% were receiving on-demand treatment. Patients receiving prophylactic treatment were on average 10.1 years younger than patients receiving the on-demand treatment (mean age, prophylactic: 16.1 years; on-demand: 26.2 years). Figure 2 shows a scatterplot of the distribution of treatment regimens of patients with hemophilia A by age and total annual FVIII IUs dispensed in

TABLE 1  
HERE

FIGURE 2  
HERE

the specialty databases. For increasing age, annual units of FVIII increased on average for both treatment regimens, with the increase in units more pronounced for younger patients receiving prophylactic treatment. At every age, quadratic distribution curves show that patients on prophylactic treatment are expected to receive more units of FVIII annually, supporting the underlying assumption of the algorithm developed that higher annual FVIII IUs is indicating of increased likelihood of receiving prophylactic treatment.

### ***Calibration of Treatment Regimen Prediction Algorithm***

The optimization of the algorithm required iteratively evaluating all possible combinations of  $T_1$ ,  $T_2$ , and each observed value of annual FVIII units within the resulting age categories as cut-offs. To reduce the computational burden of this process, we limited the upper bound of  $T_2$  to 35. This resulted in a total of 45,786 possible combinations. Of these, 20,358 (44.5%) met the requirements of PPV and NPV greater than 0.80. These candidate algorithms were ranked based on the product of their sensitivity and specificity.

TABLE 2 HERE
-----------------

The ten best performing algorithms are listed in Table 2. Across these ten candidate algorithms, as well as the subsequent 55 algorithms,  $T_2$  was determined to be age 21.  $T_1$  varied slightly among the top candidate algorithms, taking values of 6 or 7, but the cut-offs for the annual units of FVIII across the algorithms' first two age categories shows strong consistency. Overall, the performance of the top 10 candidate algorithms was robust, with performance measures varying by less than 1%: sensitivity ranged from 0.857 to 0.863, specificity ranged from 0.843 to 0.848, and their product ranged from 0.7273 to 0.7278. The best performing algorithm (Candidate 1 in Table 2) has a sensitivity of 0.860, a specificity of 0.846, a PPV of 0.827 and an NPV of 0.877. The optimal age groups were determined to be 2 to 7, 8 to 12, 13 to 16, 17 to 21, and 22 and above, with cut-offs of annual FVIII IUs of 16,480 IU, 32,770 IU, 66,920 IU, 122,757 IU, and 204,552 IU for each age group, respectively.

**Medicaid Sample Selection and Predictive Output of the Treatment Pattern Algorithm**

TABLE 3 HERE
-----------------

A total of 2,408 Medicaid patients were identified as having at least 2 diagnoses for hemophilia A, with 796 of those having at least 2 pharmacy claims for FVIII (Table 3). Considering these 796 patients among the approximately 7.4 million males in the combined five State Medicaid databases, the projected population rate of 1 in 9,296 males is close to the national prevalence estimate of 1 in approximately 13,000 males.<sup>3</sup> After applying the remaining sample selection criteria, a total of 448 patients were included from the Medicaid databases.

Applying the parameters of the best performing algorithm to the Medicaid sample resulted in a nearly equal split of patients identified as receiving prophylactic (225 [50.2%]) versus on-demand treatment (223 [49.8%]). Younger patients aged 2 to 16 were more likely to receive prophylactic treatment, patients 17 to 21 years old were as likely to receive either one of the regimens, and patients 22 and older predominantly received on-demand treatment ( $p < 0.0001$ ).

**Baseline Characteristics of Medicaid Patients**

TABLE 4 HERE
-----------------

Table 4 compares baseline characteristics of patients in the two regimen cohorts. Patients receiving prophylactic FVIII therapy were 8 years younger on average than patients receiving on-demand treatment (mean age, prophylactic: 10.7 years old; on-demand: 18.7 years old;  $p < 0.0001$ ). Both groups of patients were followed up in the Medicaid databases for an average of more than 5.5 years. The distribution of index dates was similar for the two treatment regimens between 1996 and 2011, though a statistically significant difference was observed ( $p = 0.0428$ ). The primary exceptions to the equal distribution occur for index dates in 1996-1997, when on-demand treatment was more frequently used than prophylactic treatment (21.5% versus 10.2% of patients,  $p = 0.0011$ ), and for index dates in 2006-2007, when prophylactic treatment was more frequently used than on-demand treatment (12.9% versus 7.2% of,  $p = 0.0443$ ).

