WORLDWIDE CLINICAL TRIALS

WHITE PAPER

PROACTIVELY ADDRESSING ACCESS AND REIMBURSEMENT CHALLENGES FOR ALS THERAPEUTICS

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Regulatory approval of a new therapy can bring much-needed relief to patients—as long as they can access that therapy. Internationally, a diverse set of organizations ultimately facilitates or encumbers access to a novel pharmacotherapy based upon the estimated "value" of a new therapeutic within a system of clinical care. In healthcare systems with competing demands for resources, these assessments constitute a set of necessary steps preceding the addition of a new therapy to formulary with reimbursement for product acquisition at a level commensurate with its clinical utility. However, measures of disease severity or disease progression embedded within randomized controlled trials may create an incomplete framework for supporting such complex assessments. As a consequence, a product may become available under evidentiary standards for approval but remain inaccessible when stakeholders with different perspectives and points of emphasis review the portfolio of data.

Payer Perspectives

Indications characterized by significant morbidity and mortality, such as amyotrophic lateral sclerosis (ALS), frequently are subject to considerable scrutiny, given that the total cost of therapy may outweigh the demonstrated magnitude and durability of a therapeutic effect, creating uncertainty regarding the impact of that therapy on a system of care. Pharmacometric analyses also may vary considerably from country to country due to commercial provider policy differences and the existence of joint commercial- and government-funded programs. Thus, clinical, economic, and humanistic outcomes acquire a different valence as they are differentially weighted, further complicating decisions impacting access.[1] When payers controlling patient access within commercial plans in the United States lack utilization and cost data associated with a therapy at the time of launch, for example, they may create policies that effectively restrict access. Such policies can include high coinsurance or prohibitive copays, or coverage may require preauthorization requirements that effectively limit patient access (such as stepped therapy, a method of prior authorization that begins medication for a medical disorder with the most preferred drug therapy and progresses to other therapies only if necessary based on prespecified criteria).

In 2016, for example, Sarepta Therapeutics Inc. faced just this issue with the approval of a Duchenne muscular dystrophy (DMD) drug, Eteplirsen (ExonDys 51). Although the product was approved by the FDA for DMD patients with the appropriate genetic mutation, several major health insurance companies in the United States declined to cover Eteplirsen or placed significant restrictions on its coverage.[2, 3] Similarly, the U.S. market introduction of Radicava®(edaravone) for ALS in 2017 initially had limited commercial success. Even though evidentiary standards for approval were met, there was a lack of clinical data supporting the value of the drug within the U.S. healthcare system at the time of new drug application (NDA).[4-6]

These experiences serve as reminders that, in a competitive setting with constrained resources, the novelty of a new chemical or biological entity may have limited cachet in the absence of data demonstrating a clinically notable benefit and a favorable reduction in healthcare utilization and costs within the healthcare system where the product will be marketed. The type of data required to influence an assessment of those benefits also may vary by the nature of the payer (e.g., Centers for Medicare and Medicaid Services [CMS] or the Veterans Administration [VA] versus commercial plans), as well as by regional demands that will weigh budget impact and quality-of-life changes in different ways.

Understandably, the data informing decision processes may also change over time. The evolution of coverage divisions for edaravone for the treatment of ALS in the United States is illustrative of how additional data, and changes in community sentiment regarding product utility among practitioners, can impact coverage decisions.[7] In this example, current criteria for initial coverage versus continued coverage decisions differ, and these vary by plan including practice topology (specialist in ALS versus general neurologist), the need to demonstrate a specific decline in a commonly used rating instrument (ALSFRS-R), the presence or absence of invasive ventilation, or combinations of the above.

The absence of consistency in policy regarding continual coverage as ALS patients transition through stages is particularly striking and accentuates the need for additional cost utilization information prior to—as well as following—product approval. At the same time, it should be noted that cost-effectiveness measures can, somewhat

counterintuitively, also have a very limited impact on a commercial plan's review process given the small fraction of plan membership with ALS and thus its relatively limited budget burden.

