

Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden

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ABSTRACT

Hereditary angioedema (HAE) due to C1 inhibitor deficiency is a rare disease characterized by attacks of edema, known to impact quality of life (QoL). This study investigates the burden of HAE in Swedish patients, both children and adults. We used a retrospective registry study of Swedish patients with HAE, captured by the Sweha-Reg census. Data were collected using a paper-based survey. Patients completed EuroQoL 5 Dimensions 5 Levels (EQ5D-5L) questionnaires for both the attack-free state (EQ5D today), and the last HAE attack (EQ5D attack). Questions related to patient's age and sex and other variables, such as attack location and severity, were included to better understand the burden of HAE. EQ5D-5L values were estimated for the two HAE disease states. Patient-reported sick leave was also analyzed. A total of 103 responses were analyzed from 139 surveys (74% response rate). One hundred one reported an EQ5D today score (mean, 0.825) and 78 reported an EQ5D attack score (mean, 0.512) with significant differences between the two states ($p < 0.0001$). This difference was observed for both mild ($p < 0.05$), moderate ($p < 0.0001$), and severe attacks ($p < 0.0001$). Attack frequency had a negative effect on EQ5D today. Patients with >30 attacks a year had a significantly lower EQ5D today score than those with less frequent attacks. Of 74 participants, 33 (44.6%) had been absent from work or school during the latest attack and, of those with a severe attack, 81% had been absent. HAE has a significant impact on QoL both during and between attacks and on absenteeism during attacks.

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Hereditary angioedema (HAE) due to C1 inhibitor deficiency is a rare disease, with a prevalence of $\sim 1/50,000$.^{1,2} HAE is characterized by attacks of edema in subcutaneous tissue and mucous membranes that can affect many parts of the body. Angioedema in HAE can develop in the face, mouth, tongue, and larynx, where it can be life-threatening. Other locations could include the intestines, which may provoke severe abdominal pain. Angioedema

can also occur in the subcutaneous tissue, often resulting in swelling of the hands or feet, which is known to impair daily living. Untreated, an attack can last up to 5 days. Between attacks patients usually have no symptoms.^{3,4}

HAE is known to impact patient quality of life (QoL) and productivity^{5,6} but, although studies are under way and some results recently arrived,^{7,8} there still remains a shortage of data to quantify the burden of HAE. The aim of this present study was to investigate the burden of HAE in a large cohort of Swedish patients, both children and adults.

METHODS

Subjects

A retrospective patient survey was implemented to investigate the burden of HAE in Sweden using Sweha-Reg, a population-based census of HAE in Sweden.⁹ An Institutional Review Board Ethics Committee of Karolinska Institutet approved this study. All known persons with HAE in Sweden were offered to participate in this study with the help of the Swedish Patient Organization and by contacting the two special laboratories for complement deficiency and all departments of internal medicine, otorhinolaryngology, allergy, dermatology, and pediatrics in Sweden for known patients with HAE. A total of 629 contacts were

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made, which led to 239 replies. That resulted in a total of 145 patients in the database of Sweha-Reg on June 1, 2011, giving a calculated prevalence of 1/66,000 in Sweden.

Although we have 145 patients in our registry, only 139 questionnaires were sent out because of prior information from the first survey that 5 patients did not want to participate in any further investigations and 1 was dead. From the total of 107 responses collected, 4 blank questionnaires were excluded to leave 103 for analysis. Of those 103, 54 were female patients (mean, 44 years; range, 10–88 years) and 48 were male patients (mean, 41 years; range, 4–89 years). Of the 48 male patients, 5 were <12 years old and 6 were between 12 and 18 years old. Of the 54 female patients, 2 were <12 years old and 4 were between 12 and 18 years old.

Questionnaires

The EuroQol 5 Dimensions 5 Levels (EQ5D-5L) instrument was used in the survey. Patients completed two EQ5D-5L questionnaires: one to describe their current health state (EQ5D today) and one retrospective to estimate the patient health state during their most recent HAE attack (EQ5D attack). EQ5D-5L is a generic instrument for describing and valuing health, based on a descriptive system that defines health in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five response categories ranging between no problems and extreme problems. The instrument is designed for self-completion, and respondents also rate their overall health on the day of completion on a 0–100 hash-marked, vertical visual analog scale.

