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Predictors Of Response In The Multimodal Treatment Of Attention Deficit And Hyperactivity Disorder Trial

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Predictors of Response in the Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder (MTA)

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ABSTRACT/SUMMARY

Baseline clinical characteristics can be used to predict treatment response in children with Attention Deficit and Hyperactivity Disorder (ADHD). This analysis aimed to identify empirically derived subgroups of children with ADHD based on likelihood of response to treatment within the 4 randomly assigned treatment groups of the Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA).

To identify clinical characteristics of predictive value selected data points were utilized for regression and receiver operating curve (ROC) analysis. Response to treatment at 14 months (defined as a 25-30% reduction in standardized score of symptoms obtained from the SNAP scale) for each treatment group was utilized as the binary outcome for ROC testing. The response rate in the 4 MTA-delivered treatment arms ranged from 77% (medication management and combination treatment groups) to 60% in the behavioral treatment group. By comparison, the response rate with community treatment was 57%.

ROC analysis identified subgroups of children with very different likelihoods of treatment response (ranging from 18-93%) using baseline clinical characteristic. These differential response rates are useful to identify patient subgroups that would most benefit from specific

treatment strategies, and provide useful prognostic data in the treatment of childhood ADHD.

Acknowledgements

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The Multimodal Treatment Study of Children with ADHD (MTA) was a

National Institute of Mental Health (NIMH) cooperative agreement randomized clinical trial involving six clinical sites. Collaborators from NIMH: Peter S. Jensen, M.D. (currently at REACH Institute and Mayo Clinic), L. Eugene Arnold, M.D., M.Ed. (currently at Ohio State University), Joanne B. Severe, M.S. (Clinical Trials Operations and Biostatistics Unit, Division of Services and Intervention Research), Benedetto Vitiello, M.D. (Child & Adolescent Treatment and Preventive Interventions Research Branch), John Richters, Ph.D. (currently at National Institute of Nursing Research), Donald Vereen, M.D. (currently at National Institute on Drug Abuse). Principal investigators and co-investigators from the 6 sites were: University of California, Berkeley/San Francisco: Stephen P. Hinshaw, Ph.D. (Berkeley), Glen R. Elliott, Ph.D., M.D. (San Francisco); Duke University: C. Keith Conners, Ph.D., Karen C. Wells, Ph.D., John March, M.D., M.P.H.; University of California, Irvine/Los Angeles: James Swanson, Ph.D. (Irvine), Dennis P. Cantwell, M.D., (deceased, Los Angeles), Timothy Wigal, Ph.D. (Irvine); Long Island Jewish Medical Center/Montreal Children's Hospital: Howard B. Abikoff, Ph.D. (currently at New York University School of Medicine), Lily Hechtman, M.D. (McGill University); New York State Psychiatric Institute/Columbia University/Mount Sinai Medical Center: Laurence L. Greenhill, M.D. (Columbia), Jeffrey H. Newcorn, M.D. (Mount Sinai School of Medicine); University of Pittsburgh: William E. Pelham, Ph.D. (currently at Florida International University), Betsy Hoza, Ph.D. (currently at University of

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Introduction:

Established treatment modalities for Attention–Deficit/Hyperactivity Disorder (ADHD) primarily include FDA-approved medication (especially stimulants) and behavioral therapy. With concerns for stimulant treatment in children, variation in treatment practices, and few controlled studies to guide the long-term treatment of ADHD, in 1992 the National Institute of Mental Health and Department of Education sponsored the Multimodal Treatment Study of Children with ADHD (MTA). The MTA was a multi-site randomized clinical trial of 579 patients who were treated with either careful medical management (MedMgt), multicomponent behavioral therapy (Beh), MedMgt + Beh (Comb), or routine community care (CC). Subjects were selected after careful assessment and diagnosis of DSM-IV ADHD Combined Type, and were not excluded for comorbid disorders (oppositional-defiant, conduct, and internalizing disorders or specific learning disabilities) as long as the comorbidity was not incompatible with study treatments.

Children were randomly assigned to one of the four treatment groups. Outcomes were assessed at baseline, 3 months, 9 months, and treatment

endpoint of 14 months to measure relative effectiveness of each treatment strategy (7). Random-effects (mixed effects) regression was used whenever possible for the intent-to-treat analysis, and outcome measures were organized into 6 domains (ADHD symptoms, Aggression/ODD, Internalizing symptoms, social skills, parent-child relations, and academic achievement) that were represented by a total of 19 measures.

