

# Improving Acute Otitis Media Outcomes Through Proper Antibiotic Use and Adherence

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## Abstract

This article will discuss how therapy adherence may have an impact on acute otitis media (AOM) outcomes. Although the relationship between therapy adherence and treatment failures in AOM has not been proved beyond question, many believe that adherence with antibiotic therapy plays a key role in patient outcomes. Poor adherence may contribute to treatment failures; treatment failures are known to result in poorer health outcomes, higher total costs of care, and an increased potential for bacterial resistance. As such, managed care organizations should consider strategies for achieving better patient adherence with antibiotic regimens for AOM.

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Acute otitis media (AOM) is a highly prevalent and costly disease. When AOM has been diagnosed and the decision to treat the infection with antibiotic therapy has been made, practitioners and parents should consider issues such as efficacy, therapy adherence, spectrum of activity, and health outcomes when selecting therapy. Several agents appear to be equally efficacious in the treatment of recurrent AOM; however, there are other factors that differentiate these agents. The microbiology of AOM is shifting, and there will be clinical consequences related to the selection of therapy.<sup>1</sup> The first-line therapy for the treatment of uncomplicated AOM (amoxicillin) is unlikely to be affected by this shift because of its safety and low cost, but there are potential implications for therapy in recurrent AOM. Although the relationship between therapy adherence and treatment failures in AOM has not been proven beyond question, many believe that adherence with antibiotic therapy plays a key role in patient outcomes.<sup>2-7</sup> Poor adherence may contribute to treatment failures; treatment failures are

known to result in poorer health outcomes, higher total costs of care, and an increased potential for bacterial resistance.

## Direct and Indirect Costs of AOM

The total annual costs of AOM in the United States have been estimated to be between \$1.4 billion and \$4.1 billion.<sup>8-12</sup> A review of these estimates can be found in **Table 1**; these estimates vary based on differences in the age ranges of the population and estimates of disease incidence used in the analyses. Of these estimates, the most reliable estimate appears to have been completed by the Southern California Evidence-based Practice Center. Based on data from the 1995 National Ambulatory Medical Care Surveys (NAMCS) and the National Hospital Ambulatory Medical Care Surveys (NHAMCS), an estimated 5.18 million episodes of AOM occurred among children 0 to 17 years old, resulting in a total annual cost of \$2.98 billion.<sup>8</sup>

When evaluating the total costs of AOM, it may be useful to examine the 2 components of total cost (direct costs and indirect costs) separately. Direct medical costs, defined as fixed and variable costs associated directly with a medical condition or healthcare intervention,<sup>13</sup> often include components such as office visit, hospitalization, medication, and surgical costs. A retrospective analysis of a fee-for-service Medicaid program claims database led to a national estimate of \$4.1 billion in direct medical costs incurred by otitis media in children younger than 14 years old.<sup>9</sup> This analysis also demonstrated that more than 40% of national expenditures on otitis media were generated by children between 1 and 3 years old and that the largest component of direct medical costs was office

**Table 1.** Estimates of the Total Annual Costs of Acute Otitis Media in the United States

Reference	Year investigated	Definition of illness	Age group examined	2005 Adjusted national cost estimate (\$ billions)	National cost estimate (\$ billions)*
Stool et al <sup>12</sup>	1987	Otitis media	0-6 years	2.2-3.4	3.8-5.8
Berman et al <sup>10</sup>	1992	Persistent middle ear effusion	0-1 years	1.4-4.9	1.9-6.8
Bondy et al <sup>9</sup>	1992	Otitis media	0-12 years	4.1	5.7
Gates <sup>11</sup>	1994	Acute otitis media	0-4 years	3.2	4.2
Marcy et al <sup>8</sup>	1995	Acute otitis media	0-17 years	3.0	3.8

\*National cost estimate available at: <http://minneapolisfed.org/Research/data/us/calc/index.cfm>.

visits. Other estimates of the total annual direct costs of AOM in children have ranged from \$1.3 billion to \$3.2 billion.<sup>8,11,12</sup>