Preference-based measures, such as the EQ5D, allow the health status of patients to be linked to a societal utility value, which aims to be representative of the values of the population of a particular country. This is obtained *via* large valuation studies in the general population, which attribute a utility value to each possible health state described by the questionnaire. The utility value is provided on a scale ranging from 1 (equivalent to full health) to 0 (equivalent to death), with the potential in some measures for states considered “worse than death,” values below 0.¹⁰

Because value sets for the EQ5D-5L are still being developed, calculating utility values from EQ5D-5L responses currently requires use of crosswalk data provided by EuroQoL.¹¹ These data were generated *via* a coordinated study that administered both the 3-level and 5-level versions of the EQ5D to develop a “crosswalk” between the EQ5D-3L value sets and the new EQ5D-5L descriptive system. In the absence

of Swedish reference values, the U.K. crosswalk value set for EQ5D-5L was used to define utility values from the responses provided by the Swedish HAE population. U.K. values are widely used and published and thus provide an opportunity to compare the impact of HAE with peer-reviewed data sets published for other disease states. EQ5D-5L values were used to calculate utilities for both questionnaires EQ5D today and EQ5D attack. Questions were asked about patient demographics (age and sex) and other variables, such as attack location and frequency. They were also asked about attack severity, as defined by the patient on a three grade scale:

Mild—noticeable symptoms but they did not impact activities of daily living. For example, your hand was swollen but you could still hold a pencil or grip a utensil.

Moderate—wanted intervention for symptoms during your attack or your activities of daily living were affected. For example, if your hands were swollen and you could not button your shirt or your feet were swollen and wearing shoes was uncomfortable.

Severe—treatment or intervention was required or you were unable to perform activities of daily living. For example, if your throat was swollen and you were having difficulty breathing or your lips were swollen and you could not eat.

Patient-reported absenteeism, time out of work or school, was analyzed to assess levels of productivity loss.

After Ethics Committee approval (Karolinska Institutet), data were collected using a paper-based survey sent to the subjects during autumn 2011.

Statistics

Standard descriptive statistics were used to analyze the data and the utility value and reported with mean and SD. To test significance Wilcoxon signed-rank test, Mann-Whitney *U* test, Mantel-Haenszel χ^2 -test, and Spearman's rank correlation test were used; $p < 0.05$ was considered significant.

RESULTS

One-hundred one of 103 patients reported an EQ5D today score (mean, 0.825 ± 0.207) and 78 of 103 patients reported an EQ5D attack score (mean, 0.512 ± 0.299 ; $p < 0.0001$; Fig. 1). There was a trend that female patients had a lower EQ5D today value than male patients (0.802 ± 0.209 versus 0.85 ± 0.203 ; $p = 0.07$). The female patients also had lower EQ5D attack values than men, but the difference was not significant. With increasing attack severity, the EQ5D attack utility value was lower and the difference between EQ5D today and EQ5D attack was larger. A significant dif-

Figure 1. EuroQoL 5 Dimensions 5 Levels for the attack-free state (EQ5D today; $n = 103$) and EQ5D for the last hereditary angioedema attack (EQ5D attack; $n = 79$) values. Results are shown as mean $\pm$ SD.