ADHD and oppositional/aggressive symptoms were measured with the respective subscales of the parent- and teacher-completed Swanson, Nolan, and Pelham (SNAP) Rating Scale (1). The SNAP contains 18 ADHD and 8 Oppositional-Defiant Disorder symptoms scored on a 4-point Likert scale (0 "not at all' to 3 "very much") (1). The primary outcome of our study (partial response to treatment criterion) was defined as a 25-30% reduction in standardized score of symptoms (partial response) obtained from the SNAP scale (2). This response criteria is different than those employed in other studies, which limit response to "excellent responders". This measure was chosen to complement clinical interpretability of a previous ROC analysis, which used "excellent response" (essentially a remission criterion, a mean of 1.0 on the average of parent and teacher SNAP) as the outcome measure (3). "Excellent response" (4) criterion limit the interpretability of moderator subgroups to excellent responders.

This narrows the range of applicability in treatment populations, and may overlook some of the most at-risk and difficult to treat children, who show some improvement without achieving remission (3, 5). Further, prognostic information throughout treatment is still valuable for children who do not reach full remission criteria, and again is especially important for children whose initial symptoms are more severe (which is associated with poorer outcomes, and lower likelihood of reaching full remission (3, 48, 49).

Meta-analysis has previously demonstrated that psychostimulant medications, several non-psychostimulant medications and behavioral interventions are effective treatments for ADHD over the short-term (6-11). The MTA trial also demonstrated the superiority of the medication management treatment strategy compared to behavioral treatment and community care. The MTA primary analyses on separate domains found that medication management alone was not significantly inferior to combined treatment (with added behavioral intervention). However, secondary analyses using composited measures (Swanson et al, 2001; Conners et al, 2001) showed superiority of Comb over MedMgt by a small effect size (d=0.28). A 24-month follow-up with no further treatment by the study found MedMgt and Comb still superior to Beh and CC, but by

only half as much as at 14 months (MTA Cooperative Group, 2004). The MTA thus suggested that even over fairly long periods of time, (24 months), medication management appeared to be the most effective intervention in reducing ADHD symptoms in the overall study population, and that behavioral treatment provided little added benefit over medications alone.

Additionally, MTA trial results suggested a rational, evidence-based pharmacological approach to ADHD symptoms, which provided much greater symptom improvement than the routine community pharmacological management and behavioral treatment strategies. Based on the MTA results, ADHD appears to be one of the few child psychiatric conditions in which medication appears to work better than optimal behavioral treatment strategies.

The important findings from the MTA also extend far beyond the primary findings of the trial. Several secondary MTA analyses have focused on moderators of treatment effects. These secondary analyses examined whether certain baseline patient characteristics (for example comorbid clinical disorders, socioeconomic status and/or family factors) are associated with treatment outcomes in study participants, and could thus serve as "predictors" of treatment response. Secondary analysis

demonstrated that in children with ADHD and comorbid anxiety disorders, behavioral treatment was better than community care and very nearly reached the efficacy of medication in parent reported ADHD symptoms(12, 13).

Other secondary analyses of MTA trial data have associated family income, parents' marital status, parental history of depression, ineffective/negative parenting style, child IQ, complex comorbidities, parental cognitions, and ethnicity with treatment outcomes (3, 14-18). These analyses have clear implications for treatment approaches and tailoring effective strategies to children who will benefit the most from different interventions.

The previously conducted moderator analyses of the MTA trial have provided important information that can benefit the evidence-based treatment of children with Attention Deficit and Hyperactivity Disorder. However, there are several reasons that moderator analyses could be extended upon with a more integrated, data-driven analysis. These reasons include: (1) several baseline characteristics in the MTA trial have not been examined as potential predictors or moderators of outcome; (2) the relative clinical importance of implicated moderating variables still remains unclear; and (3) interactions between potential moderating

variables have not been fully explored. Our goal was to examine the potential moderating effect of baseline characteristics associated with treatment outcome using traditional logistic regression and receiver operating curve (ROC) analysis. These analyses were performed within each of the four treatment arms of the MTA data set.

Receiver operating curve analysis has several advantages over regression analyses in that: (1) Receiver operating curve allows for exploration of higher-order interactions between clinical variables and (2) is also hypothesis independent. We will use ROC analysis to identify empirically derived subgroups of children with ADHD who have similar likelihood of response to treatment within each of the 4 treatment arms of the MTA trial.

Receiver Operating Curve analysis has been used for a wide range of purposes, from evaluating medical tests (Kraemer HC., 1992) to utilizing baseline clinical variables as predictors/moderators of treatment response (19-21). Also, as the analysis relies on binary outcomes (response/non-response) in order to identify subgroups with differential prognosis (22), it is useful in generating empirically derived decision trees for treatment(3, 23). This is important to inform clinical treatment by identifying who will benefit (and from which intervention), as well as

potentially creating meaningful cutoff values necessary to guide public policy decision-making (24). These characteristics described also create an opportunity for tailoring treatment based on subgroup characteristics and likelihood for response to treatment.