Whereas indirect costs attributed to illness are often overlooked, these costs can represent a large percentage of total illness costs and can present a significant burden to patients and caregivers. As 2 wage-earner families have become the largest employee group in the United States,<sup>14</sup> one parent often has to stay home to care for a child suffering from AOM, as daycare providers will not care for a sick, febrile child.<sup>15</sup> The value of work time lost, transportation costs (actually a direct cost), alternate childcare fees, ancillary medication costs (direct cost), and charges for treatment of adverse effects (direct cost) are often included in calculations of the indirect costs of AOM.<sup>4,16</sup> As part of a safety and efficacy study, parents or guardians of children being treated for AOM completed a questionnaire 12 to 14 days after the first dose of antibiotic therapy. A total of 60% of the parents completing the survey worked, and, of those, 32% missed an average of 1.2 days of work (range 0.5-3 days) because of the child's illness. Of the parents who used daycare for their children, 42% of the children missed an average of 1.7 days from daycare because of the illness.<sup>17</sup> In studies that have examined both direct and indirect costs of AOM, it has been estimated that the indirect costs of AOM represent between 9.8% and 57.1% of the total costs of illness.<sup>8,11,12</sup> Further, these cost esti-

mates fail to account for the sizable impact that AOM has on the quality of life of both the child and their caregivers.<sup>18</sup>

**Prescription Antibiotic Use in AOM**

A retrospective analysis using NAMCS data documented a large increase in antimicrobial prescribing for otitis media.<sup>19</sup> Between 1980 and 1992, the number of antibiotic prescriptions written for AOM nearly doubled from 11.9 million per year to 23.6 million per year, fueled by large increases in the rate of amoxicillin and cephalosporin use. Among children younger than 15 years old, the office visit rate for otitis media increased significantly, from approximately 275 visits per year to approximately 425 visits per year per 1000 children ( $P = .004$ ). The increase in office visits for otitis media likely represents an actual increase in the incidence of the disease, because widespread use of daycare facilities by infants and toddlers evolved during this period.<sup>20-22</sup>

A follow-up study compared antimicrobial prescribing for the periods of 1989-1990 and 1999-2000.<sup>23</sup> In this analysis, the investigators determined that the mean annual office visit rate for otitis media per 1000 children and adolescents younger than 15 years old decreased from 428 visits per year to 230 visits per year ( $P < .001$ ) between the 2 time periods. Similar decreases were seen in office visits for pharyngitis and bronchitis. Overall, the mean number of antimicrobial

prescriptions per year for respiratory tract infections per 1000 children and adolescents decreased by 47% during the study period, from 347 prescriptions in 1989-1990 to 184 prescriptions in 1999-2000 ( $P < .001$ ), yet there was no change in visit-based prescribing rates for AOM.<sup>22</sup> Decreased office visits for AOM can be attributed to physicians being less likely to schedule follow-up visits the first few weeks after AOM treatment because antimicrobials ceased to be recommended for the management of uncomplicated AOM.<sup>23</sup>

#### **Adherence Issues in AOM: Clinical and Economic Impact**

Adherence with antibiotic therapies is generally poor among adults; a survey of 3600 Europeans showed that only 65% of working adults completed the full course of antibiotic therapy, 87% of the patients who discontinued antibiotic therapy did so because they felt better, and more than 20% of the respondents also felt it was reasonable to save unused antibiotics for future use.<sup>2</sup> Fortunately, adult attitudes regarding antibiotic prescriptions for their children are different. In the same survey, a much higher percentage (81%) of mothers reported that their children completed the full course of antibiotic therapy; similar results were seen in a survey of 400 parents and caregivers in Massachusetts.<sup>24</sup> As parental and caregiver attitudes indicate an increased desire for antibiotic adherence among their children, antibiotics with indications for childhood diseases (such as AOM) should possess characteristics designed to improve adherence with therapy.

Lack of adherence to antibiotic therapy for AOM may have both clinical and economic implications to the health plan and their members. As discussed earlier, some thought leaders believe that a lack of adherence to antibiotic therapy may promote treatment failure in otitis media.<sup>2,5</sup> Treatment failure can lead to recurrent AOM, which can increase both the health burden of illness (prolonged discomfort of the child) and the economic burden of disease (eg, through more frequent office visits, laboratory expenses, and procedure costs).<sup>25</sup> Further, persistent and recurrent otitis

media has been associated with serious long-term effects in children, such as hearing loss and language impairment.<sup>26,27</sup>

The economic costs of treatment failure include increased doctor visits, additional days of work missed, and sequelae, such as otitis media with effusion and chronic middle ear infection. Improved treatment adherence may result in improved outcomes because of less treatment failures and recurrent disease, which would lead to better economic outcomes by decreasing office visits, avoiding time missed from work, and decreasing overall healthcare costs. Increased treatment failures from inadequate coverage of the implicated pathogens may be the result of the shift in AOM microbiology.<sup>1</sup> The economic impact of this is not fully known and will become more evident as changing pathogens evolve caused by increased and sustained use of pneumococcal conjugate vaccine.