The older on-demand treatment cohort experienced more medical comorbidities. Patients receiving on-demand treatment were four times more likely than those receiving prophylaxis to have hepatitis C (5.4% versus 1.3%,  $p = 0.0173$ ) and three times more likely to have HIV (12.6% versus 3.6%,  $p = 0.0005$ ). The difference between the cohorts' rates of viral infections may explain the greater use of antivirals (14.2% versus 4.8%,  $p = 0.0007$ ) and analgesics (20.1% versus 10.9%,  $p = 0.0072$ ) among patients' receiving on-demand treatment. Patients receiving on-demand therapy exhibited marginally higher rates of arthritis, liver fibrosis, and hypertension, but no statistically significant difference in these or other cardiovascular conditions were observed. The only additional difference in concomitant drug use was that of anti-coagulants by patients receiving prophylactic treatment at a rate more than 5 times that of patients receiving on-demand therapy ( $p = 0.0019$ ), though the rate was overall small.

## Discussion

While current clinical guidelines recognize the benefit of primary prophylactic treatment of hemophilia A and recommend it for young patients [1], opinions diverge on continuing prophylaxis and/or initiating secondary prophylaxis in older patients [9, 23, 25, 32, 33]. Real-world data on comparative clinical and economic outcomes for patients with hemophilia A receiving prophylactic versus on-demand treatment would provide useful evidence to decision makers – physicians, patients, and payers. In this study, we developed a method of assessing patient FVIII treatment regimen in health care claims data, thus providing a useful tool in using a heretofore inaccessible but rich source of information on treatment patterns and outcomes of patients with hemophilia A.

We first designed and calibrated a flexible classification algorithm that allows identification of prophylactic versus on-demand FVIII treatment regimens among patients with hemophilia A in health care claims databases. Estimated using a large sample of specialty pharmacy patients, the best performing algorithm achieved a sensitivity of 0.860, specificity of 0.846, PPV of 0.827, and

NPV of 0.877. The overall performance of the algorithm design was robust to small variations in age groups and annual FVIII cut-offs.

Applying the top performing algorithm to a population of 448 Medicaid patients, we found that while overall prophylactic and on-demand treatment with FVIII are almost equally used in this population of patients with hemophilia A, a greater proportion of patients under 17 years of age received prophylactic FVIII treatment. These results are consistent with current clinical guidelines and several survey reporting that older patients generally receive on-demand treatment, starting in adolescence [11, 34], as treatment adherence to prophylaxis tends to decrease at that age [11]. In the present research, we believe that underestimation of prophylactic treatments was minimal as the observed proportion of patients on a prophylactic regimen, especially in the younger age group, was actually higher than that previously reported by the Centers for Disease Control and Prevention (all severity levels): 2–5 years, 37.6%; 6–12 years, 43.4%; 13–18 years, 33.1%; 19+ years, 15.7% [35].

Assessing the patient characteristics in the baseline period, the older cohort of patients receiving on-demand treatment were more likely to have viral infections, reflecting the fact that more patients may have initiated FVIII treatment with plasma-derived concentrates containing virus contaminants in the 1970s and 1980s [5, 36]. Overall, we found no evidence suggesting sample selection which would bias future analyses.