Inconsistency in coverage decisions can extend across orphan products in other therapeutic areas. For example, an analysis of the coverage of 17 outpatient orphan drugs approved from 2009 through 2012 by the 10 largest U.S. Medicare Part D plans (in terms of numbers of covered Medicare beneficiaries) revealed that 18% of the drugs (3 of 17) were not covered by at least one plan. Prior authorization was used by at least one plan for 82% of these drugs.[8] The study of U.S. CMS orphan drug coverage included data from coverage decisions made by health authorities in the UK and Netherlands, finding that orphan drugs had more coverage restrictions than non-orphan drugs. These data reinforce the observation that policies facilitating or restricting access can vary considerably between and within geographic regions. Variations can be substantive, reflecting differences in standards of care, the emphasis placed upon economic versus quality-of-life data, and other product attributes.[9, 10]

The considerable costs that may be associated with products targeting ALS heightens payer sensitivity to the cost, particularly in light of increased numbers of new clinical development programs in ALS in recent years (see Figure 1) and the appreciable economic burden associated with this illness.[8, 9]

Navigating through Complex Environments

The payer landscape for ensuring coverage of ALS therapies is complex. In the United States, approximately 66% of ALS patients are covered by Medicare, 17% are covered by private insurance, 9% by military or VA insurance coverage, and a little more than 2% are covered by Medicaid.[10] Recent analyses corroborate differences in the proportion of patients covered by health plan type based on fee-for-service, health maintenance organizations (HMO), or point of service coverage. This heterogeneity emphasizes the need for formal payer surveys that are contemporaneous within the region where a product may eventually be introduced, the stage of illness for which the product is intended, and the type of service considered in order to direct protocol design and data acquisition activities during clinical development.[11]

One of the more comprehensive and erudite evaluations regarding the value of pharmacotherapy in ALS illustrates the cost variables that must be accessible in clinical research to inform post-approval coverage decisions.[12] Particularly in ALS, it is important to distinguish recurrent costs for care (e.g., monthly expenditures potentially ascertained throughout clinical program) from one-time costs for