#### **Factors Affecting Adherence**

Adherence to antimicrobial therapy and health outcomes can be influenced by factors such as tolerability, dosing schedule, duration of therapy, and the preferences of patients and caregivers (including palatability, satisfaction with therapy, and prescription cost or copayment level).<sup>28</sup>

**Tolerability.** Assuming all else is equal, antibiotic tolerability and ease of administration are the primary considerations in the antibiotic selection process. Contemplation of these items can increase adherence to prescribed therapy.<sup>29</sup> If the child experiences adverse drug events, such as vomiting, nausea, or diarrhea, they are less likely to take the antibiotic, and their parents or caregivers will be less likely to administer it.<sup>29</sup> This can prolong the duration of illness and the length of time a parent would have to stay home to care for the child.

The various antibiotics indicated for treatment of AOM have different tolerability profiles. In a study by Block et al, 425 patients aged 6 months to 6 years old with non-refractory AOM were randomized to a 5-day course of cefdinir treatment (14 mg/kg, divided twice daily) or a 10-day course of amoxicillin/clavulanate treatment (45/6.4 mg/kg,

divided twice daily).<sup>30</sup> In this trial, 24% of subjects receiving cefdinir experienced a drug-related adverse event, significantly less than the 38% of subjects receiving amoxicillin/clavulanate ( $P < .002$ ), and fewer subjects receiving cefdinir discontinued therapy because of drug-related adverse events (0.5%) than subjects receiving amoxicillin/clavulanate (1.9%). A study of 388 caregivers by Cifaldi et al examining the same agents, doses, and duration of therapies for the treatment of AOM as Block et al found a higher percentage of amoxicillin/clavulanate patients with vomiting compared with cefdinir (16% vs 8%;  $P = .016$ ), and more parents of children in the cefdinir group reported that their child took 100% of their medication (68% vs 53%;  $P = .005$ ).<sup>17</sup>

Numerous studies have examined the use of azithromycin in AOM. In a study by Arrieta et al,<sup>31</sup> 300 patients 6 months to 6 years of age with recurrent or persistent AOM were randomized to receive either high-dose azithromycin (20 mg/kg once daily) for 3 days or high-dose amoxicillin/clavulanate (amoxicillin/clavulanate 45/6.4 mg/kg, divided twice daily plus amoxicillin 45 mg/kg, divided twice daily) for 10 days. Rates of treatment-related adverse events were not statistically different between azithromycin and amoxicillin/clavulanate (32% vs 42%;  $P = .095$ ), although the incidence of diarrhea was significantly lower in the azithromycin group (30% vs 44%;  $P = .045$ ). Parent-reported compliance with therapy (defined as >80% of the prescribed regimen) was 99% for azithromycin and 93% for amoxicillin/clavulanate ( $P = .018$ ). In another trial, a comparison of 5 days of therapy with azithromycin (10 mg/kg on day 1, 5 mg/kg on days 2-5) or cefdinir (7 mg/kg twice daily) in 357 children between the ages of 6 months and 6 years revealed no difference between agents in the incidence of adverse events.<sup>32</sup> Parent-reported compliance with therapy (defined as >80% of the prescribed regimen) was 99% for both the azithromycin and cefdinir groups.

