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Escalation to Major Depressive Disorder among Adolescents with Subthreshold Depressive Symptoms: Evidence of Distinct Subgroups at Risk

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Abstract

Background—The presence of subthreshold depressive symptoms (SubD) in adolescence is associated with high prospective risk of developing Major Depressive Disorder (MDD). Little is known about variables that predict escalation from SubD to MDD. This study used a longitudinal prospective design in a community sample of adolescents to identify combinations of risk factors that predicted escalation from SubD to MDD.

Methods—Classification tree analysis was used to identify combinations of risk factors that improved the sensitivity and specificity of prediction of MDD onset among 424 adolescents with a lifetime history of SubD.

Results—Of the 424, 144 developed MDD during the follow-up period. Evidence for multiple subgroups was found: Among adolescents with poor friend support, the highest risk of escalation was among participants with lifetime histories of an anxiety or substance use disorder. Among adolescents with high friend support, those reporting multiple major life events in the past year or with a history of an anxiety disorder were at highest risk of escalation.

Limitations—Study findings may not inform prevention efforts for individuals who first develop SubD during adulthood. This study did not examine the temporal ordering of predictors involved in escalation from SubD to MDD.

Conclusions—Adolescents with a history of SubD were at highest risk of escalation to MDD in the presence of poor friend support and an anxiety or substance use disorder, or in the presence of

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Conflict of Interest

The authors have no conflicts of interest to report.

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better friend support, multiple major life events, and an anxiety disorder. Findings may inform case identification approaches for adolescent depression prevention programs.

Keywords

Depression; Onset; Adolescence; Subthreshold depression

As many as 26% of adolescents endorse subthreshold depressive symptoms (SubD) that cause impairment, yet fall short of DSM-IV criteria for a diagnosis of MDD (Klein et al., 2009). The presence of SubD is associated with high prospective risk of developing MDD (Pine et al., 1999, Georgiades et al., 2006, Keenan et al., 2008, Shankman et al., 2009), although approximately 2/3 of adolescents who experience SubD never escalate to full syndrome MDD (Shankman *et al.*, 2009). A recent meta-analysis concluded that SubD and MDD show similar clinical characteristics and outcomes in children and adolescents (Wesselhoeft et al., 2013). Research is needed to identify those adolescents with SubD who are at highest risk of escalation to MDD and who are, therefore, most in need of prevention services. Identification of variables that increase risk of escalation from SubD to MDD has the potential to improve the accuracy and efficiency of screening procedures and focus prevention programs on targets that are most likely to reduce the risk of symptom escalations. Indicated prevention programs enroll adolescents based on the presence of depressive symptoms, usually without consideration of additional risk factors (for a review of indicated depression prevention programs for adolescents, see Garber et al., 2009). Selective prevention programs enroll adolescents based on the presence of MDD risk factors such as family conflict (Gillham et al., 1995, Jaycox et al., 1994, Yu and Seligman, 2002), environmental stressors (e.g., poverty, Cardemil et al., 2002), or predisposing vulnerabilities (e.g., negative attributional style, Seligman et al., 1999), usually without consideration of existing symptoms of depression. Both indicated and selective approaches cast a wide net, identifying and enrolling a large number of at risk adolescents, many of whom would not develop MDD without intervention. Refinement of case identification through the use of combined selective and indicated identification strategies may result in greater selection accuracy, which would promote more efficient use of limited prevention resources.

The purpose of the present study was to identify combinations of risk factors that predict escalation from SubD to MDD. As noted previously, only a portion of adolescents with a history of SubD will escalate to MDD. Additional factors (other predisposing vulnerabilities, environmental changes, and/or protective factors) may start, sustain, or disrupt the depressogenic cycle. To our knowledge, three past studies have addressed this issue (Cuijpers et al., 2006, Cuijpers et al., 2005, Klein et al., 2009), the last of which used a subset of the present study sample. Those studies found that greater severity of subthreshold depressive symptoms and the presence of medical problems, suicidal ideation, history of anxiety disorder, and a family history of MDD significantly predicted escalation to MDD. Those studies were important in identifying factors that prospectively predicted escalation from SubD to MDD, but did not examine combinations of predictor variables that may identify different subgroups of adolescents likely to escalate to MDD.