As the primary aim of this work is to identify subgroups of patients with differential probability of response to treatment -including how baseline characteristics may interact to influence the likelihood of response- ROC analysis is a valuable addition to traditional regression analysis. ROC analysis is sensitive to higher-order interactions, and can evaluate a large number of predictor variables and their interactions (with no issues of multicollinearity). The ROC approach can also tolerate missing data from one subject without losing the other data collected from that subject. Finally, the cut points determined by the ROC approach are designed to minimize false positives and false negatives, but allows for fine adjustments in the weight of these two factors for optimal accuracy (22, 25-27).

STATEMENT OF PURPOSE

Optimization of treatment regimen and outcomes is an important part of determining clinical course and navigating various treatment options.

This is especially important when available treatment strategies include the use of stimulant medications in pediatric populations, or resource-intensive behavioral interventions.

Further, analysis of publically available MTA study data may allow for an increased availability of prognostic data based on standardized treatment regimens, and identification of subgroups of patients (based on baseline clinical characteristics) who are most likely to benefit from various treatment strategies.

We hypothesize that (1) baseline clinical characteristics will predict treatment response in children with ADHD and (2) informative baseline clinical characteristics predicting treatment response will differ based on treatment modality. The aim of this analysis is to identify empirically derived subgroups of children with ADHD based on their likelihood of response to treatment in the four subgroups of the MTA trail.

Methods:

Dr. Bloch acquired the MTA data set, and he supervised and advised us throughout the process. My role was to review all variables collected for the MTA trail, maintain documents and files of data and scales/measures, compete an extensive literature search, define response variables, and

evaluate the data generated from evaluation with the help of my research advisor and Mr. Jakubovski. After my literature search variables were selected based on previous studies showing relevance/predictive value. Other variables were selected because they had not been reported in the literature, and finally some were deemed worth inclusion after a discussion of their clinical relevance or ease of baseline assessment. I was also responsible for generating diagrams of relevant data.

Study Overview:

The rationale, design, aims, and methods of the MTA trial have been described elsewhere (28-30). All participants and their parents provided informed consent (and assent). The National Institutes of Health as well as the Institutional Review Boards at each of the clinical research sites approved the research protocol. No additional ethics review processes were required to access this data set.

Subjects:

Five hundred seventy-nine children were recruited. A detailed description of the demographic and clinical characteristics of the subjects in each treatment group can be found in the original MTA publication(30, 31). Subjects were recruited to represent a wide range of demographic characteristics and comorbidities associated with Attention Deficit and Hyperactivity Disorder. The selection aimed to create a representative

sample of the children seen in clinical practice from all six sites across the United States and Canada. To be included in the MTA trial subjects of either sex were required to be between the ages of 7 and 9.9 (grades 1-4) and in residence with the same primary caretaker for at least the last 6 months and meet DSM-IV criteria for ADHD Combined type, using the Diagnostic Interview Schedule for Children (DISC version 3.0) supplemented with 2 teacher reported symptoms for children close to the diagnostic threshold.

Exclusion criteria included the inability to participate in all components of the study (e.g., hospitalization, if the child had a history of intolerance to MTA medication, or non-English speaking primary caretaker). Children were also excluded if they required other treatments that were incompatible with any of the four possible MTA treatment assignments (for example, Bipolar Disorder, Tourette Syndrome, or any neuroleptic medications in the last 6 months).

Assessment:

Participants in the MTA study were assessed at their baseline, 3 months, 9 months, and at 14 months. ADHD and oppositional/aggressive symptoms were measured with the respective subscales of the parent- and teacher-

completed Swanson, Nolan, and Pelham (SNAP) Rating Scale (1). The SNAP is a standardized scale contains 18 ADHD and 8 Oppositional-Defiant Disorder symptoms scored on a 4-point Likert scale (0 "not at all' to 3 "very much") (1). The primary outcome of our study (response to treatment) was defined as a 25-30% reduction in standardized score of symptoms obtained from the SNAP scale (2).

Social skills and internalizing symptoms were assessed with the corresponding subscales of the parent- and teacher-rated Social Skills Rating System (SSRS) (32). Parent Child Relations were measured with a parent child relationship questionnaire (33). Parent Practices were assessed using the Alabama Parenting Questionnaire, specifically in the domain of parental involvement (34). Internalizing and Externalizing scores were collected with the Child Behavior Checklist (CBCL) (35). The CPT Impulsivity score was used in the assessment of attention and impulsivity (36). Child IQ was determined using the Wechsler Intelligence Scale for children (37). Parent, teacher, and child ratings were supplemented with blinded ratings of school observations.

The Yale Global Tic Severity Scale (YGTSS) (both current and worst ever) (38), Beck Depression Inventory (BDI)(39), and the multidimensional

anxiety scale (40) were also collected as clinical variables. Behavior Problems were recorded using self-reported antisocial behavior.