**Dosing Schedule and Duration of Therapy.** Agents recommended for the treatment of AOM by the American Academy of Pediatrics<sup>33</sup> can be divided by once- and twice-daily dosing regimens (Table 2). As a

general rule, compliance with antimicrobial therapy is better when the patient requires fewer doses per day.<sup>34</sup> A meta-analysis of interventions designed to improve therapy adherence showed that dosing schedule changes can improve adherence an average of  $12\% \pm 8\%$ .<sup>35</sup>

Agents recommended for the treatment of AOM by the American Academy of Pediatrics<sup>33</sup> can also be sorted by those requiring a duration of therapy of 5 or fewer days and those requiring 7 to 10 days of use (Table 3). Evidence has demonstrated that antibiotic regimens of short duration can be effective for the treatment of AOM. A 5-day course of therapy is appropriate for older children, as there is a high rate of resolution and cure with 3 to 5 days of therapy.<sup>29,36,37</sup> In 1997, a comprehensive review of 27 efficacy trials (6932 patients) comparing shorter and longer courses of treatment for AOM in children found that 3 to 5 days of therapy was as effective as 10 days of treatment.<sup>36</sup> More recent studies have demonstrated the efficacy of shorter courses of antibiotic therapy compared with regimens of longer duration.<sup>30,31</sup>

The duration of antibiotic therapy can also impact therapy compliance. In a study by Steele et al,<sup>38</sup> a group of 86 healthcare personnel was asked to rate the palatability of 11 antibiotic suspensions for children in categories of appearance, smell, texture, taste, and aftertaste. Once scored, the participants were asked to adjust their palatability scores once the product's cost, treatment duration, and dosing interval was

**Table 2.** Dosing Frequency of Agents Recommended by the American Academy of Pediatrics for the Treatment of Acute Otitis Media

Agents dosed once daily	Agents dosed twice or more daily
Azithromycin	Amoxicillin
Cefdinir*	Amoxicillin/Clavulanate
Cefpodoxime*	Cefdinir*
Ceftriaxone	Cefpodoxime*
Cefuroxime	Clarithromycin

\*Can be dosed once or twice daily.

**Table 3.** Duration of Therapy Recommended by the American Academy of Pediatrics for the Treatment of Acute Otitis Media

Agents with 5 or less days of therapy	Agents with 7 or more days of therapy
Azithromycin	Amoxicillin
Cefdinir*	Amoxicillin/Clavulanate
Ceftriaxone	Cefdinir*
	Cefuroxime
	Cefpodoxime
	Clarithromycin

\*Indicated for use with a 5- or 10-day regimen.

made known. The analysis showed that the antibiotics with a 5-day duration of therapy were rated more favorably than antibiotics with a 10-day duration of therapy. Further, duration of therapy was considered by the evaluators to be more important than dosing interval, except for those antibiotics dosed 3 to 4 times per day.<sup>38</sup>

**Patient and Caregiver Preferences.** Patient and caregiver preferences play an important factor in compliance with therapy and therapy outcomes and should not be overlooked by physicians and managed care plans when prescribing therapy or making formulary decisions. However, prescribers may have incorrect assumptions about the importance that caregivers place on different antibiotic factors. A survey of 400 parents and 100 pediatricians was conducted to determine parents' opinions on antibiotics and to compare the results with the opinions of pediatricians.<sup>24</sup> When asked to choose 2 of 5 antibiotic factors (cost, dosing schedule, side effects, strength/effectiveness, or taste) that they considered to be most important, parents selected side effects (82%) twice as frequently as any other factor. When asked to choose 2 of the same 5 antibiotic factors that they felt parents considered to be most important, physicians selected dosing schedule (63%) most frequently, and ranked side effects least important (15%).<sup>24</sup> Evidence of this disconnect between caregivers and physicians should spur physicians to

speak to caregivers and patients about their preferences regarding antibiotic therapy, in particular medication palatability, satisfaction with past therapy, and medication cost.

**Palatability.** In pediatric patients, the only motivation to take an antibiotic for AOM may be the taste of the suspension,<sup>39,40</sup> and compliance with therapy can be predicated on taste.<sup>38</sup> Although many physicians feel this is true based on clinical experience, some historical evidence suggests that palatability may be a minor issue because it relates to compliance in the pediatric population.<sup>41,42</sup> However, more recent evidence failed to find taste differences in the pediatric population and children based on age, concluding that taste is well developed in early therapy.<sup>40</sup> If a better-tasting product improves adherence, a product with a more expensive acquisition cost could be justified as cost effective.<sup>40</sup>