This research is subject to some limitations. First, there is a level of uncertainty associated with the use of a prediction algorithm to estimate actual FVIII regimens. The design of the algorithm was limited to the common fields available in both the specialty pharmacy and health care claims databases. Age was used as a proxy of weight, with age groupings empirically optimized to further attempt to overcome the lack of weight information. Moreover, disease severity is an important determinant in the amount of FVIII a patient needs and it could not be controlled for. Compounding the issue of limited information is the measurement error introduced as a result of implementing any imperfect prediction algorithm. If the algorithm equally (randomly) misclassified

patients' regimens, differences between patients receiving prophylactic versus on-demand therapy would be smaller in magnitude and as a result harder to detect statistically.

A second limitation results from the choice of measure for evaluating the candidate algorithms. We chose to maximize the product of the sensitivity and specificity at the expense of other measures of algorithm performance (PPV and NPV). This choice is consistent with the motivation of correctly identifying a patient's true FVIII treatment regimen. However, for comparative outcomes analyses in claims data, an alternative approach may include a greater focus on a high PPV. A higher PPV suggests that those patients misclassified after applying the algorithm are more likely to be patients receiving prophylactic treatment (misclassified as receiving on-demand). Under the hypothesis that prophylaxis improves patient outcomes, the misclassification would improve the average outcome of the on-demand cohort, such that differences between patients receiving prophylactic versus on-demand therapy would be smaller in magnitude and as a result harder to detect statistically. Thus, real-world applications of the algorithm would likely produce conservative estimates of the benefit associated with prophylactic FVIII therapy.

The third set of limitations is primarily inherent to analysis using specialty pharmacy records and health care claims data. Although the current algorithm was developed using a large sample of specialty pharmacy users, each patient contributed only one year of data, and any evolution of a patient's treatment regimen was ignored. Though this limitation bolsters our confidence in the observed regimen, it may also affect the stability and generalizability of the algorithm beyond its selected age-specific thresholds. Further refinement of the classification algorithm using larger populations and longitudinal data may be warranted. Within the claims data, we chose to use a patient's earliest eligible period of observation, so that the treatment regimen comparisons reflect treatment patterns used earlier in patients' observation period. Because treatment patterns have been found to be dynamic and age-specific [11, 34, 37], we believe that capturing the earliest treatment is important, but this may result in a less accurate picture of

treatment patterns in adults. Finally, because health care claims data do not include laboratory values and physician notes, this analysis infers or omits important components of FVIII therapy, such as underlying disease severity and blended prophylaxis/on-demand treatment regimens.

### ***Conclusions***

This study is the first to use a validated algorithm in order to identify patients with hemophilia A receiving prophylactic versus on-demand FVIII treatment in health care claims. Claims data have the advantage of both presenting for the analysis of large groups of patients with a rare disease than could be obtained in most non-retrospective observational studies, as well as providing instant information compared to carrying out long-term longitudinal studies. With an average patient observation period of more than 5.5 years, claims data from Medicaid programs used in the current application shows the potential for extensive follow up to assess the relative efficacy of prophylaxis versus on-demand FVIII regimens in decreasing the incidence of bleeding events and other outcomes. Further studies are warranted to investigate outcomes of patients receiving these treatment regimens in a real-world setting.

### **Acknowledgements**

The authors thank Alex Trahey, BA, and Wendy Cheng, MPhil, MPH, employees of Analysis Group Inc., for their research assistance, and Ana Bozas, PhD, and Lucia Antràs, PhD, also of Analysis Group Inc., for contributing to the preparation and editing of the manuscript.

### **Author Contributions**

All authors contributed to the research design and interpretation of data. JL and FV performed the statistical analyses and drafted the manuscript. JP, AG, and MSD critically revised the manuscript. All authors reviewed the paper and approved the final version.

## **Disclosures**

Financial support for this study was provided by Bayer HealthCare Pharmaceuticals Inc. JP and AG are employees of Bayer HealthCare Pharmaceuticals Inc. and own stock/stock options. JL, MSD, and FV are employees of Analysis Group, which has received research grants from Bayer HealthCare Pharmaceuticals Inc.