Behavioral problems that were recorded for study purposes included property destruction, stealing, and physical aggression. The total score on the Child behavior Checklist (CBCL) was recorded, acting as a measure of social problems, and both internalizing and externalizing symptoms. The Parent Rated Social Skills Rating System(32) also had a total score, with subscales measuring cooperation, assertiveness, responsibility, social conduct, internalizing and externalizing symptoms, and hyperactivity (35). The SCID - Antisocial Personality Scale – for Parents(41) also recorded the history of Conduct Disorder and Antisocial Personality Disorder, while the parent rated Aggression and Conduct Problems Scale created from DSM-IV checklists collected other measures of conduct problems and aggression.

Problems at school were measured with the number of days absent from school in the previous 12 months, history of expulsions from school, use of school services, special education received by the child and the homework problem checklist(42). Parent-Child relationship measures were also collected, which included the Alabama Parenting Questionnaire

parent-rated discipline (inconsistent, harsh, appropriate), parental involvement, supervision, and positive parenting (43). The parent and child ratings from the Parent-Child Relationship Questionnaire (33) (including praise, parental rationale, shared decision making, possessiveness/protectiveness, affection, quarreling, affection, pro-social behaviors, similarity, dominance, intimacy, physical punishment, admiration (of and for parents both parents and children), nurturance, companionship, and guilt induction) were also recorded in the study. Additionally, parental variables including knowledge about behavioral principles, parental expectations questionnaire (total expectation on child obedience as rated by parents), and parenting stress index (PSI) (defensive responding, parent distress, parent-child dysfunction, difficulty of child) were analyzed(44).

Intervention:

Participants were randomized to one of four treatment arms (medication management, behavioral treatment, combined treatment with medication management and behavioral treatment, and community care) for 14 months. Each of these treatment arms was designed as a management strategy that would be flexible to each patient's unique and individual

clinical needs throughout treatment. Full details regarding the treatment received in each of these randomized treatment groups is defined elsewhere (45, 46).

These treatment strategies were modeled after treatment strategies for ADHD with previously well-established efficacy. Behavioral treatment included 35 sessions of integrated parent training (45, 46), as well as child-focused treatments (an intensive child-focused summer training program)(47)and school based interventions that were integrated within the participant's school year. This treatment arm also included an intensive child-focused summer training program(47). To be consistent with clinical practice, these treatments were tapered with the ultimate goal of parent-managed behavioral treatment.

Medication management involved a 28-day double blind, placebo-controlled titration of methylphenidate hydrochloride with subsequent monthly monitoring and algorithm guided dose adjustments. For subjects not responding to methylphenidate, openly titrated amphetamine and other medications were utilized. Combined treatment provided both the behavioral treatment and medication management. Regular supervision of pharmacotherapists and psychotherapists was emphasized to ensure strict adherence to protocols across all sites.

Subjects randomized to the community care arm of the MTA study did not receive treatment from the MTA, but instead were provided an extensive list of the local community mental health referral resources and their initial study assessments. Data on the treatments received in the community mental health resources was collected at each time point, with most children (67.4%) receiving medication at some point. All 6 sites were crossed with all treatment conditions, such that all interventions were provided at all of the MTA trail sites.

Statistical Analysis:

Data preparation was conducted using SAS version 9.2 and Microsoft Excel. Both logistic regression models and signal detection methodology were used to find the best prediction model. SAS was used for simple and multiple logistic regression models. The ROC analysis was performed using free software available online from Ruth O'Hara at Stanford University (http://www.stanford.edu/~yesavage/ROC.html). Data utilized in this study was obtained from the National Institute of Mental Health MTA Data Set.

Logistic regression models assessed the association of the demographic, social, and clinical characteristics with response using change from baseline on the SNAP total score as the outcome variable. Not surprisingly, studies have found that increased initial severity of ADHD symptoms is associated with worse treatment response (3, 48, 49). The definition of response to treatment for this study was a reduction of 25-30% in symptoms (as measured by the SNAP scale) at the end of 14 months (2). As previously noted, this measure was chosen to extend clinical interpretability to include partial responders. In contrast many previous analyses have used full remission criteria or "excellent responders".

First, all predictor variables were tested separately. Next, significant predictors ($p<.05$) from the simple regression models were entered into a backward step-wise multiple logistic regression model to assess the unique and independent contribution of these variables to the response rate in each of the four treatment arms of the MTA trial.

Receiver Operating Curve analysis was used as an alternative, non-parametric method that operates via recursive partitioning. It aims at

identifying subgroups of children who have a differential probability of achieving a particular binary outcome that have been defined (27). Across all predictor variables, the cut-off point that yields the best prediction is then used to divide the total sample in two subsamples. The same procedure is repeated systematically in each subsample again and again. This iterative process continues until a subgroup contains less than ten individuals or the group difference is not significant at an alpha level of 0.05. We also stopped the analysis at the three-way interaction level. Models were calculated for response and remission on all four scales as the outcome variable.