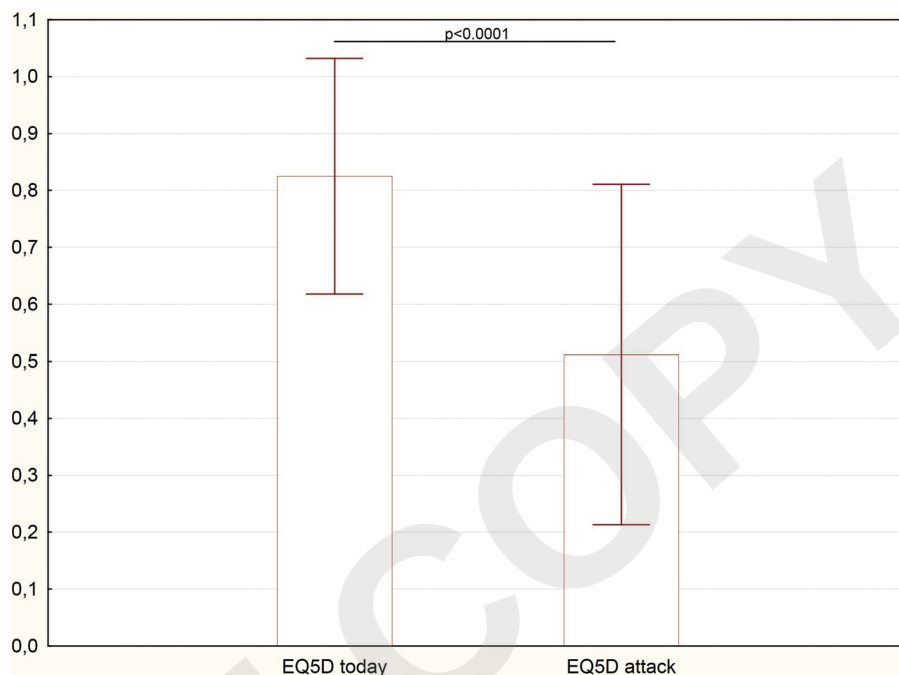
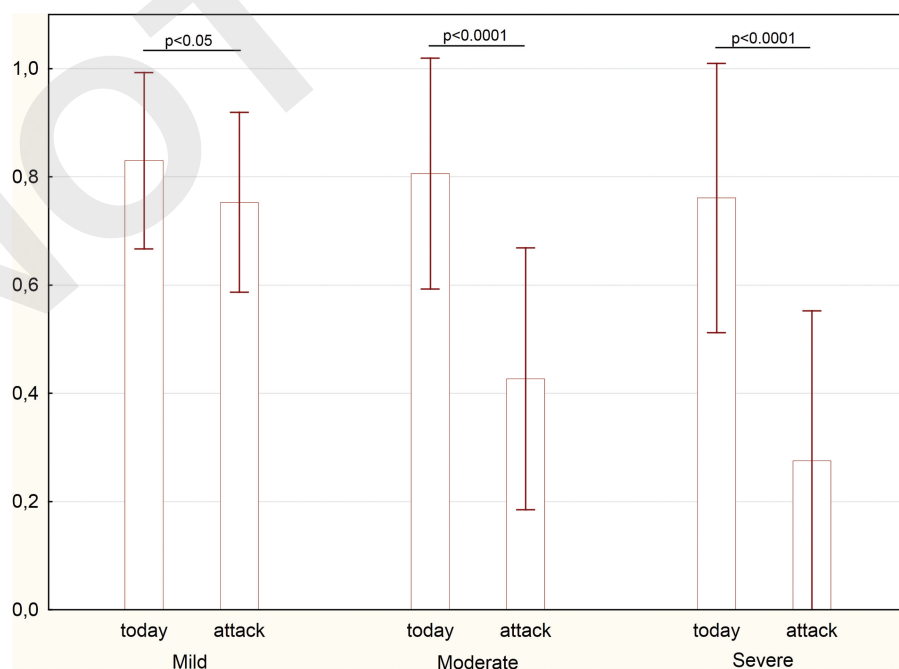


Figure 2. EuroQoL 5 Dimensions 5 Levels for the attack-free state (EQ5D today) and EQ5D for the last hereditary angioedema attack (EQ5D attack) values grouped as a function of the severity of the last attack. Mild, moderate, and severe today refers to the EQ5D today value in patients reporting that their last attack was mild ($n = 30$), moderate ($n = 27$), and severe ($n = 20$). Results are shown as mean $\pm$ SD.



ference between the EQ5D today and EQ5D attack scores of their latest attack was observed for mild (0.07; $p < 0.05$), moderate (0.369; $p < 0.0001$), and severe attacks (0.486; $p < 0.0001$; Fig. 2).