## References

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Kitchen S, Llinas A *et al.* Guidelines for the management of hemophilia. *Haemophilia* 2013; 19: e1–47.
2. Soucie JM, Evatt B, Jackson D. Occurrence of hemophilia in the United States. The Hemophilia Surveillance System Project Investigators. *Am J Hematol* 1998; 59: 288–94.
3. Health Grades Inc. Prevalence and incidence of hemophilia. In: *RightDiagnosis.com* 2009.
4. Zaiden RA, Jardine LF, Lorenzana A *et al.* Hemophilia A. In: *Medscape Reference*.
5. Young G. New challenges in hemophilia: long-term outcomes and complications. *Am Soc Hematol Educ Program* 2012 ; 2012: 362–8.
6. National Hemophila Foundation. What are Bleeding Disorders? Psychosocial Issues. In: *hemophilia.org* 2006.
7. Berntorp E, Boulyjenkov V, Brettler D, Chandy M, Jones P, Lee C *et al.* Modern treatment of haemophilia. *Bull World Health Organ* 1995; 73: 691–701.
8. Berntorp E, Astermark J, Björkman S, Blanchette VS, Fischer K, Giangrande PL *et al.* Consensus perspectives on prophylactic therapy for haemophilia: summary statement. *Haemophilia* 2003; 9 Suppl 1: 1–4.
9. Tagliaferri A, Di Perna C, Rivolta GF. Secondary prophylaxis in adolescent and adult haemophiliacs. *Blood Transfus* 2008; 6 Suppl 2: s17–20.
10. Collins PW. Personalized prophylaxis. *Haemophilia* 2012; 18 Suppl 4: 131–5.
11. Zappa S, McDaniel M, Marandola J, Allen G. Treatment trends for haemophilia A and haemophilia B in the United States: results from the 2010 practice patterns survey. *Haemophilia* 2012; 18: e140–53.

12. Manco-Johnson MJ, Kempton CL, Reding MT, Lissitchkov T, Goranov S, Gercheva L *et al.* Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART). *J Thromb Haemost* 2013; 11: 1119–27.
13. Valentino LA, Mamonov V, Hellmann A, Quon DV, Chybicka A, Schroth P *et al.* A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *J Thromb Haemost* 2012; 10: 359–67.
14. Gringeri A, Lundin B, von Mackensen S, Mantovani L, Mannucci PM, ESPRIT Study Group. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J Thromb Haemost* 2011; 9: 700–10.
15. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R *et al.* Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; 357: 535–44.
16. Bayer Healthcare Pharmaceuticals Inc. BAY14-2222 Prophylaxis and Joint Function Improvement ( Adults). In: *ClinicalTrials.gov*, Bethesda (MD): National Library of Medicine (US). December 21, 2007 – December 6, 2012.
17. Manco-Johnson MJ, Sanders J, Ewing N, Rodriguz N, Tarantino M, Humphries T, TEEN/TWEN Study Group. Consequences of switching from prophylactic treatment to on-demand treatment in late teens and early adults with severe haemophilia A: the TEEN/TWEN study. *Haemophilia* 2013; 19: 727–35.
18. Collins P, Faradji A, Morfini M, Enriquez NM, Schwartz L. Efficacy and safety of secondary prophylactic vs. on-demand sucrose-formulated recombinant factor VIII treatment