Numerous studies have been conducted to evaluate the taste of medications in children (Table 4).<sup>40,43-47</sup> A series of 6 randomized, single-blind, crossover trials compared the palatability of cefdinir with the oral suspensions of amoxicillin/clavulanate, cefprozil, and azithromycin.<sup>46</sup> The study group consisted of 715 healthy children 4 to 8 years of age, who rated the taste and smell of the suspensions on a smile-face scale. For taste acceptance, cefdinir was rated as significantly better than amoxicillin/clavulanate, cefprozil, and azithromycin. A total of 85% of subjects rated cefdinir as tasting good or really good, compared with 63% of subjects for the comparator products. For smell acceptance, cefdinir was rated significantly better than amoxicillin/clavulanate and azithromycin and was rated equivalent to cefprozil. The authors concluded that cefdinir is a palatable and well-accepted suspension, supporting its use in pediatric patients with infection.<sup>46</sup>

An open-label study was conducted with more than 12 000 children younger than 12 years of age with infections treated on an outpatient basis.<sup>47</sup> These children received 1 of 10 antibiotics, and after administration their caregivers filled out a questionnaire in which the taste of the antibiotic was graded on a 5-category scale (very unpleasant to

**Table 4.** Select Studies Evaluating the Taste of Oral Antibiotic Suspensions in Children

Reference	Sample size	Comparators	Results
Angelilli et al <sup>45</sup>	30 children 5-8 years old	AZI, AMC, CFZ, CFX	Taste: CFX > AZI = CFZ = AMC
Matsui et al (1996) <sup>44</sup>	20 children 6-12 years old	CLX, CPL, ERY, FSA	Taste: CPL = ERY = FSA > CLX
Matsui et al (1997) <sup>43</sup>	50 children 4-9 years old	AMC, AZI, CLA, EES	Taste: AZI > AMC > EES = CLA
Powers et al <sup>46</sup>	715 children 4-8 years old	AMC, AZI, CFD, CFZ	Taste: CFD > AMC, AZI, CFZ Smell: CFD > AMC, AZI; CFD = CFZ
Steele et al (2002) <sup>47</sup>	11 913 children <12 years old	AMC, AZI, CFC, CFD, CFX, CFP, CFZ, CFU, CLA, LOR	Taste: "Very Pleasant" or "Pleasant" scores >50% of patients: LOR, CFD, CFX, CFC; 30%-50% of patients: AZI, CFZ; <30% of patients: AMC, CLA, CFU, CFP

AZI indicates azithromycin; AMC, amoxicillin/clavulanate; CFZ, cefprozil; CFX, cefixime; CLX, cloxacillin; CPL, cephalixin; ERY, erythromycin; FSA, fusidic acid; CLA, clarithromycin; EES, erythromycin ethylsuccinate/sulfisoxazole; CFD, cefdinir; CFC, cefaclor; CFP, cefpodoxime; CFU, cefuroxime; LOR, loracarbef.

very pleasant). Of the 10 antibiotics examined, only loracarbef, cefdinir, and cefixime were rated as very pleasant, pleasant, or okay by more than 80% of patients; alternately, the agents clarithromycin, cefuroxime, and cefpodoxime were rated as unpleasant or very unpleasant by 50% or more of patients.<sup>47</sup>

Smaller palatability studies (20-50 subjects each) of antibiotic suspensions in healthy children have had various results. Two different studies examined the taste of antibiotic suspensions effective against beta-lactamase-producing bacteria; one found cefixime to have a higher taste score than azithromycin, cefprozil, and amoxicillin/clavulanate,<sup>45</sup> whereas the other found that azithromycin had a higher taste score than amoxicillin/clavulanate, erythromycin, ethylsuccinate/sulfisoxazole, and clarithromycin.<sup>43</sup> A study of antibiotic suspensions commonly used for skin infections found cloxacillin to have significantly lower taste scores than cephalixin, erythromycin, and fusidic acid.<sup>44</sup>

Managed care plans may wish to consider the palatability of antibiotic suspensions when making formulary decisions. Evidence from large studies of children suggests that agents such as cefdinir, loracarbef, and cefixime may be more palatable than comparator antibiotic suspensions. The improved palatability of these agents may improve therapy adherence, leading to

improved clinical and economic outcomes for both patients and the health plan.