The 103 patients that reported an EQ5D today score were split into three subgroups defined by reported annual attack frequency; 0–14 attacks per year ($n = 84$), 15–29 attacks per year ($n = 8$), and ≥ 30 attacks per year ($n = 11$). Increased attack frequency was seen to have a negative impact on “between

attack” patient QoL (Spearman rank correlation; $R_s = -0.30$; $p = 0.002$).

Regression analysis provides an understanding of elements that influence reported EQ5D today and EQ5D attack utility weights. Attack frequency and age have a negative correlation with EQ5D today scores with more attacks (-0.0043 per attack; $p < 0.0001$) and greater age (-0.02205 per 10 years of age; $p < 0.0001$) contributing to a reduced QoL (utility score). Days since last attack has a positive cor-

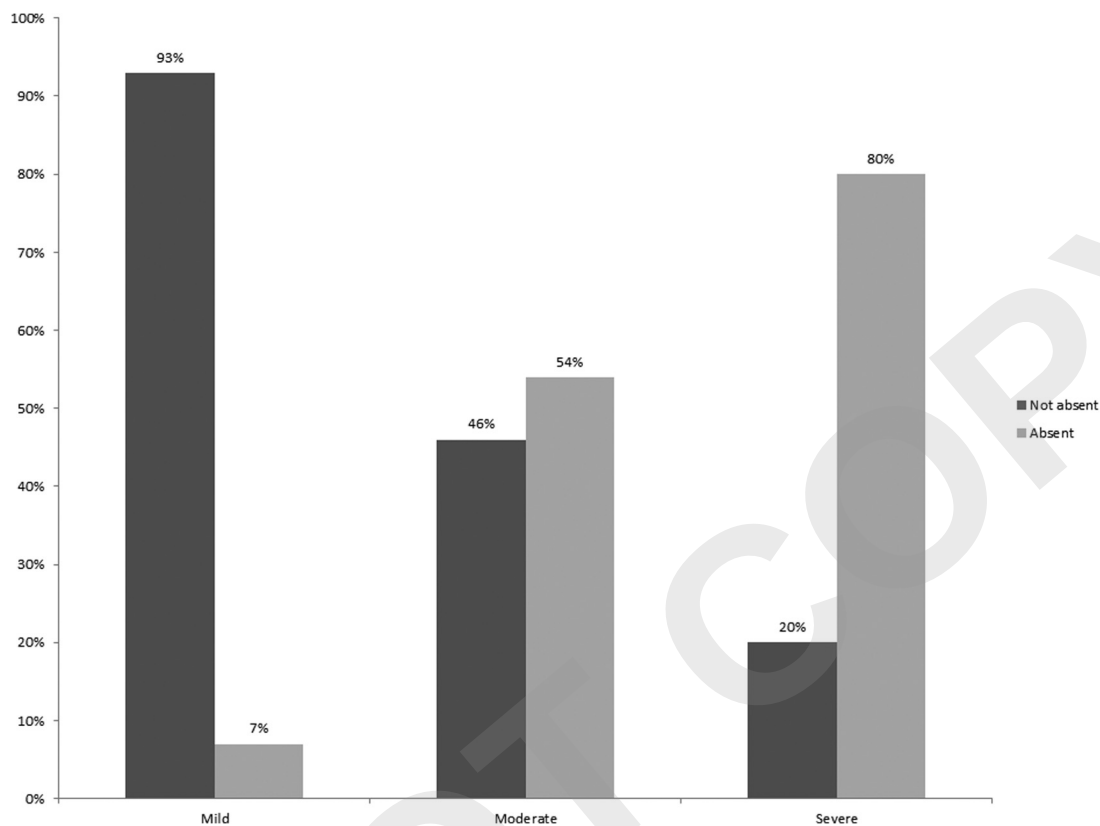


Figure 3. Percent absenteeism in relation to self-reported attack severity for the last attack. Two of 27 patients with mild attacks, 11 of 24 patients with moderate attacks, and 16 of 20 patients with severe attacks reported absenteeism. Absenteeism was significantly more likely with increasing attack severity ($p < 0.0001$, Mantel-Haenszel χ^2 -test).

relation with EQ5D today scores, which suggests an improvement in QoL as the time since last attack increases ($R^2 = 0.3058$).