- in adults with severe hemophilia A: results from a 13-month crossover study. *J Thromb Haemost* 2010; 8: 83–9.
19. Stobart K, Iorio A, Wu JK. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. *Cochrane Database Syst Rev* 2006; (2): CD003429.
  20. Berntorp E, Fischer K, Miners A. Models of prophylaxis. *Haemophilia* 2012; 18 Suppl 4: 136–40.
  21. Fischer K, Astermark J, van der Bom JG, Ljung R, Berntorp E, Grobbee DE van den Berg HM. Prophylactic treatment for severe haemophilia: comparison of an intermediate-dose to a high-dose regimen. *Haemophilia* 2002; 8: 753–60.
  22. Fischer K, Steen Carlsson K, Petrini P, Holmström M, Ljung R, van den Berg HM, Berntorp E. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s. *Blood* 2013; 122: 1129–36.
  23. Tagliaferri A, Franchini M, Coppola A, Rivolta GF, Santoro C, Rossetti G *et al.* Effects of secondary prophylaxis started in adolescent and adult haemophiliacs. *Haemophilia*. 2008; 14: 945–51.
  24. Steen Carlsson KS, Höjgård S, Glomstein A, Lethagen S, Schulman S, Tengborn L *et al.* On-demand vs. prophylactic treatment for severe haemophilia in Norway and Sweden: differences in treatment characteristics and outcome. *Haemophilia* 2003; 9: 555–66.
  25. Fischer K, Van Den Berg M. Prophylaxis for severe haemophilia: clinical and economical issues. *Haemophilia* 2003; 9: 376–81.
  26. Schobess R, Kurnik K, Friedrichs F, Halimeh S, Krümpel A, Bidlingmaier C, Nowak-Göttl U. Effects of primary and secondary prophylaxis on the clinical expression of joint damage

- in children with severe haemophilia A. Results of a multicenter non-concurrent cohort study. *Thromb Haemost* 2008; 99: 71–6.
27. Blankenship CS. To manage costs of hemophilia, patients need more than clotting factor. *Biotechnol Healthc* 2008; 5: 37–40.
28. Glaros AG, Kline RB. Understanding the accuracy of tests with cutting scores: the sensitivity, specificity, and predictive value model. *J Clin Psychol* 1988; 44: 1013–23.
29. Dolan G, Cruz JA, Steinhagen-Thiessen E, Kessler C, Haaning J, Altisent C *et al.* Advances in hemophilia care: report of two symposia at the Hemophilia 2010 World Congress. *Adv Ther* 2012; 29 Suppl 1: 1–16.
30. Khleif AA, Rodriguez N, Brown D, Escobar MA. Multiple Comorbid Conditions among Middle-Aged and Elderly Hemophilia Patients: Prevalence Estimates and Implications for Future Care. *J Aging Res* 2011; 2011: 985703.
31. Fransen van de Putte DE, Fischer K, Pulles AE, Roosendaal G, Biesma DH, Schutgens RE, Mauser-Bunschoten EP. Non-fatal cardiovascular disease, malignancies, and other co-morbidity in adult haemophilia patients. *Thromb Res* 2012; 130: 157–62.
32. Mondorf W, Kalnins W, Klamroth R. Patient-reported outcomes of 182 adults with severe haemophilia in Germany comparing prophylactic vs. on-demand replacement therapy. *Haemophilia* 2013; 19: 558–63.
33. Noone D, O’Mahony B, van Dijk JP, Prihodova L. A survey of the outcome of prophylaxis, on-demand treatment or combined treatment in 18-35-year old men with severe haemophilia in six countries. *Haemophilia* 2013; 19: 44–50.
34. Butler RB, McClure W, Wulff K. Practice patterns in haemophilia A therapy--a survey of treatment centres in the United States. *Haemophilia* 2003; 9: 549–54.

35. U. S. Centers for Disease Control and Prevention. *Summary Report of UDC Activity – National – Risk by Age (Hemophilia)*. Atlanta, GA, USA: 2013.
36. Franchini M. The modern treatment of haemophilia: a narrative review. *Blood Transfus* 2013; 11: 178–82.
37. Geraghty S, Dunkley T, Harrington C, Lindvall K, Maahs J, Sek J. Practice patterns in haemophilia A therapy -- global progress towards optimal care. *Haemophilia* 2006; 12: 75–81.