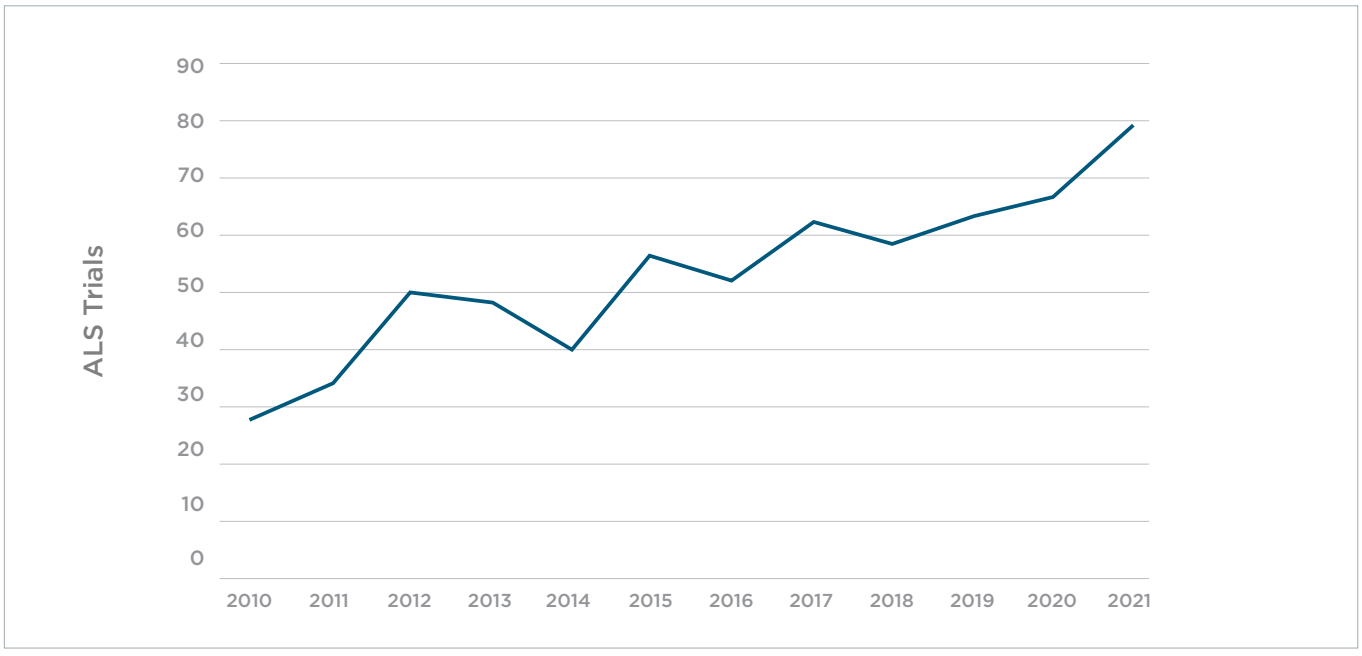

Figure 1: Number of ALS trials on Clinicaltrials.gov by study start year

transitional events, such as the acquisition of a motorized wheelchair (also known as "tollgate" costs).[12] Therefore examining both sets of costs using a disease staging model that is based on established clinical criteria such as King's clinical staging system or the MiToS functional staging system is informative.[13] Either are readily applicable to prospective clinical trials or retrospective data analysis.

Finally, it is important to consider the analytical methodologies underpinning the estimate for economic impact. For example, analyzing the cost of ALS using the friction cost method (FCM) attempts to quantify the direct and indirect costs of the disease.[14] In a complementary fashion, analyzing the social costs of ALS using the human capital approach (HCA) attempts to quantify the social burden of ALS in terms of the societal cost of factors such as absenteeism.[15] Both evaluations are critical within a decision process, contingent on a stakeholder's perspective.

In Figure 2 and Figure 3, researchers used the FT9 staging method to identify the stages that would frame the analysis of recurring and tollgate costs. The FT9 staging method derives from the ALSFRS-R, a widely used 12-question, five-level instrument that is comprised of four subscores (based on bulbar, fine motor, gross motor, and respiratory performance).[16] They then analyzed costs from both healthcare and social cost perspectives (using both the FCM and HCA methodologies). The value of an ALS medication can appear very different depending on the analyses applied. Collecting relevant clinical data during development enables both.

To obtain relevant data in a structured and controlled fashion, more granular assessments of a new product's impact on cost burden—and more varied methodologies of calculating cost burden—must be incorporated into clinical development programs in ALS. These activities can facilitate patient access following introduction of a new therapeutic, as they provide evidence-based value to payers prior to an NDA or market access application (MAA). By creating a living and evolving dossier of clinical information, it is possible to accommodate changing therapeutic standards. A program in ALS that anticipates these activities can be instrumental in business development.[18]

But identifying data that can be captured in the context of clinical development may represent appreciable challenges that extend beyond the initial objective of obtaining market authorization within the EU or approval within the United States. Data of interest to both private and governmental payers in the United States (including Medicare, Medicaid, and military/VA) require data collection that extends beyond

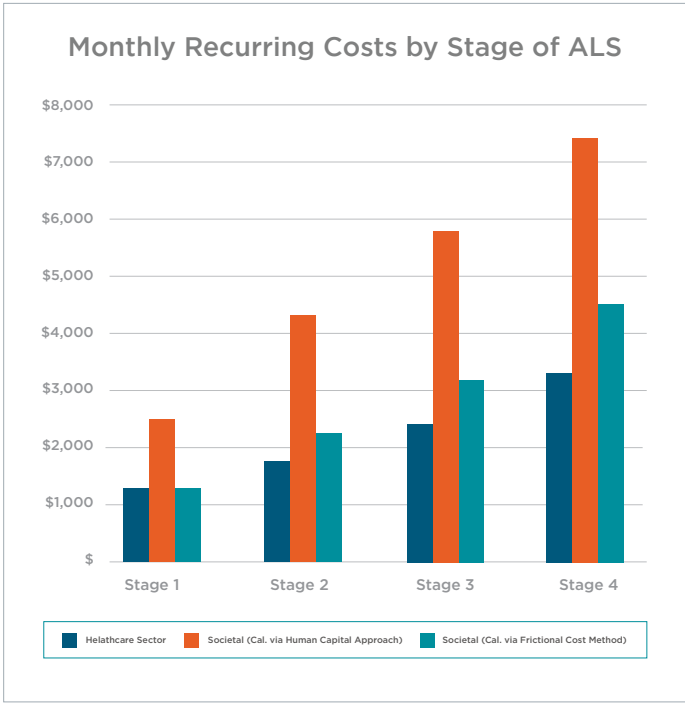

Figure 2: Monthly recurring costs by stage of ALS[17]