**Satisfaction with Therapy.** Parental satisfaction with therapy can play a role in therapy selection and adherence.<sup>28,48</sup> In a study by Cifaldi et al, caregivers of 388 patients aged 6 months to 6 years with nonrefractory AOM were surveyed 12 to 14 days after the start of a 5-day course of cefdinir treatment (14 mg/kg, divided twice daily) or a 10-day course of amoxicillin/clavulanate treatment (45/6.4 mg/kg, divided twice daily).<sup>17</sup> The questionnaire included 4 questions to assess satisfaction with therapy: questions about general satisfaction and whether the parents would use the medication again, and questions about ease of use and taste. Although there was no difference between the cefdinir and amoxicillin/clavulanate groups in overall satisfaction and willingness to use the medication again, parents whose children received cefdinir rated ease of use and taste significantly higher than parents of children who received amoxicillin/clavulanate (Table 5).

In the previously described open-label study of more than 12 000 children by Steele et al,<sup>47</sup> parents and caregivers were asked to rate their satisfaction with 1 of the 10 study antibiotics on a 5-category scale (extremely satisfied to extremely dissatisfied). Of the 10 antibiotics examined, 9 achieved scores

**Table 5.** Cefdinir vs Amoxicillin/Clavulanate: Results of a Parent Questionnaire

Criteria	Agents	P value
Overall satisfaction	Cefdinir = Amox/Clav	
Use again	Cefdinir = Amox/Clav	
Ease of use	Cefdinir > Amox/Clav	.009
Taste	Cefdinir > Amox/Clav	<.0001
Took full dose	Cefdinir > Amox/Clav	.005
Missed work	Cefdinir = Amox/Clav	

Amox/Clav indicates amoxicillin/clavulanate.  
 Source: Reference 16.

of extremely satisfied or satisfied at least 80% of the time, with only cefuroxime receiving less than 80% (65.2%). Further, only 2 agents, clarithromycin and cefuroxime, had 10% or more of the parents rate their satisfaction with therapy as dissatisfied or extremely dissatisfied. The poor parent satisfaction scores with cefuroxime were attributed to the agent's poor taste and a higher overall failure rate.<sup>47</sup>

**Prescription Cost/Copayment Level.** The cost of a prescription can be an important factor in determining patient adherence with therapy. Numerous analyses have determined that higher prescription costs or copayment levels are associated with lower adherence to therapy.<sup>49-52</sup> Costs can play an even larger role in patient adherence for families that do not have health insurance plans with outpatient prescription coverage.

Physicians often consider antibiotic cost when prescribing therapy for AOM,<sup>4</sup> which in addition to treatment guidelines promoting its use,<sup>33,53</sup> might account for the continued use of amoxicillin as first-line therapy. Physicians participating in an antibiotic suspension palatability study<sup>38</sup> were asked to reevaluate each product once the cost of a course of therapy was made known to them. The palatability of trimethoprim/sulfamethoxazole was particularly judged to be more acceptable based on the relatively low cost of the product. Alternatively, the palatability scores of ciprofloxacin and amoxicillin/clavulanate declined precipitously once the relatively high costs of those products

were considered, whereas the taste perceptions of loracarbef, cefdinir, and cefixime maintained their top ranking after adjustments were made for cost. A lower cost product can be far more expensive in the long run if the patient refuses to adhere to the prescribed regimen because of the taste.

**Conclusion**

AOM is a highly prevalent and costly disease to young children and their parents, health plans, and society. As the shift in AOM pathogens continues, it will be important to analyze any further increase in costs related to treatment failures caused by inadequate coverage of the implicated pathogens. In addition, other factors that may affect AOM health outcomes, such as therapy adherence, should be considered. Nonadherence to antibiotic therapy for AOM may increase the risk of treatment failure, which is known to lead to poorer health outcomes and increased costs of care. Factors contributing to poor adherence include poor tolerability, inconvenient dosing regimens, prolonged treatment regimens, and the preferences of patients and caregivers.

Managed care organizations should consider strategies for achieving better patient adherence with antibiotic regimens for AOM. These strategies may include providing plan practitioners with appropriate educational materials (treatment guidelines, prescribing guidelines, etc) to ensure proper antibiotic utilization and selection, and securing both antibiotics shown to be palatable to a pediatric population and antibiotics with less frequent dosing and shortened treatment durations available on the formulary. These steps may lead to improved clinical outcomes for patients and improved economic outcomes for patients, their caregivers, and the health plan.

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