## Tables and Figures

**Table 1. Specialty Pharmacy Data Sample Selection**

<i>Step</i>	<i>Criterion</i>	<i>Total</i>
1	All Patients Receiving FVIII	5,451
2	Male Patients	5,406
3	Patients With At Least 1 Diagnosis for Hemophilia A <sup>1</sup>	5,321
4	Patients At Least 2 Years of Age	5,001
5	Patients Without Bypassing Agents <sup>2</sup>	4,912
6	Patients with Only 1 Observed Treatment Regimen for Hemophilia (Prophylactic or On-Demand)	3,645

**Notes:**

1. ICD-9-CM code 286.0

2. Bypassing agents included anti-inhibitor and FVIIa therapies.

**Table 2. Best Performing Algorithm Parameters and Performance Measures**

Algorithm	Age Group Cutoffs		Factor VIII Units To Determine Regimen Type <sup>1</sup>					Sensitivity	Specificity	PPV <sup>2</sup>	NPV <sup>3</sup>
	$T_1$	$T_2$	Age 2 to $T_1$	Age ( $T_1+1$ ) to 12	Age 13 to 16	Age 17 to $T_2$	Age > $T_2$				
<b>1</b>	<b>7</b>	<b>21</b>	<b>16,480</b>	<b>32,770</b>	<b>66,920</b>	<b>122,757</b>	<b>204,552</b>	<b>0.860</b>	<b>0.846</b>	<b>0.827</b>	<b>0.877</b>
2	7	21	16,723	32,770	66,920	122,757	204,552	0.860	0.846	0.827	0.876
3	7	21	16,723	32,770	66,920	122,757	207,090	0.859	0.847	0.827	0.876
4	7	21	16,480	32,770	66,920	117,946	204,552	0.863	0.843	0.825	0.878
5	6	21	16,480	32,770	66,920	122,757	204,552	0.859	0.847	0.828	0.875
6	7	21	16,723	32,770	66,920	117,946	204,552	0.862	0.844	0.825	0.878
7	6	21	16,723	32,770	66,920	122,757	204,552	0.858	0.848	0.828	0.875
8	7	21	16,480	32,770	66,920	120,020	204,552	0.862	0.844	0.825	0.877
9	6	21	16,723	32,770	66,920	122,757	207,090	0.857	0.848	0.828	0.875
<b>10</b>	<b>6</b>	<b>21</b>	<b>16,480</b>	<b>32,770</b>	<b>66,920</b>	<b>117,946</b>	<b>204,552</b>	<b>0.861</b>	<b>0.845</b>	<b>0.826</b>	<b>0.877</b>

**Notes:**

1. Regimen type is based on age and total FVIII units dispensed during the index year. Patients' regimens above the given cutoff were classified as receiving prophylactic treatment, and those below the cutoff were classified as receiving on-demand treatment.  $T_1$  and  $T_2$  are age group cutoffs defined empirically within the algorithm optimization process.

2. PPV: positive predictive value

3. NPV: negative predictive value

**Table 3. Medicaid Data Sample Selection**

<i>Step</i>	<i>Criterion</i>	<i>Total</i>	<i>Florida</i>	<i>Iowa</i>	<i>Kansas</i>	<i>Missouri</i>	<i>New Jersey</i>
<b>1</b>	All Patients With At Least 2 Diagnoses for Hemophilia A <sup>1</sup>	2,408	1,006	166	164	435	637
<b>2</b>	Patients With At Least 2 Pharmacy Claims for FVIII	796	341	67	54	165	169
<b>3</b>	Patients with Continuous Insurance Eligibility At Least 6 Months Before and 1 Year After Any FVIII Pharmacy Claim	616	277	44	47	144	104
<b>4</b>	No Claims for Bypassing Agents <sup>2</sup> or Desmopressins During Observation Period	515	228	37	37	122	91
<b>5</b>	Patients without von Willebrand Disease <sup>3</sup>	448	187	28	36	114	83

