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

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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 ≥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, ≥2 filled FVIII prescriptions after age 2, continuous coverage ≥6 months before and ≥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.
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 FVII 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
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.

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

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. 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 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.

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**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


## Tables and Figures

### Table 1. Specialty Pharmacy Data Sample Selection

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<thead>
<tr>
<th>Step</th>
<th>Criterion</th>
<th>Total</th>
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<td>1</td>
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<td>Male Patients</td>
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<td>Patients With At Least 1 Diagnosis for Hemophilia A&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>4</td>
<td>Patients At Least 2 Years of Age</td>
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<td>Patients Without Bypassing Agents&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>Patients with Only 1 Observed Treatment Regimen for Hemophilia (Prophylactic or On-Demand)</td>
<td>3,645</td>
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**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

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Age Group Cutoffs</th>
<th>Factor VIII Units To Determine Regimen Type(^1)</th>
<th>Sensitivity</th>
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<td>117,946</td>
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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

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<th>Step</th>
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<th>Kansas</th>
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<th>New Jersey</th>
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<td>2,408</td>
<td>1,006</td>
<td>166</td>
<td>164</td>
<td>435</td>
<td>637</td>
</tr>
<tr>
<td>2</td>
<td>Patients With At Least 2 Pharmacy Claims for FVIII</td>
<td>796</td>
<td>341</td>
<td>67</td>
<td>54</td>
<td>165</td>
<td>169</td>
</tr>
<tr>
<td>3</td>
<td>Patients with Continuous Insurance Eligibility At Least 6 Months Before and 1 Year After Any FVIII Pharmacy Claim</td>
<td>616</td>
<td>277</td>
<td>44</td>
<td>47</td>
<td>144</td>
<td>104</td>
</tr>
<tr>
<td>4</td>
<td>No Claims for Bypassing Agents&lt;sup&gt;2&lt;/sup&gt; or Desmopressins During Observation Period</td>
<td>515</td>
<td>228</td>
<td>37</td>
<td>37</td>
<td>122</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>Patients without von Willebrand Disease&lt;sup&gt;3&lt;/sup&gt;</td>
<td>448</td>
<td>187</td>
<td>28</td>
<td>36</td>
<td>114</td>
<td>83</td>
</tr>
</tbody>
</table>

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 FVIIa Therapy

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

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

First day of single period of continuous Medicaid eligibility

**Index Date:** Date of first FVIII receipt occurring (1) after at least 6 months of prior eligibility, and (2) after second birthday

**Regimen Type Determination:** Period of 12 months after index date over which total Factor VIII units are aggregated. Age and total units are compared to calibrated algorithm results and patient is assigned a therapy type.

**End of Follow Up Period:** Last date of single period of continuous Medicaid eligibility

**Baseline Period:** 6 months of eligibility before the index date

Filled prescriptions of Factor VIII

**Follow Up Period:** At least 12 months of continued eligibility, with additional years of follow up as long as the patient is continuously enrolled in Medicaid

**Study Period:** First continuous Medicaid eligibility period at least 18 months long (for required 6 months baseline and 12 months of follow up) after any Factor VIII dispensing. Patients must have no evidence of bypassing agents or desmopressins and no more than one claim on a unique day (in case of rule out diagnosis) with a von Willebrand Disease diagnosis.
Figure 2. Distributions of Total Annual Dispensed FVIII IUs for Patients Receiving Prophylactic and On-Demand FVIII Therapy from Specialty Pharmacies

Note: Each marker in the scatterplot represents an individual patient's total prescribed FVIII IUs over 12 months of observation. Modeled distribution curves are based on the second-order polynomial function of the total prescribed dose by age for the respective regimen.