The present study examined prospective predictors of escalation from SubD to full syndrome MDD in a school-based sample of adolescents, the Oregon Adolescent Depression Project (OADP). Because prior research has examined univariate predictors of escalation to MDD (Cuijpers 2005; Klein 2009), the present study focused specifically on the identification of combinations of risk factors (i.e., interactions) that predicted escalation. A statistical approach called classification tree analysis (CTA) was used to identify such interactive effects. CTA allows for the identification of combinations of risk factors that improve the sensitivity and specificity of prediction. CTA generates a classification tree; branches on the tree reflect significant interactions between risk factors resulting in enhanced prediction of escalation to MDD. The terminal nodes of the classification tree (points where the classification tree fails to branch) indicate that no further significant improvements in classification were available based on the data provided. Terminal nodes represent distinct subgroups of individuals likely to escalate (or not) from SubD to MDD.

Based on prior research on SubD and the larger literature on predictors of MDD onset, several predictors were examined: female gender as a status variable (e.g., Klein et al., 2009); the presence of environmental changes, such as major negative life events (e.g., Hammen, 2005) and minor hassles (e.g., Lewinsohn et al., 1994); the presence of psychiatric risk factors, such as history of anxiety disorder (e.g., Klein et al., 2009), history of substance abuse or dependence (e.g., Rao et al., 2000), and depressive symptoms (e.g., Klein et al., 2009); and the presence of cognitive-interpersonal risk factors, such as dysfunctional attitudes, emotional reliance, and family support and friend support (e.g., Lewinsohn et al., 1994).

Method

OADP participants were randomly selected from nine high schools in western Oregon. A total of 1709 adolescents (ages 14–18; mean = 16.6, SD = 1.2) completed an initial (T1) assessment between 1987–1989. A total of 8.9% were non-White; 71.3% were living with two parents, and 53% were living with two biological parents. Parental education (maximum value for mother or father) was as follows: 1.9% did not complete high school, 16.1% completed high school, 35.1% had some college, and 46.9% had an academic or professional degree.

Approximately one year later, 1507 (88%) returned for a second evaluation (T2; mean age = 17.7, SD = 1.2). Differences between the sample and the larger population from which it was selected, and between participants and those who declined to participate or dropped out of the study before T2, were small (Lewinsohn et al., 1993). At age 24, all participants with a history of Axis I psychopathology ($n = 644$) by T2 and a random sample with no history of Axis I psychopathology ($n = 457$) were invited to participate in a third (T3) evaluation. Of the 1101 T2 participants selected for a T3 interview, 941 (85.4%) completed the evaluation. At age 30, all T3 participants were invited to participate in a T4 evaluation. Of the 941 T3 participants, 816 (86.7%) completed the T4 interview, of which 484 (59.3%) were women. Among those invited to T3 and T4 assessments, women were more likely than men to complete evaluations, χ^2 's > 5.99 , p 's $< .05$. Participation did not differ as a function of other demographic variables or previous diagnoses.

The sample for the current investigation included the 424 participants (58.0% women, 92.5% white) who met criteria for a lifetime diagnosis of SubD at T1 (Lewinsohn et al., 2004), had no prior history of MDD, dysthymia, or bipolar disorder, and completed at least one follow-up assessment. The research described in this manuscript was reviewed and approved by the appropriate institutional review boards.

Diagnostic Status

Participants were interviewed with a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) at T1, T2, and T3 that combined features of the Present Episode and Epidemiologic versions (Chambers, 1985, Orvaschel et al., 1982). In conjunction with the K-SADS, the Longitudinal Interval Followup Evaluation (LIFE, Keller et al., 1987) was used to evaluate the presence and course of disorders since the previous diagnostic interview. T4 diagnostic assessments were based on the Structured Clinical Interview for Axis I DSM-IV Disorders–Non-Patient Edition (SCID-NP, First et al., 1995), with the LIFE also used to evaluate disorder presence and course since T3. Diagnoses were derived using DSM-III-R criteria (American Psychiatric Association, 1987) at T1 and T2 and DSM-IV criteria (American Psychiatric Association, 1994) at T3 and T4. Interviews at T3 and T4 were conducted by telephone, which generally provides comparable validity to face-to-face interviews (Rohde et al., 1997, Sobin et al., 1993).