**Notes:**

1. ICD-9-CM code 286.0

2. Bypassing agents included anti-inhibitor and FVIIa therapies.

3. ICD-9-CM code 286.4. No more than one day with a diagnosis was allowed at any point during the study period.

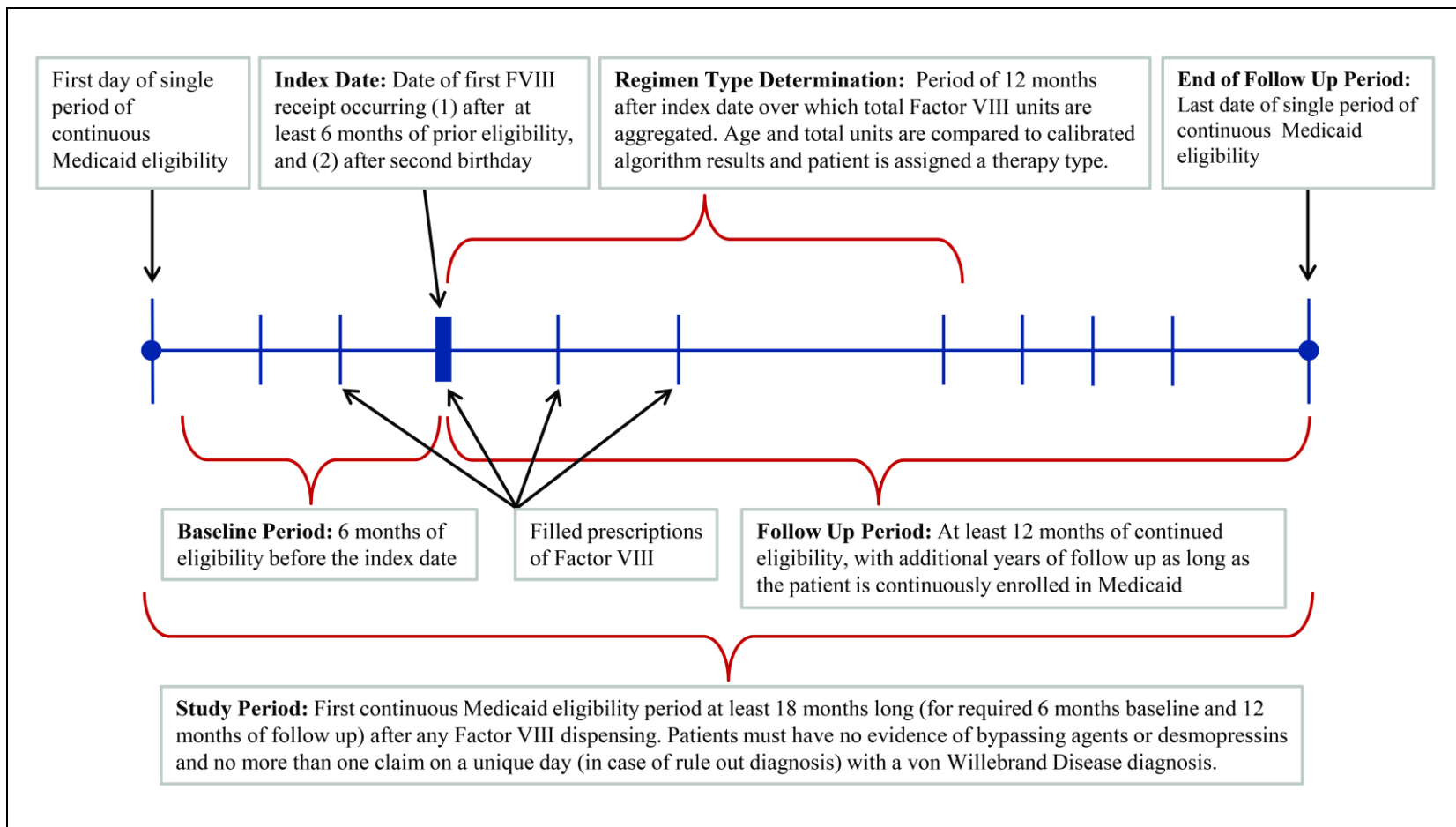
**Table 4. Baseline Characteristics of Patients in Medicaid Data Receiving Prophylactic and On-Demand FVIII Therapy**

