

# *“Best of INFORMS—Modeling the global latent therapeutic demand for hemophilia A”*

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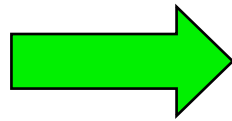
# ***EXECUTIVE SUMMARY***

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**A new model based on probability-encoding principles and discrete approximation techniques from decision analysis was developed to estimate the global latent therapeutic demand (LTD) for hemophilia A using population-based epidemiology and treatment modalities. The LTD model resulted in a better understanding of the future therapeutic needs of the global hemophilia community and improved decision-making within Bayer.**

# *AGENDA*

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**INTRODUCTION**

**METHODOLOGY**

**RESULTS**

**CONCLUSIONS**

## ***What is latent therapeutic demand (LTD)?***

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***Latent therapeutic demand (LTD) is an estimate for the underlying demand on how physicians would prescribe treatment and how patients would follow or comply with the prescribed treatment if ample supplies of drugs were available and affordable***

**To our knowledge, this is first study to model the variability in population-based epidemiological data together with the variability in treatment modalities to estimate LTD (hemophilia A)**

**With an improved understanding of LTD, the industry can better respond to the needs of the global hemophilia A community**

**improve chronic morbidity in the developed world**

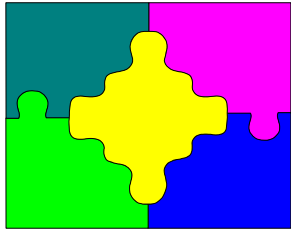
**improve mortality in the developing world**

## *When it comes to hemophilia A, did you know...*

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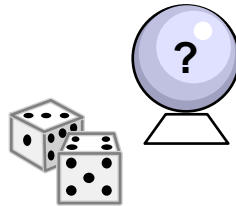
- **Hemophilia A is an inherited genetic disorder in which the blood does not clot properly due to the absence or deficiency of factor VIII, a protein in human blood critical for blood coagulation**
- **Hemophilia A is estimated to affect nearly 400,000 people worldwide**
- **About 80% of the world's hemophilia population remain untreated**
  - **Left untreated, severe hemophiliacs die**
  - **Without proper treatment, hemophiliacs live in crippling pain and chronic joint destruction**
- **People with severe hemophilia A (<1%) have frequent spontaneous bleeding episodes while those with a moderate or a mild form of the disease have less bleeds**
- **To treat hemophilia A, you must replace deficient factor VIII through intravenous infusions**
- **Factor VIII replacement drug therapy can stop the acute bleeding from hemophilia A when enough factor VIII reaches the bleeding site, but is not a cure**
- **Factor VIII drug therapy can also be used to prevent or minimize bleeding (prophylaxis)**

*The enormous costs and long timelines for R&D as well as the staggering odds against technical and commercial success make drug development decisions critically important and challenging.*