Dichotomously-coded variables were created to represent the lifetime presence of SubD at T1, any anxiety disorder at T1 (ANX, $n = 38$, 9.0% of the sample), and any substance use disorder at T1 (SUD; $n = 27$, 6.4%). Consistent with prior research, SubD was operationally defined an episode of depressed mood or loss of interest or pleasure lasting at least one week, and at least two of the seven other DSM-IV MDD criteria symptoms (Klein et al., 2009, Lewinsohn et al., 2004, Shankman et al., 2009). Exclusion criteria for SubD included a lifetime history of full syndrome dysthymic disorder, MDD, or bipolar disorder. Independent review of randomly selected T1 cases revealed excellent inter-rater reliability ($\kappa = .80$) for SubD and SUD and acceptable inter-rater reliability ($\kappa = .53$) for T1 lifetime ANX. In addition, a dichotomous variable was created to represent the lifetime presence of MDD by T2, T3, or T4. The reliability of MDD diagnosis across the 4 waves was high (κ ranged from 0.81 to 0.86; Olino et al., 2012).

T1 Measures

The following psychosocial measures were assessed at T1. These measures and their reliability in the OADP sample have been described in detail in previous publications (Andrews et al., 1993, Lewinsohn et al., 1994, Mathew et al., 2011). A brief description of each construct is given below.

Depressive symptoms—This measure assessed the severity of subthreshold depressive symptoms using the Beck Depression Inventory (21 items; Beck et al., 1988). In the present sample, the mean T1 BDI score was 7.61 ($SD = 7.07$). The internal consistency (Cronbach's α) in the present sample was 0.87.

Major life events—This measure assessed the occurrence of 14 negative major life events to self in the year preceding T1. Events were selected from the Schedule of Recent Experiences (Holmes and Rahe, 1967) and the Life Events Schedule (Sandler and Block, 1979). The mean number of major life events was .92 ($SD = 1.16$).

Minor hassles—This measure assessed the frequency of occurrence of unpleasant events in the month preceding T1 (20 items; Unpleasant Events Schedule, Lewinsohn et al., 1985). The mean score on the measure of minor hassles was 48.58 ($SD = 11.39$). The internal consistency in the present sample was 0.87.

Dysfunctional attitudes—This assessed dysfunctional attitudes, the tendency to generalize from a specific bad outcome to a negative sense of self-worth (9 items; DAS; Weissman and Beck, 1978). The internal consistency in the present sample was 0.74.

Emotional reliance—The extent to which participants desired more support and approval from others, were anxious about being alone or abandoned, and were interpersonally sensitive was assessed with the emotional reliance subscale of the Interpersonal Dependency Inventory (10 items; Hirschfeld et al., 1977). The mean score on emotional reliance was 23.24 ($SD = 6.14$). The internal consistency in the present sample was 0.83.

Family social support—This construct was measured with eight continuously-scored items. Example items include “How well do you get along with your siblings?” and “How well do you get along with your parents?” Higher scores indicate lower support from family. The mean score was 8.22 ($SD = 7.07$). The internal consistency in the present sample was 0.77.

Friend social support—This construct was assessed with seven continuously-scored items. Example items include “How many close friends do you have?” and “How well do you get along with other kids?” Higher scores indicate lower support from friends. The mean score was 29.56 ($SD = 3.55$). The internal consistency in the present sample was 0.72.

Data Analysis

CTA was run using Optimal Data Analysis software (Yarnold and Soltysik, 2005). All T1 risk and protective factor variables were entered as predictors of MDD onset. Prior to analysis, sampling weights were applied to account for sampling selection at the T3 evaluation. CTA identifies the optimal cut point for each predictor variable that maximizes the accuracy of that predictor for classifying subjects and then tests whether the optimal cut point provides a statistically significant improvement in prediction of the outcome. All statistically significant predictors were examined and the predictor with the greatest effect strength for sensitivity (ESS) was retained, a branch was created, and the procedure was repeated separately for each branch. This procedure was repeated until there were no statistically significant predictors of MDD onset within each branch. ESS is a measure of improvement in classification over chance classification provided by a given predictor variable and optimal cut point. An ESS of 0% represents no improvement over chance classification, whereas an ESS of 100% represents perfect classification (Yarnold and

Soltysik, 2010). ESS values from 0 to 25% are considered small effects, from 25% to 50% are considered medium effects, and greater than 50% are considered large effects (Stalans et al., 2004). To set the overall Type I error rate of .05, the CTA was adjusted using a progressively restrictive Bonferroni procedure, such that at each tier the alpha level was defined as .05 divided by the number of potential tests that could be conducted at that tier. Thus, for the first tier, alpha was set to .05, for the second tier, where two branches were possible, alpha was set to .025, for the third tier, where four branches were possible, alpha was set to .0125.