Variables associated with the last HAE attack, such as patient-reported severity, pain, and absenteeism, show nonsignificant correlation with EQ5D today index score, indicating that the last attack is not sufficient to explain overall QoL.

Patient-reported attack severity and abdominal attack location have a negative correlation with EQ5D attack scores. Increasing attack severity by category, e.g., mild > moderate (-0.2231 ; $p < 0.0001$) and abdominal attacks (-0.2359 ; $p < 0.0001$) are correlated with a reduction in QoL ($R^2 = 0.5871$).

The results of the regression models provide an indication of the variables that influence the reported EQ5D today and EQ5D attack utility weights.

Seventy-four of 103 participants (71.8%) answered the question about absenteeism during latest acute attack and about the attack severity level. In total, 33 of 74 participants reported that they had been absent from work or school during the latest attack. With increasing attack severity, the proportion of patients being absent was found to be significantly increased ($p < 0.0001$; Mantel-Haenszel χ^2 -test). Absenteeism

during mild attacks was 7%, during moderate attacks, 46%, and during severe attacks, 80% (Fig. 3). No significant relationship was found between the location of the attack and patient absenteeism.

DISCUSSION

We have shown that HAE has an impact on perceived health in Swedish patients. In the absence of a validated disease-specific instrument in 2011, the EQ5D-5L was selected as a recognized tool for assessing health status, providing an opportunity to compare the impact of HAE with the impact of other chronic diseases. Comparison with other chronic diseases characterized by paroxysmal attacks, such as asthma and migraine, gives an indication of burden suffered by patients with HAE. The EQ5D today for HAE was 0.83 in our present study, and EQ5D today values in studies of controlled asthma or migraine between attacks have been 0.86 and 0.87, respectively.^{12,13}

The strength of our study is that it included a significant number of the Swedish HAE population, in all 72% of diagnosed population, including both children and adolescents. The prevalence of HAE in Sweden

based on SwehaReg is 1/66,000, which compares with a reported prevalence of 1/70,900 in Denmark and 1/91,700 in Spain.^{1,2} The Swedish prevalence is close to the accepted average prevalence of 1/50,000.¹⁴ The weakness of our study is that the questionnaire was retrospective with respect to EQ5D attack and other attack-related questions. The temporal association with the attack and the time of the survey may influence the results. Actually, our study shows that EQ5D attack utility values were lower, closer to the last attack (1 week, $n = 27$, 0.382; 1 month, $n = 41$, 0.587; ≥ 3 month or longer, $n = 25$, 0.577).

Higher attack frequency decreased perceived health between attacks. Patients with >30 attacks per year had significantly lower values, whereas there was no difference between the groups with 0–15 and 15–30 attacks per year. This addresses the importance of when to start prophylactic treatment. There are several recommendations about this if one considers attack frequency. For example, The Hereditary Angioedema International Working Group as well as Craig *et al.* have suggested starting prophylaxis with >12 attacks per year.^{15,16} Bowen *et al.* states that one could consider long-term prophylaxis if patients have more than one severe attack a month.¹⁷ The World Allergy Organization guideline does not state any attack frequency, but does mention that one should consider patient QoL among other things when assessing the need for prophylaxis.¹⁴ Results from our survey suggest that EQ5D-5L could be used to measure HAE disease impact.