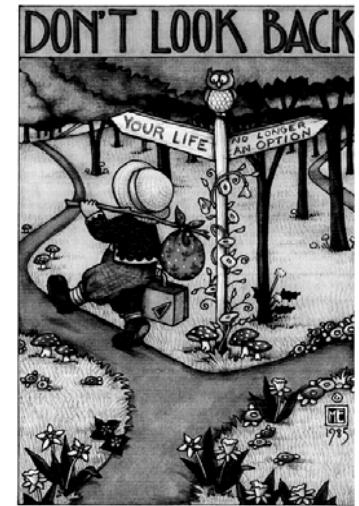
*Interdependencies*

*Uncertain & changing information*



*Cross-functional communication*

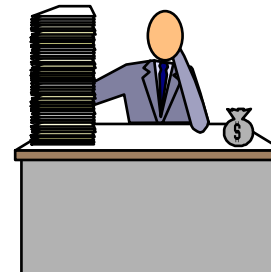
*Future looking*



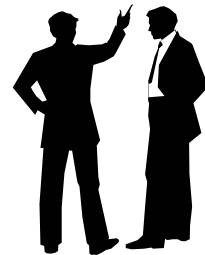
*Decisions subject to critical review*



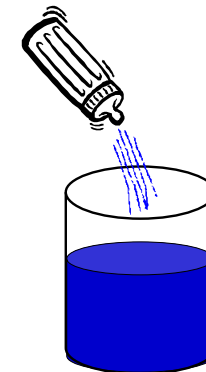
*Investments*



*Not enough resources*



*Differing views on what is most important*



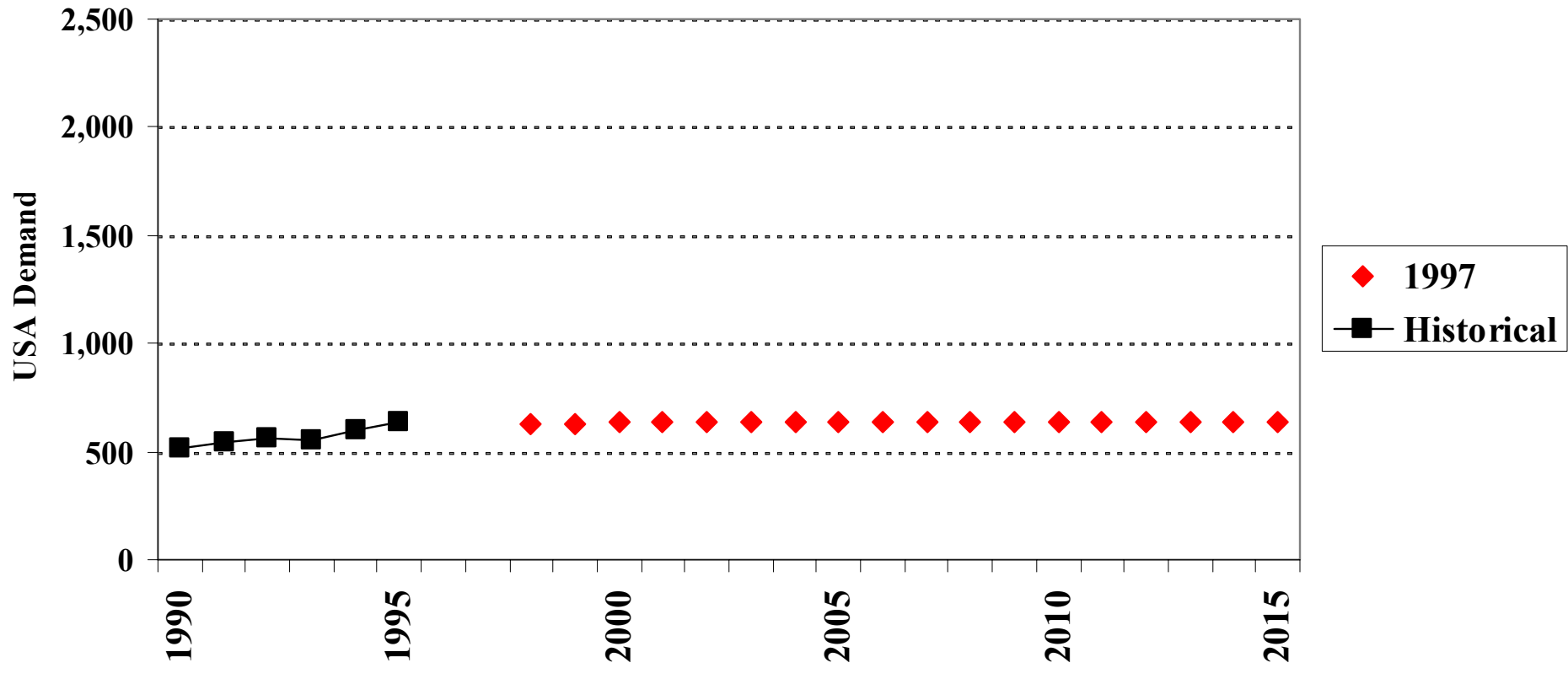
*Demand versus Supply*

*Bayer struggled for many years with strategic decisions regarding its drug for treating hemophilia A, in a large part due to a lack of confidence in the evolving demand estimates.*

<u>YOA</u>	<u>Task/Recommendation</u>	<u>Result</u>
1997	DA: Invest in 3rdGen product/facility	No action
1998	Market Research	Gather info on demand
1999	DA: Invest in 3rdGen product/facility	No action

**Why invest hundreds of millions of dollars in R&D and capital expenditures when the demand of factor VIII drugs seemed to be met by what the manufacturers already supply?**

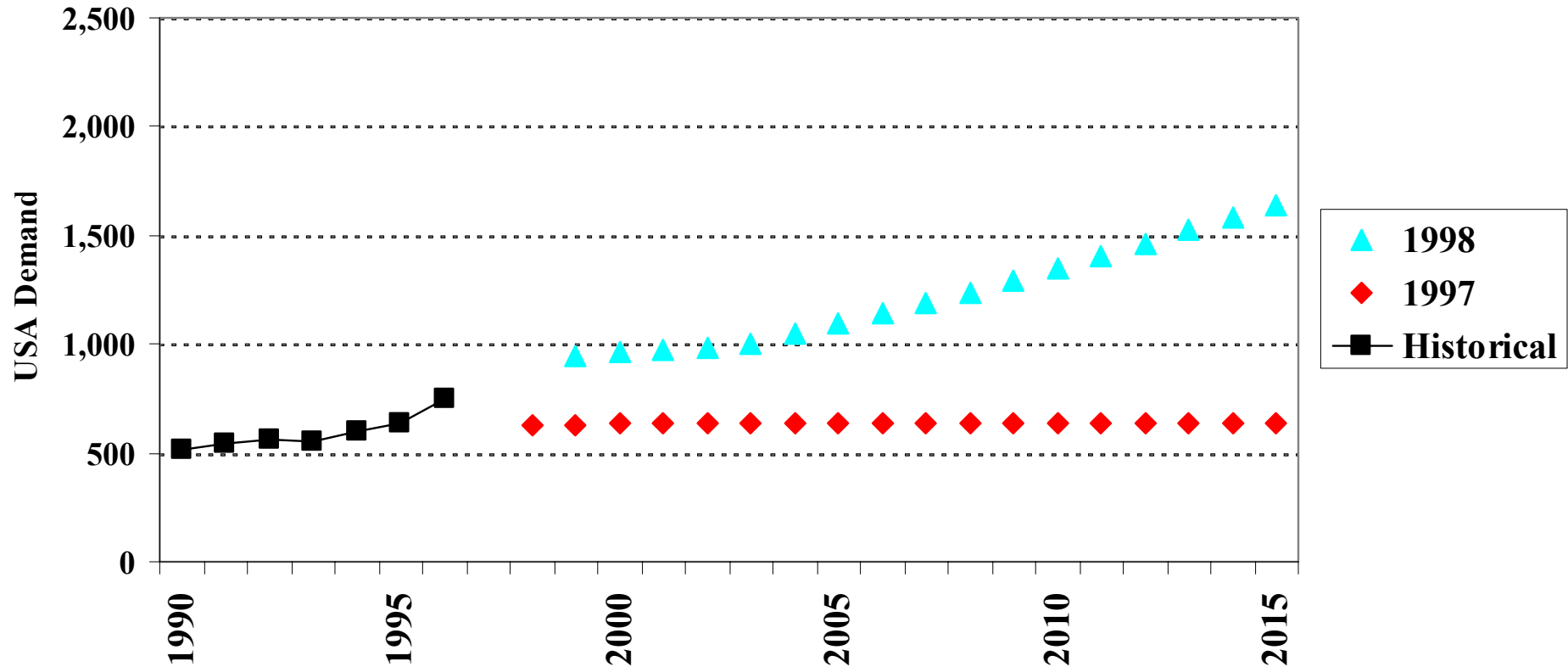
*In the 1997 decision analysis, historical sales were used to forecast a flat factor VIII demand in the United States.*