Both logistic regression and Receiver Operating Curve analysis were conducted for each of the four treatment arms separately. Baseline characteristics were entered as predictor variables into both models, including demographic variables (age of the child, race, sex, and the size of the city most lived in). Other baseline characteristics that were also collected were related to both parents (if the data was available). Variables such as parental welfare, employment status, educational achievement, and income status were collected. Information about the medical history of the mother and child (for example, neonatal history

including pregnancy length, birth weight, nicotine exposure in utero), and compliance (to medical and psychosocial treatment) was also recorded.

Additionally, neuropsychological variables included continuous performance task (CPT) which provides scores of impulsivity, inattention, and dyscontrol (36), as well as the Wechsler Intelligence Scale For Children score (37) (WISC III) measuring verbal, performance, and full scale IQ were also collected. The parent version of the Diagnostic Interview Schedule for Children (DISC) was used to provide information regarding comorbid disorders. These comorbid disorders include anxiety (both separation type and generalized), phobia (including simple and social), panic disorder, tics (both chronic and transient), and depression. Information regarding family of Attention Deficient and Hyperactivity Disorder, alcohol abuse, drug abuse, tics, Tourette syndrome, anxiety, depression, obsessive-compulsive disorder, psychiatric hospitalization, and history of incarceration were also collected at each time point.

Results:

The response rate across all of the MTA-delivered treatment arms ranged from a high of 77% (medication management and combination treatment groups) to a low of 60% in the behavioral treatment group. By comparison, the response rate with community treatment was 57%. Response rates in specific subgroups of patients are detailed below.

Combination Treatment:

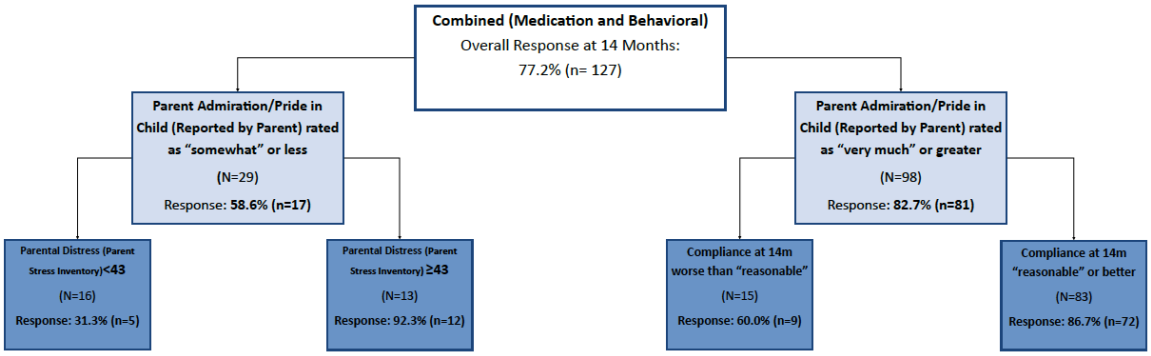

Figure 1 depicts the empirically derived hierarchical prognostic subgroups for response to combination (behavioral + pharmacologic) treatment in the MTA. N= Total Number of Children in the group, n=number of responders

Across all predictor variables, the cut-off point that yields the best prediction (in this example Parent Admiration/Pride in the child, as

reported by parent score of 4) is then used to divide the total sample in two subsamples (seen here as 29 children with a score of less than 4, and 98 with a score greater than or equal to 4). The same procedure is repeated systematically in each subsample (in this example with compliance to treatment at 14 months and Parental Distress Scores) until a subgroup contains less than ten individuals or the group difference is not significant at an alpha level of 0.05.

The overall response to treatment in this combination treatment group was 77.2%. Baseline clinical characteristics were able to identify subgroups with as low as a 31.3% likelihood of responding to combination treatment (parent admiration of child reported by parent as "somewhat" or less, and also parents who believe their child is "about as difficult or less" than expected) to as high as a 92.3% likelihood of responding to combination treatment (parent admiration of child reported by parent as "somewhat" or less, and parents who believe their child is "about as or more difficult than expected"). The most discriminative predictor of response was the level of parent admiration/pride in child (as reported by parent). [$\chi 2$ (1, N=127)=7.34, p<.01].

In logistic regression analysis (Table A) maternal (gestational) smoking during pregnancy was associated with poor response to combination treatment.