That absenteeism correlates with increasing patient-reported attack severity and not location of attack suggests that patient experience may provide a more accurate measurement of disease severity. For example, a peripheral attack in a hand that may, from a clinical perspective, be diagnosed as a mild attack can still have a significant impact on your ability to work if you are a pianist or a carpenter or have any other work that requires dexterity. Conversely, some patients may be able to continue working despite suffering an attack that would be diagnosed as severe by the physician (*e.g.*, abdominal). Caballero *et al.* show also in the Burden of Illness Study in Europe that an HAE attack impacts daily activities regardless of body site of the attack.⁸

The fact that age has a negative effect on QoL between attacks, as seen here, is well known from other QoL studies.¹⁸ In many patients attack frequency decreases with age, but it seems that the negative factor of age is greater than the positive effect of decreasing attack frequency.

Survey results indicate that female sex had negative effect on EQ5D today utility value. This aligns with previous observations that female subjects suffer more frequent and more severe attacks than male subjects.¹⁹

In conclusion, this investigation was performed to highlight and quantify the impact of HAE on patient-perceived health. The results suggest that patients with frequent and severe attacks, as defined by the patient, appear to have a lower QoL than patients with fewer, milder attacks and thus could benefit from access to treatment that aims to reduce the frequency and severity of HAE attacks. This is likely to have a positive impact on HAE patients' ability to live a normal life while also reducing the burden that HAE has on society.

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REFERENCES

1. Bygum A. Hereditary angio-oedema in Denmark: A nationwide survey. *Br J Dermatol* 161:1153–1158, 2009.
2. Roche O, Blanch A, Caballero T, et al. Hereditary angioedema due to C1 inhibitor deficiency: Patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol* 94:498–503, 2005.
3. Bork K, Meng G, Staubach P, et al. Hereditary angioedema: New findings concerning symptoms, affected organs, and course. *Am J Med* 119:267–274, 2006.
4. Bork K, Staubach P, Eckardt AJ, and Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. *Am J Gastroenterol* 101: 619–627, 2006.
5. Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc* 31:407–414, 2010.
6. Bernstein JA. HAE update: Epidemiology and burden of disease. *Allergy Asthma Proc* 34:3–6, 2013.
7. Bygum A, Aygören-Pursun E, Caballero T, et al. The hereditary angioedema burden of illness study in Europe (HAE-BOIS-Europe): Background and methodology. *BMC Dermatol* 12:4, 2012.
8. Caballero T, Aygören-Pursun E, Bygum A, et al. The humanistic burden of hereditary angioedema: Results from the Burden of Illness Study in Europe. *Allergy Asthma Proc* 2013. (Epub ahead of print November 13, 2013.)
9. Mallbris L, Nordenfelt P, Björkander J, et al. The establishment and utility of Sweha-Reg: A Swedish population-based registry to understand hereditary angioedema. *BMC Dermatol* 7:6, 2007.
10. Harrison MJ, Lunt M, Verstappen SM, et al. Exploring the validity of estimating EQ-5D and SF-6D utility values from the health assessment questionnaire in patients with inflammatory arthritis. *Health Qual Life Outcomes* 8:21, 2010.
11. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 20:1727–1736, 2011.
12. Allegra L, Cremonesi G, Girbino G, et al. Real-life prospective study on asthma control in Italy: Cross-sectional phase results. *Respir Med* 106:205–214, 2012.
13. Stafford MR, Hareendran A, Ng-Mak DS, et al. EQ-5DTM-derived utility values for different levels of migraine severity from

- a UK sample of migraineurs. *Health Qual Life Outcomes* 10:65, 2012.
14. Craig T, Aygören-Pürsün EA, Bork K, et al. WAO guideline for the management of hereditary angioedema. *World Allergy Organ J* 5:182–199, 2012.
 15. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: Consensus report of an International Working Group. *Allergy* 67:147–157, 2012.
 16. Craig T, Riedl M, Dykewicz MS, et al. When is prophylaxis for hereditary angioedema necessary? *Ann Allergy Asthma Immunol* 102:366–372, 2009.
 17. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 6:24, 2010.
 18. Kind P, Dolan P, Gudex C, et al. Variations in population health status: Results from a United Kingdom national questionnaire survey. *BMJ* 316:736–741, 1998.
 19. Caballero T, Farkas H, Bouillet L, et al. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol* 129:308–320, 2012. □

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