Data are for the United States with similar results in the other regions  
Historical sales (units sold) lags in reporting by 2 years  
1997 decision analysis: demand values are base-case single-point estimates



*In the 1998 market research study, the factor VIII demand in the United States was forecasted to trend like historical sales.*



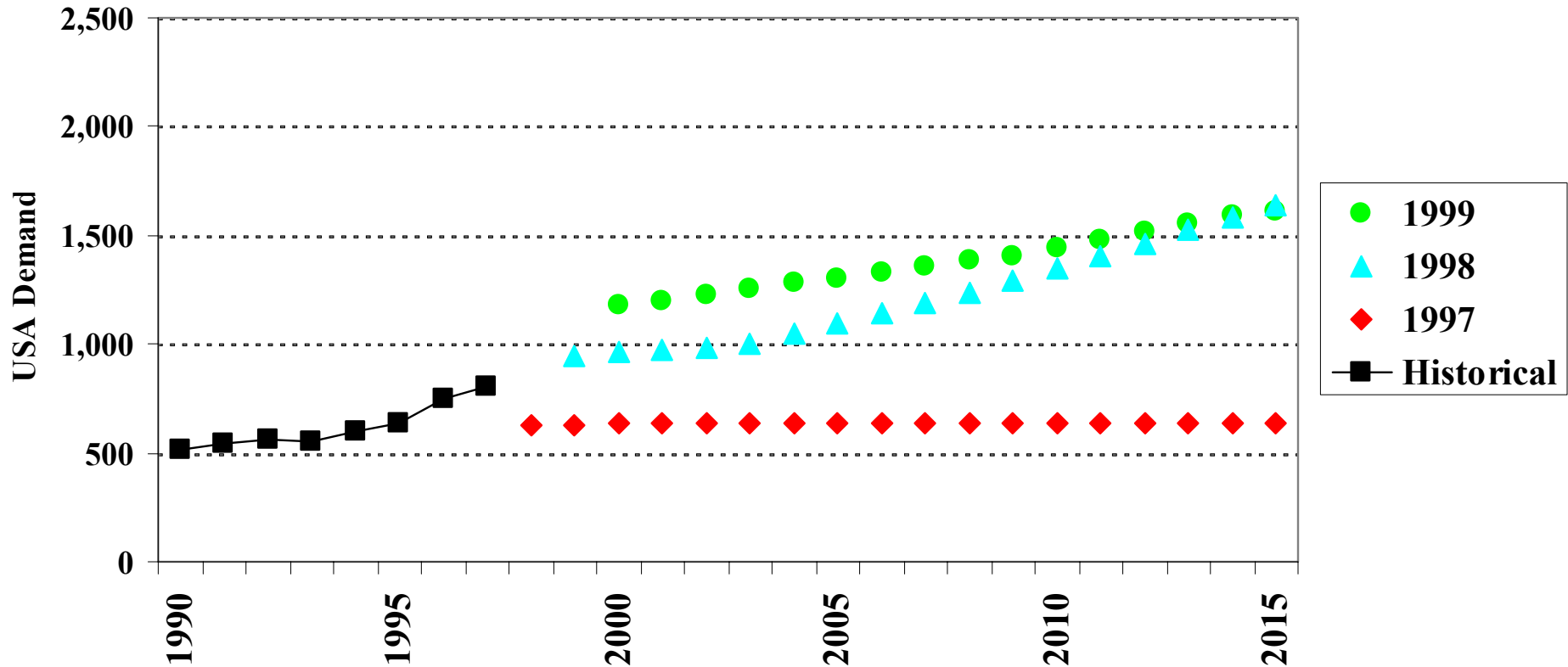
Data are for the United States with similar results in the other regions

Historical sales (units sold) lags in reporting by 2 years

1998 market research study: demand values are averages of a low-case and a high-case

1997 decision analysis: demand values are base-case single-point estimates

*In the 1999 decision analysis, the factor VIII demand in the United States was still forecasted to trend like historical sales.*