Results

Classification Tree Analysis (CTA)

CTA resulted in a classification tree with five forks and six terminal nodes. Figure 1 displays the final classification tree; the initial sample of adolescents with a history of SubD appears at the top, with subsequent branches representing distinct nodes, their sample sizes, and MDD incidence rates. The total incidence rate of MDD was 33.96%, with 144 of the 424 adolescents escalating to MDD.

The strongest predictor of escalation from SubD to MDD was friend social support, with a score of 31.3 (0.49 SD above the mean) providing the most accurate cutoff, $p < .001$, ESS = 14.42%. Other significant predictors in the analysis (but which had lower ESS values and so did not provide optimal prediction of escalation to MDD at this step) included T1 lifetime ANX, T1 lifetime SUD, and major life events. Participants with poor friend support (i.e., scores > 31.3 ; $n = 132$) were significantly more likely than participants with better friend support (i.e., scores ≤ 31.3 ; $n = 292$) to develop MDD during the follow-up period (incidence rate: 45.45% vs. 28.77%,).

Among the 132 participants with poor friend support, the strongest predictor of MDD onset was T1 lifetime ANX, $p < .001$, ESS = 10.23%. The other significant predictor in the analysis was T1 lifetime SUD. Among those with poor friend support, those with a T1 lifetime history of ANX ($n = 12$) were significantly more likely than those with no T1 lifetime history of ANX ($n = 120$) to develop MDD (incidence rate: 75.00% vs. 42.50%). For those with poor friend support and T1 lifetime ANX, there were no additional significant predictors, making this a terminal node. Among those with poor friend support and no T1 lifetime ANX, the strongest predictor of MDD onset was a T1 lifetime history of SUD, $p < .01$, ESS = 8.56%. There were no other significant predictors at this branch. Among those with poor friend support and no T1 lifetime ANX, those with T1 lifetime SUD ($n = 16$) were significantly more likely than those with no T1 lifetime SUD ($n = 104$) to develop MDD (incidence rate: 56.25% vs. 40.38%). Both of these were terminal nodes.

Among the 292 participants with better friend support, the strongest predictor of MDD onset was the presence of two or more major life events in the year preceding T1, $p < .01$, ESS = 13.67%. Other significant predictors in the analysis were T1 lifetime ANX and T1 lifetime SUD. Among those with better friend support, those with 2 or more major life events ($n = 60$) were significantly more likely than those with fewer than 2 major life events ($n = 232$) to develop MDD (incidence rate: 40.00% vs. 25.86%). For those with better friend support and

2 or more major life events, there were no additional significant predictors, making this a terminal node. Among those with better friend support and fewer than 2 major life events, the strongest predictor of MDD onset was a T1 lifetime history of ANX, $p < .001$, ESS = 14.73%¹. There were no other significant predictors at this branch. Among those with better friend support and fewer than 2 major life events, those with T1 lifetime ANX ($n = 19$) were significantly more likely than those with no T1 lifetime ANX ($n = 213$) to develop MDD (incidence rate: 68.42% vs. 22.07%). Both of these were terminal nodes.

In summary, the CTA revealed three-way interactions between friend support, T1 lifetime ANX, and T1 lifetime SUD, and between friend support, recent major life events, and T1 lifetime ANX in the prediction of MDD onset.

Screening Properties of the CTA Tree

Each tier of the classification tree represents an additional level of information (or an additional assessment measure as part of a screen). To investigate the utility of the classification tree as a screen for adolescents with a history of SubD, the sensitivity, specificity, and accuracy of each tier and of the complete tree in predicting MDD onset was analyzed.