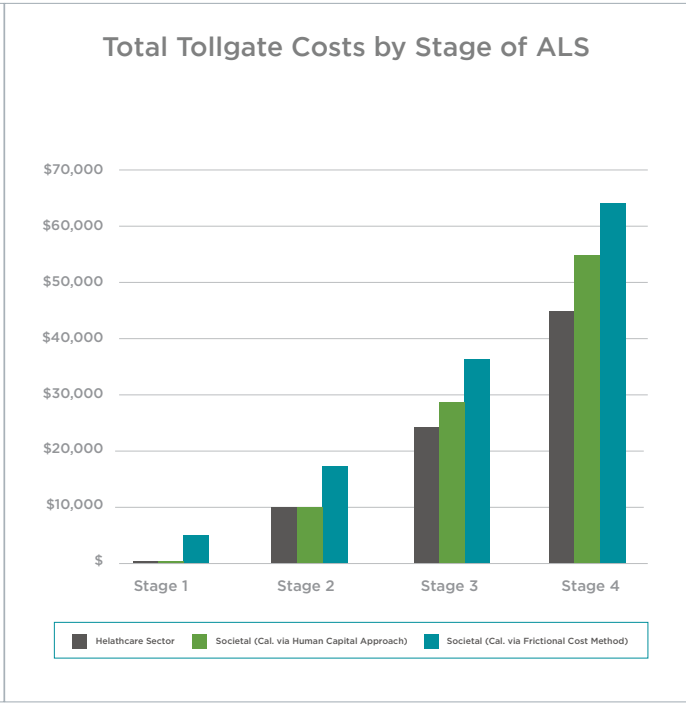

Figure 3: Total tollgate costs by stage of ALS[17]

controlled conditions into open label extensions. In ALS, cost reductions associated with new therapeutics might come from improvements in mobility, self-care and feeding, breathing ability, or mental and emotional health. These data accentuate the importance of evaluating recurring costs rather than only the costs associated through "transitions" as previously described.

It is also worth noting that healthcare costs associated with caregivers may be important to consider in assessing the value of a new therapy. Illnesses such as ALS that are characterized by chronicity and high caregiver burden can increase healthcare utilization in unaffected individuals, who may be enrollees in a payer's commercial plan.[19, 20] The impact of an illness such as ALS on caregiver family members' health status is commonly referred to as "health spillover," providing an additional informative domain for analysis.[21]

Many of these benefits can be captured from the patient's perspective by quality of life (QoL) measures and can assist sponsors in providing justification for coverage by commercial payers. Methods include "piggybacking" on to programs otherwise created for product registration, as well as bespoke, stand-alone investigations evaluating claims data discussed below.[11, 22-24]

Accessible Cost Drivers In ALS

The economic burden of an orphan disease frequently is obtained through diverse techniques. For example, one review indicated that most studies used questionnaires to patients or caregivers to collect resource utilization data (67%); others used databases or registries (48%). Sixty-eight percent (68%) of studies evaluated lost productivity costs; nonmedical and informal costs were considered in 60% and 43% of studies respectively.[25]

The potential cost drivers accessible in clinical research can be identified using information collected over the last decade that evaluated cost utilization for ALS the United States.[26] Data are largely congruent across publications, although the numerical estimates vary contingent upon sample and techniques of analyses.[27] For example, the national economic burden was estimated at more than $1 billion annually in 2010, with $236 million coming from indirect costs, $287 million from non-medical costs, and $502 million from medical costs. The mean total cost of ALS for commercial insurers was $30,934 per capita in 2010; for Medicare it was $31,563 per capita. Average annual direct non-medical costs for ALS (weighted, self- and other- paid) came to $17,889 per family, and predicted mean family weighted loss of income was $62,996 per year.[10] It is the relative portion of expenditures across these domains rather than the absolute amount that garners attention.