Data are for the United States with similar results in the other regions

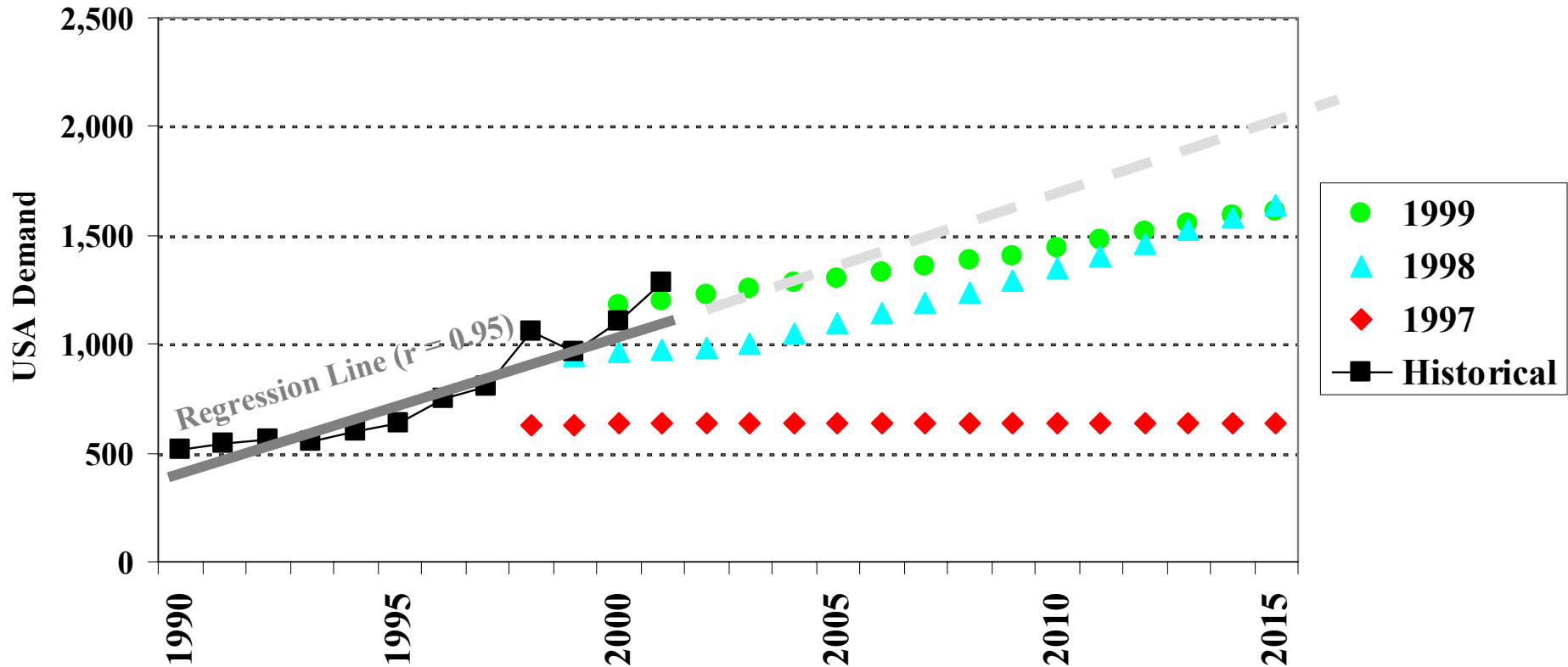
Historical supply (units sold) lags in reporting by 2 years

1999 decision analysis: demand values are probability-weighted averages

1998 market research study: demand values are averages of a low-case and a high-case

1997 decision analysis: demand values are base-case single-point estimates

*In summary, estimates for USA factor VIII demand in the 1997-99 analyses closely reflected historical sales and have led to strategic indecisiveness (why invest?) and lost opportunity.*



Data are for the United States with similar results in the other regions  
 Historical sales (units sold) lags in reporting by 2 years  
 1999 decision analysis: demand values are probability-weighted averages  
 1998 market research study: demand values are averages of a low-case and a high-case  
 1997 decision analysis: demand values are base-case single-point estimates

*The demand for factor VIII is difficult to estimate due to a lack of a therapeutic standard and uncertainty surrounding the epidemiology of hemophilia A.*

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- **Management of hemophilia A continues to evolve with technological developments and new treatment-related research**
- **No consensus on therapy (prophylaxis, episodic therapy, and immune tolerance induction therapy) resulting in variability in treatment modalities**
- **Inadequate quantities of factor VIII drugs caused by supply limitations have hampered efforts by the medical community to define the optimal treatment for patients with hemophilia A**
- **Reported prevalence of hemophilia A varies considerably in the developed world and even more so in the developing world**
- **Proportion of individuals with severe hemophilia A varies from 30% to 65%**
- **Proportion of people with hemophilia A is skewed toward the younger age groups reflecting excess mortality among the older age group due to the impact that AIDS and hepatitis has had on hemophiliacs**

# *AGENDA*

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**INTRODUCTION**



**METHODOLOGY**

**RESULTS**

**CONCLUSIONS**

***Rather than accepting supply-constrained historical sales forecasts from previous analyses, we developed the latent therapeutic demand (LTD) model.***

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- (1) We reviewed the medical literature on hemophilia A epidemiology and its treatment**
- (2) We discussed with medical and marketing experts the variables impacting latent therapeutic demand (LTD)**
- (3) We obtained approximate probability distributions for each random variable from published articles and medical experts**
- (4) We developed an influence diagram to represent the LTD model.**