As shown in Table 1, the first tier (assessment of SubD and friend support) resulted in the highest screening sensitivity (41.7%), but lowest specificity (74.3%), correctly predicting 60 of 144 participants who developed MDD over the follow-up period, but incorrectly predicting MDD onset for 72 of the 280 participants who did not develop MDD. The second tier (i.e., adding major life events for those with better friend support and lifetime history of ANX for those with poor friend support) resulted in lower sensitivity (22.9%) but higher specificity (86.1%), correctly predicting 33 participants who developed MDD, but incorrectly predicting MDD onset for 39 participants who did not develop MDD. The third tier (i.e., using the entire classification tree) resulted in a sensitivity of 38.2% and specificity of 81.4%, correctly predicting 55 participants who developed MDD and incorrectly predicting MDD onset for 52 participants who did not develop MDD.

Discussion

The current study investigated combinations of risk and protective factors that predicted escalation to MDD among 424 adolescents with a lifetime history of SubD. Approximately one-third of participants escalated to MDD by the final assessment wave in which they participated. The strongest predictor of escalation was friend social support, with a friend support score approximately one-half a standard deviation or greater above the sample mean (with high scores indicative of poorer friend support) indicating elevated risk of MDD. This is consistent with a large literature demonstrating the role of poor interpersonal functioning in the development and maintenance of depression (e.g., Pettit and Joiner, 2006).

¹As different branches of the classification tree represent distinct groups of participants, it is possible the same variables may be significant predictors on both sides of the classification tree.

Two sets of branches were found based on level of friend social support in adolescence, the first representing adolescents with poorer friend support. Among adolescents on this side of the classification tree, there were significant interactions between friend social support, lifetime history of ANX, and lifetime history of SUD in the prediction of MDD. In this side of the classification tree, the highest risk of escalation to MDD was seen in the presence of a lifetime history of ANX or a lifetime history of SUD. The finding that a lifetime history of ANX was the strongest predictor of MDD onset among adolescents with SubD and poor friend support is consistent with the well-documented high comorbidity of ANX and MDD (Mineka et al., 1998, Lewinsohn et al., 1997), and with previous work indicating that anxiety disorders prospectively predicted MDD onset across adolescence and emerging adulthood (Mathew et al., 2011). Among those with poor friend support and no lifetime history of ANX, the presence of a lifetime history of SUD was the strongest predictor of MDD onset. This is consistent with past research identifying a high comorbidity of SUD and MDD (Kandel et al., 1999, Merikangas et al., 1998) and with findings that SUD prospectively predicted the onset of MDD in emerging adulthood (Rao et al., 2000). Thus, escalation to MDD among adolescents who had poorer friend social support occurred most frequently in the presence of multiple predisposing psychiatric vulnerabilities (SubD and either ANX or SUD).

The second set of branches from SubD to MDD was found among adolescents with better friend social support. Among adolescents on this side of the classification tree, there were significant interactions between friend social support, major life events, and lifetime history of ANX in the prediction of MDD. In this side of the tree, the highest risk of escalation to MDD was seen in the presence of multiple major life events in the year preceding T1 or a lifetime history of ANX. The former branch is consistent with general diathesis stress models of depression, in that the occurrence of environmental disturbances (life events) interacted with a pre-existing vulnerability for depression (SubD) to predict escalation to MDD. The latter branch indicates that presence of multiple pre-existing vulnerabilities (SubD and ANX) was sufficient to increase the risk of MDD even in the presence of a protective factor (better friend support) and the absence of environmental disturbances (low major event stress).

The finding that multiple major negative life events in the year prior to T1 predicted escalation to MDD among adolescents with better friend support is consistent with a large body of literature demonstrating the effect of life event stress on MDD (Pettit et al., 2010, Ge et al., 2001, Hammen, 2005, Lewinsohn et al., 1994). It may be that friend support has a protective function only under certain circumstances, for example, only among adolescents who experience few or mild stressors. Alternatively, this may indicate that, among adolescents with a high friend support, a higher level of stress is required to precipitate escalation to MDD. Given a history of SubD, aversive environments may be sufficient to result in the development of a major depressive episode.