<i>Patient Characteristics<sup>1</sup></i>	<i>Patients Receiving</i>	<i>Patients Receiving</i>	<i>P-value<sup>2</sup></i>
	<i>Prophylactic Treatment</i>	<i>On-Demand Treatment</i>	
	<i>N = 225</i>	<i>N = 223</i>	
<b>Age at Index Date</b> , mean $\pm$ SD <sup>3</sup>	10.7 $\pm$ 9.8	18.7 $\pm$ 14.3	<.0001
Median [IQR] <sup>4</sup>	7.7 [3.5 - 14.5]	16.5 [5.9 - 28.0]	
Age Groups, n (%)			
2 to 7	104 (46.2%)	67 (30.0%)	0.0004
8 to 12	44 (19.6%)	19 (8.5%)	0.0008
13 to 16	34 (15.1%)	20 (9.0%)	0.0459
17 to 21	20 (8.9%)	27 (12.1%)	0.2663
22 and above	23 (10.2%)	90 (40.4%)	<.0001
<b>Years of Follow Up</b> , mean $\pm$ SD	5.5 $\pm$ 3.9	5.6 $\pm$ 4.1	0.8135
<b>Year of Index Date</b> , n (%)			
1996 to 1997	23 (10.2%)	48 (21.5%)	0.0011
1998 to 1999	51 (22.7%)	44 (19.7%)	0.4472
2000 to 2001	28 (12.4%)	26 (11.7%)	0.7985
2002 to 2003	30 (13.3%)	28 (12.6%)	0.8064
2004 to 2005	20 (8.9%)	24 (10.8%)	0.5053
2006 to 2007	29 (12.9%)	16 (7.2%)	0.0443
2008 to 2009	27 (12.0%)	25 (11.2%)	0.7943
2010 to 2011	17 (7.6%)	12 (5.4%)	0.3497
<b>State</b> , n (%)			
Florida	114 (50.7%)	73 (32.7%)	0.0001
Iowa	16 (7.1%)	12 (5.4%)	0.4495
Kansas	17 (7.6%)	19 (8.5%)	0.7073
Missouri	69 (30.7%)	45 (20.2%)	0.0108
New Jersey	9 (4.0%)	74 (33.2%)	<.0001
<b>Comorbidities</b> , n (%)			
HIV	8 (3.6%)	28 (12.6%)	0.0005
Hepatitis C	3 (1.3%)	12 (5.4%)	0.0173
Osteoporosis	0 (0.0%)	0 (0.0%)	–
Arthritis	3 (1.3%)	6 (2.7%)	0.3060
Liver Fibrosis/Cirrhosis	2 (0.9%)	2 (0.9%)	0.9928
Ischemic Heart Disease	0 (0.0%)	0 (0.0%)	–
Myocardial Infarction	0 (0.0%)	0 (0.0%)	–
Hypertension	0 (0.0%)	3 (1.3%)	0.0809
Hypercholesterolemia	0 (0.0%)	0 (0.0%)	–
Stroke	0 (0.0%)	0 (0.0%)	–
<b>Concomitant Drug Use</b> , n (%)			
Analgesics	25 (10.9%)	44 (20.1%)	0.0072
Anti-coagulants	17 (7.4%)	3 (1.4%)	0.0019
Anti-rheumatics	0 (0.0%)	0 (0.0%)	–
Anti-neoplastics	1 (0.4%)	3 (1.4%)	0.2939
Antivirals	11 (4.8%)	31 (14.2%)	0.0007
Antibiotics	62 (27.1%)	64 (29.2%)	0.6130

**Notes:**

1. Characteristics based on baseline period of 180 days before the index date.
2. P-values calculated using Wilcoxon rank sum tests for continuous variables and chi-squared tests for categorical variables.
3. SD: standard deviation
4. IQR: interquartile range

**Figure 1. Medicaid Health Care Claims Study Design**



**Figure 2. Distributions of Total Annual Dispensed FVIII IUS for Patients Receiving Prophylactic and On-Demand FVIII Therapy from Specialty Pharmacies**