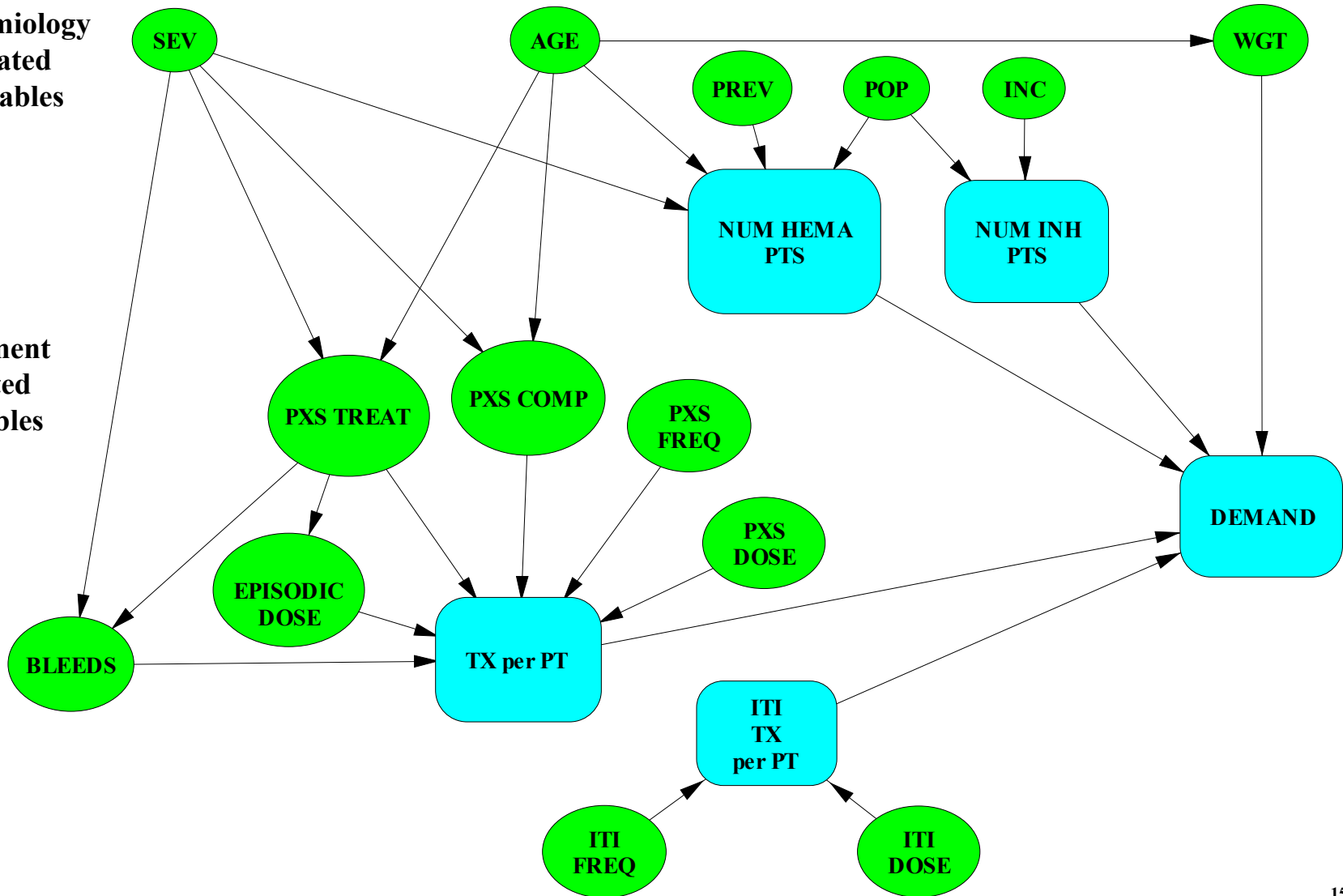
**The new demand estimates from the LTD model were not constrained by production capacity and therefore not directly related to historical sales.**

**In addition, by investigating uncertainties in the component variables that impact LTD rather than focusing on sales consumption itself, the new demand estimates are further decoupled from previous analyses.**

*Epidemiology and treatment variables were integrated into an influence diagram to illustrate probabilistic and functional relationships for latent therapeutic demand (LTD).*

Epidemiology  
Related  
Variables

Treatment  
Related  
Variables



# *We obtained probability estimates from published articles and medical experts for each random variable impacting latent therapeutic demand (LTD).*

Random Variable	Definition	Type	Source
<b>Epidemiology-related variables:</b>			
<i>POP</i>	male population in the developed world	Continuous	Literature
<i>INC</i>	percentage of reported cases of high-level factor VIII inhibitor antibodies that develop in previously untreated patients with severe hemophilia A	Continuous	Literature
<i>PREV</i>	number of reported cases of hemophilia A per 100,000 males	Continuous	Literature
<i>SEV</i>	patients with hemophilia A for a given level of severity <i>i</i> severe if the factor VIII activity level circulating within a body is <1% of normal ( <i>i</i> = 1) moderate if 1% to 5% of normal ( <i>i</i> = 2) mild between >5% and <40% of normal ( <i>i</i> = 3)	Discrete (categorical)	Literature
<i>AGE</i>	patients with hemophilia A for a given age group <i>j</i> 0 to 12 years representing parental-controlled administration ( <i>j</i> = 1) 13 to 19 years representing self-administering teenagers ( <i>j</i> = 2) ≥20 years representing self-administering adults ( <i>j</i> = 3)	Discrete (categorical)	Literature
<i>WGT</i>	weight of patients with hemophilia A for a given age group <i>j</i>	Continuous	Literature
<b>Treatment-related variables:</b>			
<i>PXS TREAT</i>	whether or not physicians would prescribe prophylaxis for patients with hemophilia A for a given level of severity <i>i</i> and age group <i>j</i>	Discrete (binary)	Probability Encoding
<i>PXS COMP</i>	whether or not patients with hemophilia A for a given level of severity <i>i</i> and age group <i>j</i> would comply with prophylaxis	Discrete (binary)	Probability Encoding
<i>BLEEDS</i>	annual number of bleeding episodes for patients with hemophilia A for a given level of severity <i>i</i> and whether or not patients are prescribed prophylaxis treatment	Mixed	Literature
<i>PXS DOSE</i>	prophylactic dose size prescribed by physicians	Continuous	Probability Encoding
<i>PXS FREQ</i>	number of prophylactic infusions administered per patient per year	Continuous	Probability Encoding
<i>EPISODIC DOSE</i>	episodic dose for patients with hemophilia A and whether patients are prescribed prophylaxis treatment	Continuous	Probability Encoding
<i>ITI DOSE</i>	immune tolerance induction (ITI) dose prescribed by physicians	Continuous	Probability Encoding
<i>ITI FREQ</i>	number of immune tolerance induction (ITI) infusions administered per patient per year	Continuous	Probability Encoding