Table A
Univariate Regression Analysis in MTA Combination Treatment Arm

	Point Estimate	95% Wald Confidence Limits		p
Mother smoked during pregnancy	0.361	0.145	0.898	0.028

Medication Management:

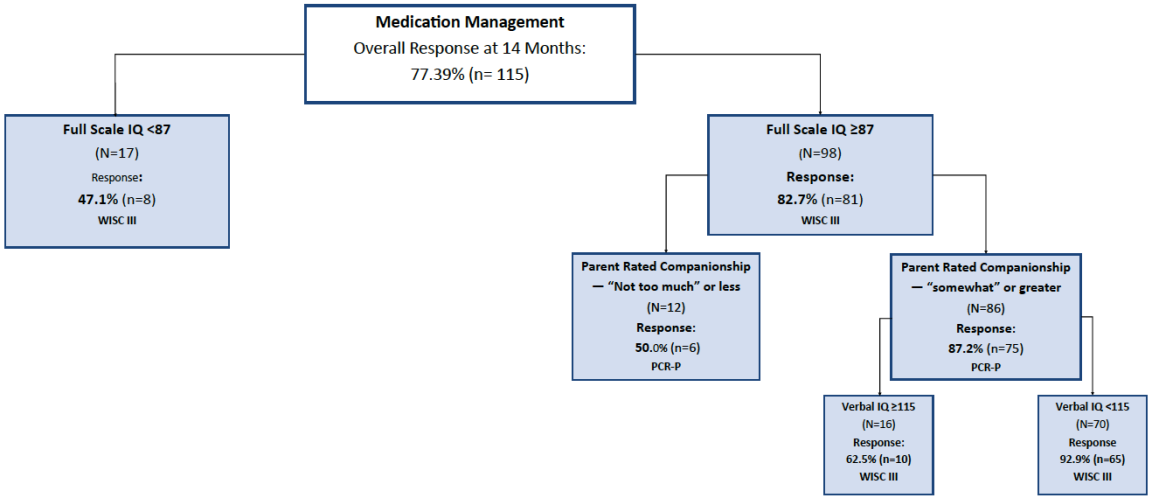

Figure 2 depicts the empirically derived hierarchical prognostic subgroups for response to medication management in the MTA Trial.

Overall response to treatment in this group was 77.4%. Baseline clinical characteristics were able to identify subgroups with as low as 47.1% likelihood of responding to medication (Full scale IQ less than 87) to as high as a 92.9% likelihood of responding to medication management (Full scale IQ greater than or equal to 87, parent-rated companionship rated as high, and a verbal IQ less than 115). The most discriminative predictor of response was the full scale IQ. [$\chi 2$ (1, N=115)=10.5, p<.001].

Baseline characteristics associated with poor response to medication management in logistic regression analysis (Table B) included number of

days the child was absent from school in the previous year, a family history of incarceration, a household member receiving welfare, and self-identifying as black. The child's perception that they shared more in decision making with the parent was also associated with decreased response to treatment. Multivariate regression analysis suggested that the best-fitting model, which accounted for 9% of the variability in response to treatment included child -rated shared decision-making.

Table B

Univariate Regression Analyses in Medication Treatment Arm

	Point Estimate	95% Wald Confidence Limits		p
FH of Incarceration	0.383	0.148	0.992	0.048
Any Part of Household on Welfare	0.351	0.125	0.983	0.0464
Ethnicity Self-reported as Black	0.323	0.119	0.878	0.0267
Shared Decision Making	0.578	0.365	0.917	0.02
Absent days at school in last 12 months	0.593	0.361	0.973	0.0386

Multivariate Regression Analysis in Medication Treatment Arm

Shared decision making	0.567	0.351	0.918	0.0209
Absent days at school in last 12 months	0.568	0.34	0.949	0.0307
R-Square	0.09			

Behavioral Treatment:

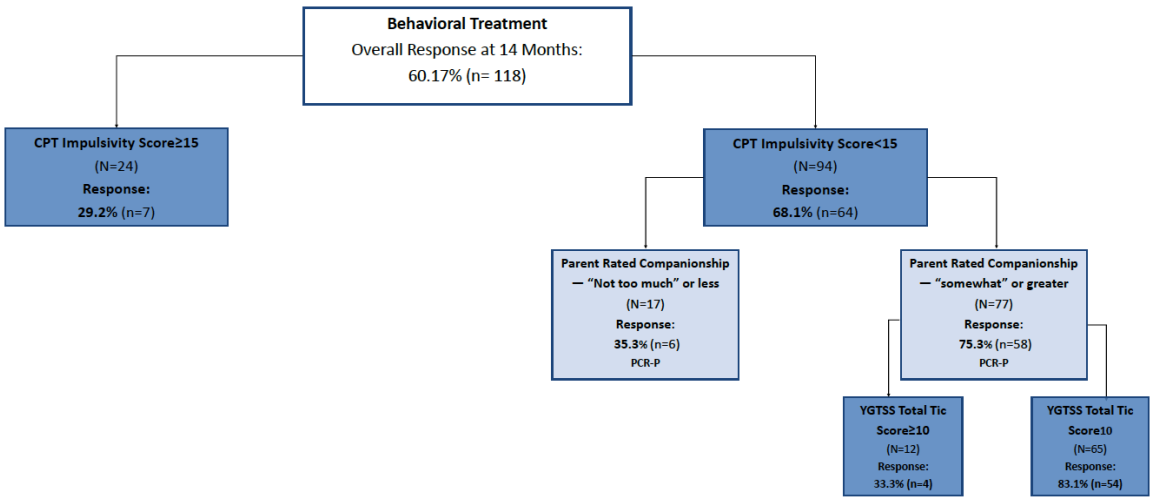

Figure 3 depicts the empirically derived hierarchical prognostic subgroups for response in the behavioral management treatment group of the MTA trial.