Several publications describing the cost of ALS care provide insights into the expenditures related to commercial insurance, the patient's household expenditures, and not for profit charities.[26, 28, 29] One study analyzed one patient's verifiable annual and disease-duration costs of care over a 10-year period (2000–2010)—from first symptom presentation to death—and calculated the total cost from all payers to be $1,433,992. The highest costs were for in-home caregivers ($669,150), ventilation ($212,430), and hospital care ($114,558).[29]

To calculate these costs, researchers compiled all expense records related to the cost of care that were collected and maintained by the family. Expenses were categorized into 16 categories and four sub-categories, and importantly, the source of payment (insurance, out-of-pocket, and charity) was separately tabulated. Categories were based on functional deficits, medical care, and services, and one specific time-period (pre-diagnosis). Data were analyzed using descriptive statistics. Total expense includes costs in all three payer groups and all 16 categories over the 10-year disease duration. The costs identified in this study were historically adjusted to estimate 2013 values using the Consumer Price Index (CPI) for non-medical expenses (home remodeling, transportation, and utilities), and the Medical CPI (using the medical care services [MCS] classification).[29]

These findings suggest the type of data that a sponsor may want to collect during clinical development of an ALS investigational product, either through interventional or observational studies, such as an open label extension that might take place in an industry-sponsored program at the conclusion of an interventional study. The pie chart in Figure 4 shows costs categories subsumed under insurance payments only, which holds implications informing trial design extend from these observations. For prototypical patients within industry-sponsored interventional studies, the cost associated with outpatient physician visits may be dominant, depending on the stage of illness, with

costs associated with home care, ventilatory support, and hospitalization becoming increasingly important with disease progression.[28] The relative importance assigned each of these categories would be ascertained through a payer's survey, prior to study initiation, that considers the details of a proposed protocol design and eligibility criteria. These surveys would identify the program elements considered most impactful in generating information that could facilitate product access.

Minimal, Moderate, High-Impact Initiatives

Although a publication strategy is the sine qua non of effective marketing, articles developed in support of most strategies are often directed toward healthcare practitioners. Yet, as noted, frontline healthcare practitioners are not the only stakeholders a sponsor must interest. Additional publication efforts also have merit. These should be developed with the unique perspectives of healthcare networks and commercial insurance plans in mind. Product attributes might then be evaluated through the prisms of economic and healthcare utilization (see ahdbonline.com or ajmc.com for examples of this approach).

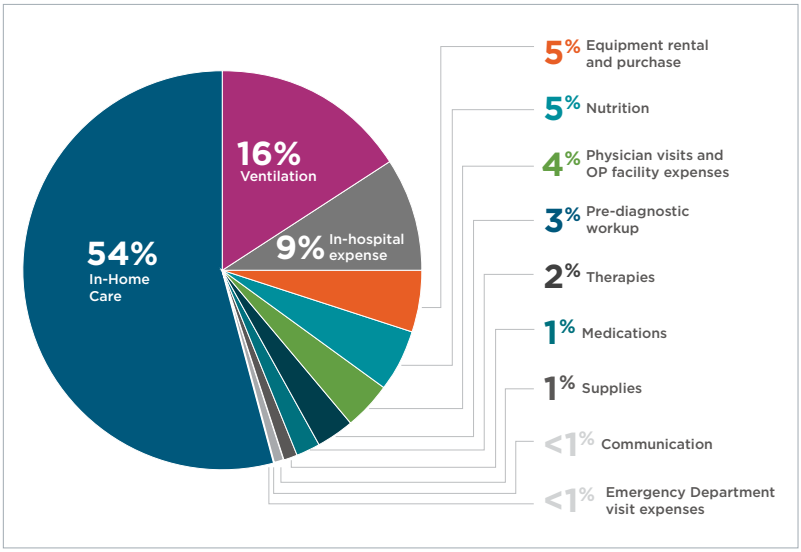

Figure 4: Cost categories, both recurrent and transitional[29]

Issues as diverse as immediate and long-term surveillance mechanisms for safety assessments, as well as the demonstration of persistence of benefits over the lifetime of the patient, are relevant. Similarly, the impact of a treatment on caregivers and their healthcare utilization (also enrollees of plans) are important dimensions for review.[20] These considerations are particularly relevant for emerging pharmacotherapy that has little precedent for the treatment of ALS but that shows considerable potential for transformative treatment effects (e.g., stem cell or gene-based therapeutics under the category of advanced therapy medicinal products).[30, 31]

Enrolling patients who "screen fail" from planned interventional studies into a prospective, longitudinal cohort study running contemporaneously has also been frequently voiced as an efficient method for evaluating overall healthcare utilization (thus economic impact). This creates a cohort of subjects who resemble, in key respects, those to be included in the planned investigational study. Indeed, the utility of real-world evidence in estimating the economic impact of ALS provides an entirely new opportunity to inform the design of interventional studies.[32]

An even more ambitious approach to capturing data might involve the creation of a research call center. This would require an ethics committee/IRB review with approval of the investigator, but once operational, it could facilitate direct-to-patient inquiries specifically focusing on a full spectrum of activities impacting healthcare in the context of a clinical trial.