*For PREV, we (1) obtained data from the medical literature, (2) derived an empirical problem distribution, and (3) determined the 10th, 50th, and 90th percentiles.*

Obs. No.	$X_m$	Observed Prevalence (per 100,000 males)	Country	Source	Probability	Cumulative Probability
1	5.7	5.2	South Korea	WFH (2004)	0.042	0.042
2	7.4	6.2	Japan	WFH (2004)	0.042	0.083
3	8.7	8.6	Finland	WFH (2004)	0.042	0.125
4	9.4	8.8	Austria	WFH (2004)	0.042	0.167
5	10.0	10.0	Germany	WFH (2004)	0.042	0.208
6	10.2	10.0	Spain	WFH (2004)	0.042	0.250
7	10.5	10.4	Australia	WFH (2002)	0.042	0.292
8	10.6	10.5	United States	Soucie et al (1998)	0.042	0.333
9	11.4	10.7	Portugal	WFH (2004)	0.042	0.375
10	12.1	12.0	Greece	Koumbarelis et al (1994)	0.042	0.417
11	12.2	12.1	Norway	WFH (2004)	0.042	0.458
12	12.3	12.2	Switzerland	WFH (2004)	0.042	0.500
13	12.3	12.3	Italy	WFH (2000)	0.042	0.542
14	12.5	12.3	Belgium	WFH (2004)	0.042	0.583
15	13.0	12.6	Denmark	WFH (2004)	0.042	0.625
16	13.5	13.3	Canada	AHCDC (2003)	0.042	0.667
17	14.2	13.6	Luxembourg	WFH (2001)	0.042	0.708
18	14.9	14.7	France	WFH (2001)	0.042	0.750
19	16.0	15.1	Sweden	WFH (2004)	0.042	0.792
20	17.2	16.8	Ireland	WFH (2004)	0.042	0.833
21	17.9	17.5	Netherlands	WFH (2004)	0.042	0.875
22	18.7	18.3	New Zealand	WFH (2004)	0.042	0.917
23	29.2	19.1	United Kingdom	UKHCDO (2003)	0.042	0.958
24		39.3	Iceland	WFH (2004)	0.042	1.000

← 10th percentile (7.9)

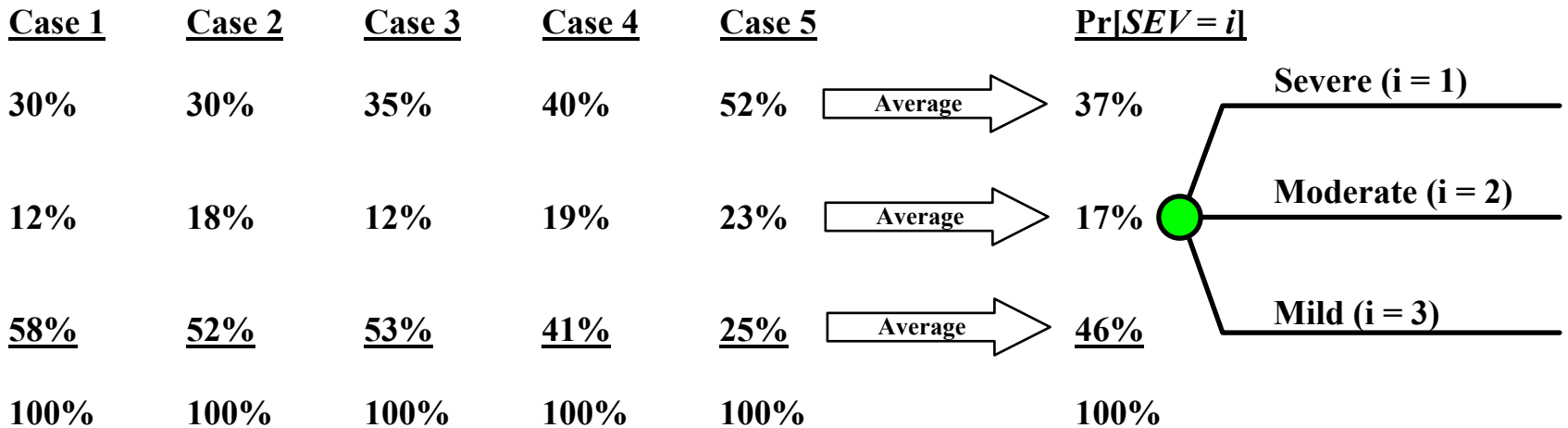
← 50th percentile (12.3)

← 90th percentile (18.4)

The value  $X_m$  is the halfway point between adjacent data points (Clemen 1996). For example, the halfway point between the first and second observed prevalence data points is  $(5.2+6.2)/2 = 5.7$ . The 10th percentile, 50th percentile, and 90th percentile were determined by interpolation. For example, the 10th percentile is determined by interpolating the  $X_m$ 's (7.4 and 8.7) corresponding to the cumulative probabilities of 0.083 and 0.125.

*For the categorical random variable SEV, we (1) obtained data from the medical literature and (2) aggregated the data by simple averaging.*

Probability estimates for the categorical random variable *SEV* and  $\Pr[SEV = i]$ —percent of patients with hemophilia A for a given level of severity *i*.