Overall response to treatment in this group was found to be 60.2%. Baseline clinical characteristics were able to identify subgroups with as low as 29.2% likelihood of responding to behavioral treatment (CPT Impulsivity score greater than or equal to 15) to as high as a 92.9% likelihood of responding (CPT Impulsivity score less than 15, parent rated companionship as "somewhat" or greater, and a YGTSS rating of less than

10). The most discriminative predictor of response was CPT Impulsivity score [$\chi 2$ (1, N=118)=12.1, p<.001].

Baseline characteristics associated with poor response to behavioral treatment in regression analysis (Table C) included being born premature, higher CPT impulsivity score, and high scores of parent-rated "nurturance (Nurturance being how much parents help/show children how to complete tasks)". In the multivariate regression analysis nurturance and CPTH Impulsivity scores account for 9% of the variability in response to treatment.

Table C

Univariate Regression Analysis in Behavioral Treatment Arm

	Point Estimate	95% Wald Confidence Limits		p
Preterm Birth	2.965	1.015	8.658	0.047
CPTH Total Impulsivity Score	0.936	0.892	0.983	0.008
Nurturance	0.6503	0.3297	3.8911	0.049

Multivariate Regression Analysis in Behavioral Treatment Arm

CPTH Total Impulsivity Score	0.938	0.891	0.987	0.013
Nurturance	2.082	1.031	4.205	0.041
R-Square	0.0904			

Community Treatment:

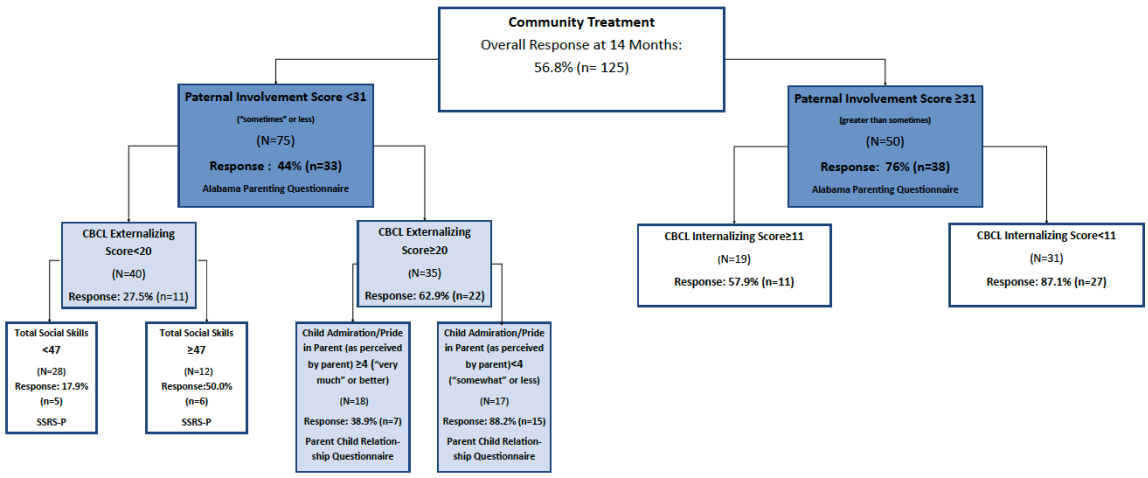

Figure 4 displays the empirically derived hierarchical prognostic subgroups for response to community treatment in the MTA.

Overall response to treatment in this group was 56.8%. Baseline clinical characteristics were able to identify subgroups with as low as 18% likelihood of responding to community treatment (father is rarely involved in daily matters (homework, conversation, friends), involvement in delinquent or aggressive behaviors either absent or minimally present, and a total social skills score less than 47) to as high as a 88.2% likelihood of responding to community treatment (father is "sometimes" involved in daily matters (homework, conversation, friends), involvement

in delinquent or aggressive behaviors present (minimally or greater), and a perception of how much child admires/respects parent -rated by parent- as between somewhat and hardly at all). The most discriminative predictor of response was the level of paternal involvement (as reported by child). [$\chi 2$ (1, N=125)=12.5, p<.001].

Baseline characteristics associated with response to community treatment in logistic regression analysis include parental factors. Paternal Involvement was associated with increased response to community treatment. "Rationale" (i.e., the degree to which parents explain why they create certain rules and deliver punishment as rated by children) was associated with decreased response to treatment. Multivariate regression analysis including these two variables explained just over 5% of the variability in response to community treatment.