Working Strategically As Well As Transactionally

How can a sponsor identify and capture the data relevant to so many distinct stakeholders? Working strategically with multiple organizations, each with a different expertise, is key. For example, a CRO specializing in program and study design can help develop and operationalize clinical trial programs where one of the exploratory objectives is to answer a wide range of questions that extend beyond those required for product approval. Surveys and other forms of observational data provided by collaborators—focusing on issues of adoption and patient access—would inform this process. Incorporating these efforts into a clinical development program will produce findings that resonate across multiple stakeholders in a complex healthcare environment. Collaboratively, the process would establish market value drivers, identify evidence gaps and optimal approaches to filling them, and inventory

available real-world data (from both internal and external data sources) that can drive data-based enthusiasm for adoption of the product.

A strategic clinical development program designed to identify and measure accessible cost drivers and changes due to novel pharmacotherapy might incorporate a range of activities requiring little to no additional expenditures. Or, it may embrace a much more ambitious set of activities. A modest solution impacting study operations might include the use of microenvironments as investigational sites during the course of product development. These investigative sites provide integrated delivery networks capable of capturing all healthcare utilization information for a given patient.[33] This increasingly encountered technique has been successfully employed for interventional research in other indications, providing a template that could be adopted to ALS.[34] Occasionally, this modest change in planned trial operations is limited by the institution's lack of familiarity in conducting GCP clinical research. However, the strategic advantage of collecting data within the system where the product ultimately might be utilized is key at some point during development, given the attributes of integrated care in ALS, which can be accessible and have been previously described.[35]

Working Strategically As Well As Transactionally

Significant value can be added to clinical research and development programs by incorporating activities designed to explore and support objectives beyond regulatory approval. These activities can produce insights that are crucial for product adoption and patient access.

- What are the most commonly used and prescribed products (FDA-approved and off-label) in this indication?
- What is the current status of drug coverage and reimbursement considering the spectrum of diverse stakeholders that might be dictating access?
- What are the existing barriers to reimbursement and coverage, and how are currently approved products navigating through these barriers?
- What mechanisms are in place to help patients gain access to innovative therapies, and may they preemptively be facilitated in the process of clinical development?
- Do the anticipated products in development imply a potential for disease modification as well as symptomatic improvement? Are the benefits of the therapy durable?
- How is drug access partitioned between pharmacy and clinical care as well as between recurring cost versus transitional cost (the "tollgates")?
- Are there predicted near- or far-term changes in disease treatment or drug approvals for this indication? And how will these changes affect the development and commercial landscape considering the long horizon of drug development?
- What innovative policies might be developed regarding access to and payment for drugs within this indication (e.g., National Coverage Determination, Clinical Decision Support Mechanisms, Value-Based Contracts [Medicare Shared Saving Program], Outcome-Based Contracts, New Technology Add-On Payment, etc.)?
- What trial data derived within, or associated with, an interventional study support access and reimbursement policies, and what policy experts and KOLs should be contacted to inform that decision?

Summary

Ensuring patient access to new ALS therapies requires more than regulatory approval of such therapies. It is access, after all, that brings much-needed relief to patients—but access is determined by many different forces within the broader healthcare environment. Programs focusing on ensuring access as well as product approval constitute a critical part of the drug development process, and these efforts are best addressed through integrated strategies attached to clinical research that commence at the earliest stages of drug development.

Rather than designing and executing clinical studies with an eye focusing exclusively on satisfying evidentiary standards of approval, CROs and sponsors can develop strategically focused initiatives designed to capture the data required to meet a much wider range of needs. This more integrated strategic approach can provide a sponsor not only with critical insights into the safety and efficacy of a new investigational product but also with critical insights into the dynamics of the market into which an approved product will be introduced. Such insights are crucial, because clinical development in ALS is ultimately as much about evaluating the impact of novel therapy on a system of care as it is on the disease presentation and trajectory of an individual patient.

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