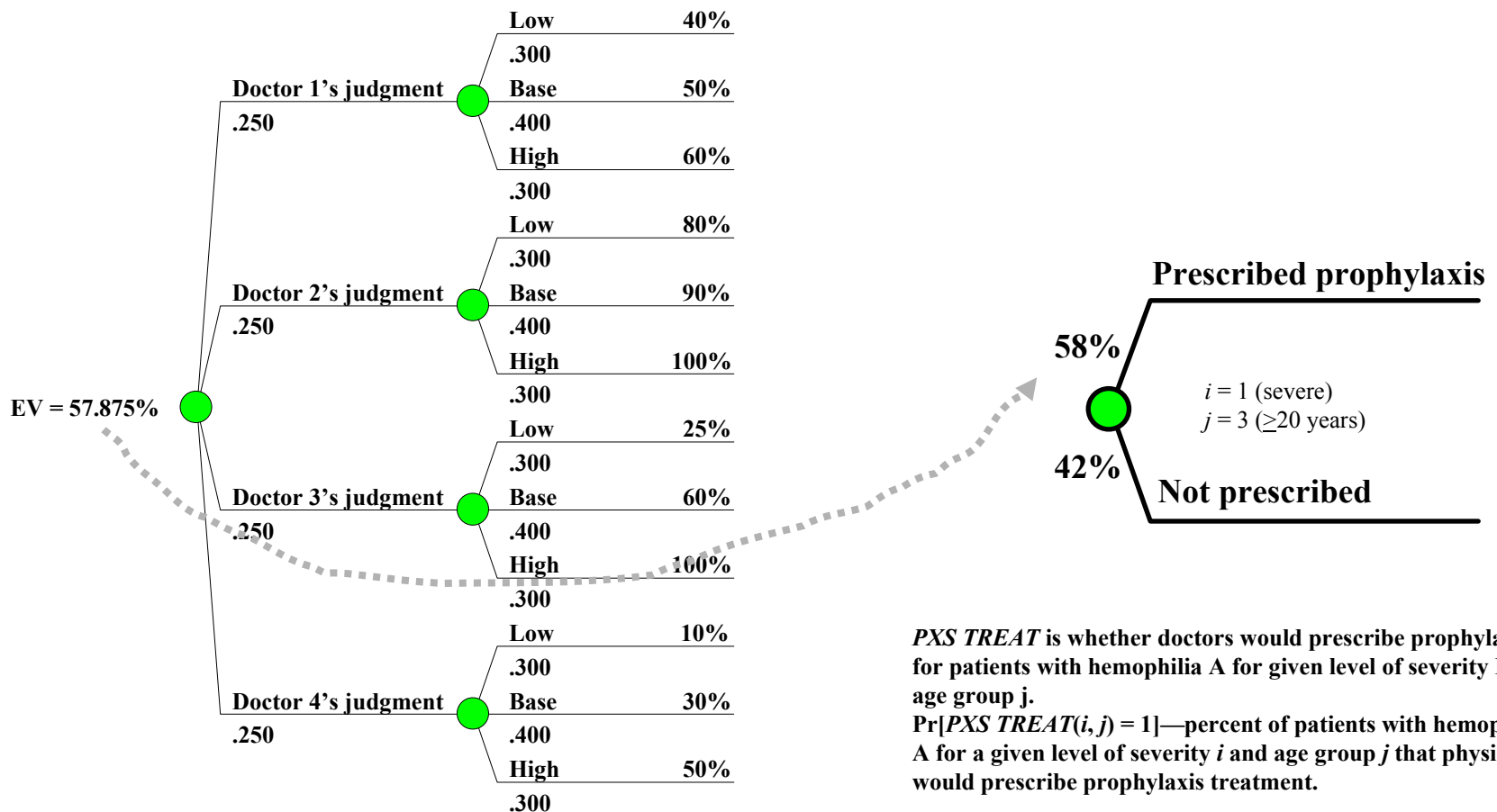
**Data Sources**

- Case 1: Canada (AHCDC 2003)
- Case 2: Greece (Koumbarelis et al 1994)
- Case 3: United Kingdom (UKHCDO 2003)
- Case 4: Netherlands (Triemstra et al 1995)
- Case 5: United States (CDC 2004)

*For the binary random variable PXS TREAT, we (1) obtained second-order uncertainty estimates from medical experts and (2) aggregated using the extended Swanson-Megil.*

**Q2: What percent of your severe hemophilia A patients in the  $\geq 20$  years age group would you prescribe prophylaxis?**

**Q3: If all doctors in your country were surveyed like you were in Q2, what range represents 80% of their opinions for the percent of patients who are prescribed prophylaxis? What is the median?**