Table D

Univariate Regression in Community Treatment Arm

	Point Estimate	95% Wald Confidence Limits		p
Involvement of Father in Child's Life	1.069	1.01	1.131	0.022
Rationale	0.716	0.513	0.998	0.049

Multivariate Regression in Community Treatment Arm

Involvement of Father in Child's Life	1.087	1.021	1.157	0.009
Rationale	0.64	0.42	0.975	0.038
R-Square	0.0522			

Discussion:

Empirically-driven moderator analysis of the MTA trial data revealed several important findings regarding treatment prognosis in childhood ADHD. These findings included:

(1) Using baseline characteristics Receiver Operating Curve analysis identified subgroups of children with very different likelihoods of treatment response (ranging from 18-93%) which is useful to prognosticate and identify patient subgroups that would most benefit from specific treatment strategies.

(2) Predictor of treatment outcome were not consistent across the different treatment arms of the MTA trial. As a rule, more biologically-based causes and measures of ADHD (CPT impulsivity score, prematurity) were most useful in predicting response to behavioral treatment while socioeconomic factors were more useful in predicting response to medication management or community treatment, which was mainly medication.

(3) Measures examining characteristics of the parent-child relationship (e.g., paternal involvement, Alabama parenting scale subscores (43)) were quite informative in predicting treatment outcome , although the specific informative measures were not consistent across treatment

groups. (4) Several baseline characteristics previously identified as risk factors for ADHD – maternal smoking and prematurity- were also associated with treatment outcome in specific MTA treatment groups.

Maternal smoking and prematurity have been associated in many previous studies with risk of ADHD (50, 51). This study extends those results by showing maternal smoking during pregnancy decreases the likelihood of response to combination treatment. In a similar manner, prematurity was associated with response rate in the behavioral treatment. Apparently these putative biological causes predict poor response to behavioral treatment.

In addition to prematurity, more biologically based measures predicted outcomes to behavioral treatment. Neuropsychological variables including the CPT Impulsivity Score and IQ were moderating variables in 2 treatment arms (in the behavioral and medication management groups, respectively). IQ has also been found to be a moderator of response in other studies, both in the MTA (3) and in earlier drug studies(52). In the Behavioral treatment group the CPT Impulsivity score -considered an

objective marker for impulsivity which has gained popularity since the 1950's as a research tool- was associated with poorer outcomes (53, 54).

In contrast to behavioral treatment, socioeconomic variables were associated with response in medication groups (community and pharmacotherapy). Welfare, a family history of incarceration, and self-identifying as black were associated with poorer outcomes in this study. Prevalence of ADHD has been reported to be higher in socioeconomically disadvantaged groups (55). The mechanism for the linkage of lower SES and development of ADHD is not completely clear, though there is literature providing alternative explanations and evidence (56). It is clear from our analysis that these socioeconomic factors are also associated with lower likelihood to respond to medication alone. This is compatible with a previous MTA finding that minority children (who tend to be disadvantaged), but not non-Latino white children, benefit more from Comb than from MedMgt (57).

This moderator analysis also suggests that parent child relationships have particularly important predictive value in ADHD. Further study is required to understand mechanisms of these effects (58, 59). Paternal involvement, which was a good indicator of response in the community

treatment group, also emerged in the regression analysis. There is much room in the literature to better understand paternal involvement in the development and resolution of children's behavioral and emotional issues (60).

Clinical Implications

These results suggest that greater parental pride in the child (as reported by the parent) predict a good combination treatment response. Also "organic" etiologies (prematurity, gestational smoke exposure) and impulsivity interfere with the efficacy of behavioral treatment. Low IQ, much absence from school, and child sharing in decision-making (which may suggest a lack of home structure) predict poor medication response. Finally a predictor of good treatment response is paternal involvement with the child.

Limitations

The results of this analysis require replication because prognostic subgroups were empirically derived without hypotheses. However, even with empirically derived subgroups, ROC analysis has the distinct advantage of analyzing higher order interactions between easily measurable baseline clinical characteristics.

Another limitation is the sample size of the MTA trial, which was designed to be large enough to have adequate power to set the lower limit of clinical significance as an effect size of .4 and 80% power (5% level of confidence), but not necessarily designed to power the generation of prognostic subgroups and moderator identification.

Other limitations of this paper stem from -and are shared with- the original MTA Study.. Other limitations that are secondary to data collection methods of the original paper include post-treatment evaluation of medication-managed children (while they were actively medicated) versus 4-6 months after fading of Beh began. (61). However, a finer-grained comparison of the 9- and 14-month assessments found that the Beh group actually improved more between the 9-month assessment, at the end of intense behavioral treatment, and the 14-month assessment, confirming that the fading/generalization procedures were successful (Arnold et al, 2004).

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