Among adolescents with better friend support and fewer than two recent major life events, more than two-thirds of those with a lifetime history of ANX escalated to MDD. In contrast, those with better friend support, fewer recent major life events, and no lifetime history of ANX had a lower risk of escalation to MDD, as approximately one in five individuals in this

group developed MDD. As noted above, this finding is consistent with the high comorbidity between anxiety disorders and MDD (Mineka et al., 1998, Lewinsohn et al., 1997) and highlights the importance of ANX in the development of MDD.

The present study yields information relevant to the selection of adolescents for depression prevention programs. The use of SubD as a selection criterion is likely to identify a high percentage of at-risk individuals, but also identify a large number of adolescents who will never develop MDD. In the present study approximately a third of those with SubD developed MDD by the final assessment wave in which they participated and the CTA approximately doubled the rate of correct classification. As discussed by Seeley, Stice, and Rohde (2009), the classification tree provides useful information for the implementation of depression prevention programs. The goal of a low cost, easily implemented prevention program is high sensitivity, and so could be disseminated to all adolescents with SubD. Higher intensity (and higher cost) interventions, which may target those at the highest risk of MDD, can improve specificity by targeting those with multiple risk factors.

The classification tree developed in the present study can inform a hybrid selected-indicated approach to selection for inclusion in depression prevention programs, which is likely to improve on the use of either SubD (indicated prevention) or another vulnerability factor (selected prevention) alone as a selection criterion. As informed by the present study, case identification would differ based on the level of social support from friends: Among adolescents with poor friend support, the highest risk groups are those with lifetime ANX or lifetime SUD. Among adolescents with better friend support with SubD, those with two or more recent major life events or lifetime ANX are at greatest risk. Directing services to these four highest risk nodes would have resulted in intervening with approximately one-fourth of participants, yet would have identified approximately 40% of participants who escalated to MDD.

The findings of the current study also suggest that friend support may prove a salient target for prevention efforts in adolescence. In addition, the findings highlight the potential utility in assessing anxiety for case identification and treating anxiety among adolescents with SubD, given that anxiety significantly predicted MDD onset on both sides of the classification tree. It is possible that successful treatment of anxiety disorders among adolescents with SubD may reduce the risk of escalation to MDD (Mathew et al., 2011, Kessler and Price, 1993).

This study has several limitations. The reference sample for this study was restricted to adolescents with a history of SubD by T1 (mean age = 16.6 years). Thus, the study findings may not inform prevention efforts for individuals who first develop SubD during adulthood. Participants may have been misclassified as not having MDD if they experienced first onset of MDD after the final assessment wave in which they participated. The lengthy follow-up period and selection of participants based on a lifetime history of SubD, rather than current SubD, did not allow examination of proximal processes involved in the escalation from SubD to MDD or the temporal ordering of SubD and the other predictors. In addition, due to the small sample size in several of the terminal nodes, there may have been insufficient statistical power to identify further branches of the classification tree. With regard to race

and ethnicity, participants were predominantly White/Caucasian but were representative of the population from which they were selected.

In summary, the present study examined combinations of risk and protective factors that prospectively predicted escalation from SubD to full syndrome MDD in a school-based sample of adolescents. Findings highlight the existence of different risk subgroups across levels of social support from friends. Among those with poor friend support, the highest risk groups are those with lifetime ANX or lifetime SUD. Among those with better friend support with SubD, those with two or more major life events or lifetime ANX are at greatest risk. These findings may be used to inform case identification approaches for depression prevention programs for adolescents.

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Figure 1.

Results of Classification Tree Analysis Predicting Onset of Major Depressive Disorder

Note. SubD = Subthreshold Depression; ANX = lifetime history of any anxiety disorder at T1; SUD = lifetime history of substance use disorder at T1; IR = Incidence rate. Higher scores on Friend Support indicate poorer social support from friends.

Table 1

Screening properties for CTA tiers.

Predictor of escalation	Sensitivity	Specificity	PPV	NPV	Accuracy	# correctly identified	# incorrectly identified	# of cases missed
Tier 1	.417	.743	.455	.712	63.2%	60	72	84
Tier 2	.229	.861	.458	.685	64.6%	33	39	111
Tier 3	.382	.814	.514	.712	66.7%	55	52	89

Note. PPV=Positive predictive value; NPV=Negative predictive value.