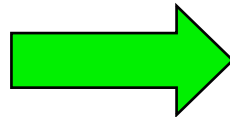


# *AGENDA*

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**RESULTS**

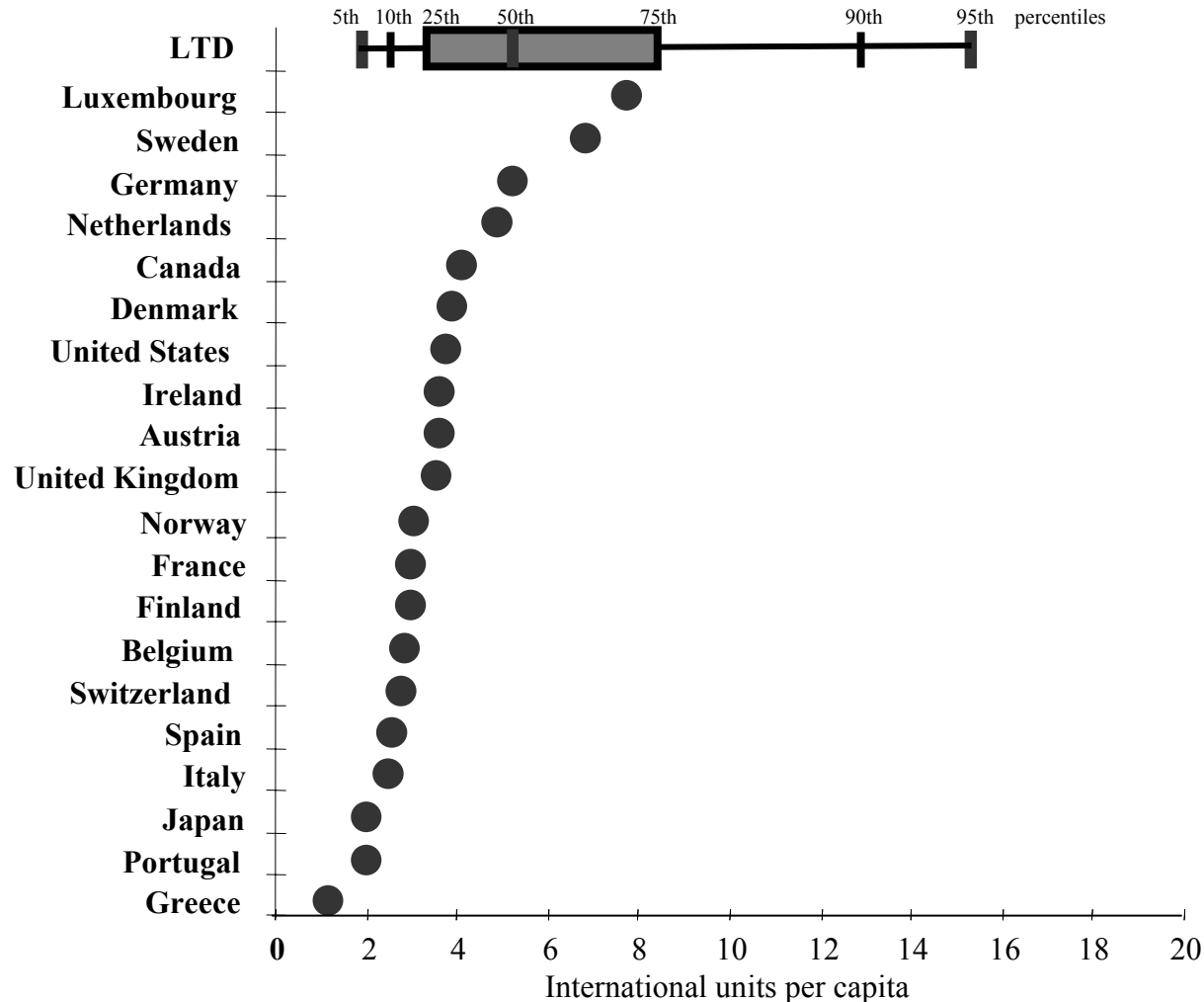
**CONCLUSIONS**

*Confidence gained from the latent therapeutic demand (LTD) model enabled Bayer to make key strategic decisions.*

<u>YOA</u>	<u>Task/Recommendation</u>	<u>Result</u>
1997	DA: Invest in 3rdGen product/facility	No action
1998	Market Research	Gather info on demand
1999	DA: Invest in 3rdGen product/facility	No action
2001	DA: Invest in 3rdGen product/facility	Do not invest
2002	DA: Invest in organic NextGen product/facility	Allocated resources
2003	Company-wide portfolio evaluation & prioritization	Hemophilia franchise is a top priority
2004	DA: Pursue in-licensing opportunity for NextGen product technology	developed deal-structure terms

The LTD model can be a crucial input for a company's new-product and facilities-expansion decisions as well as guiding efforts to grow future sales consumption and product supply to reach LTD over time through sales and marketing efforts.

*There is significant growth potential for factor VIII drug consumption in the global hemophilia A community when compared to the latent therapeutic demand (LTD) model.*



***Increasing the consumption of factor VIII drugs can result in enormous improvements in the mortality and chronic morbidity of hemophiliacs throughout the world.***

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**In the developed world, there are adult patients who did not receive adequate treatment in the past and are now living in crippling pain and chronic debilitation**

**In the developing world, the condition is even worse—many hemophiliacs are untreated and those with severe hemophilia A often die before reaching adulthood.**

**Next Steps:**

- **Model the “true” prevalence**
- **Survey doctors on future prophylaxis practice**
- **Survey patients on compliance**
- **Survey “payers” on the ability-to-pay for treatment**
- **Develop country-specific LTD models**
  - **Identify current barriers to achieve LTD**
  - **Share best-practices with the global hemophilia community**
  - **Develop ways of overcoming these barriers so as to improve mortality and morbidity**

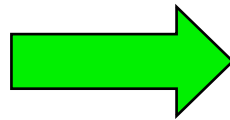
# *AGENDA*

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**INTRODUCTION**

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**CONCLUSIONS**



***The latent therapeutic demand (LTD) model is a new approach that has resulted in improved decision-making and has the potential to improve mortality and morbidity of hemophiliacs.***

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**First documented study to model the variability in population-based epidemiological data together with the variability of treatment modalities to estimate LTD (hemophilia A)**

**Improved Bayer's understanding of the global hemophilia market**

**Helped Bayer management make sound business decisions concerning the strategic direction of the company's factor VIII drug**

**Help pharmaceutical manufacturers better understand and respond to the future needs of the global hemophilia A community to prevent future drug shortages**

**Help national health-care agencies allocate resources to improve the treatment of patients with hemophilia A**

**Develop country-specific LTD models with national health-care agencies to improve mortality and morbidity of its hemophiliacs**

**Help practitioners in combining disparate data sets and sources of information (statistical, observational, and judgmental) and investigate new methods of combining such data**

**Apply the LTD modeling approach to other disease areas**