

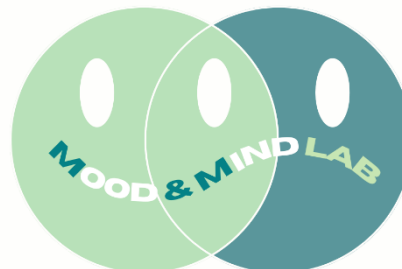
Risk Calculation and Predicting the Development of Bipolar Spectrum Disorders

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Disclosures

- ▶ Dr. Hafeman reports no conflicts of interest with ineligible companies (commercial interests).

Talk Outline

- ▶ Bipolar Spectrum Disorder: Definitions and Epidemiology
- ▶ Early Identification: Predicting Bipolar Onset (Risk Calculator)
- ▶ Predicting progression of Bipolar Disorder

Bipolar Disorder in Youth: Scope of the Problem

▶ Lifetime Prevalence

- Bipolar-I Disorder ~ 0.6% (adults=youth)
- Bipolar Spectrum ~ 2.6% (adults=1-3%)

▶ Median age of bipolar onset = 15-19 years old

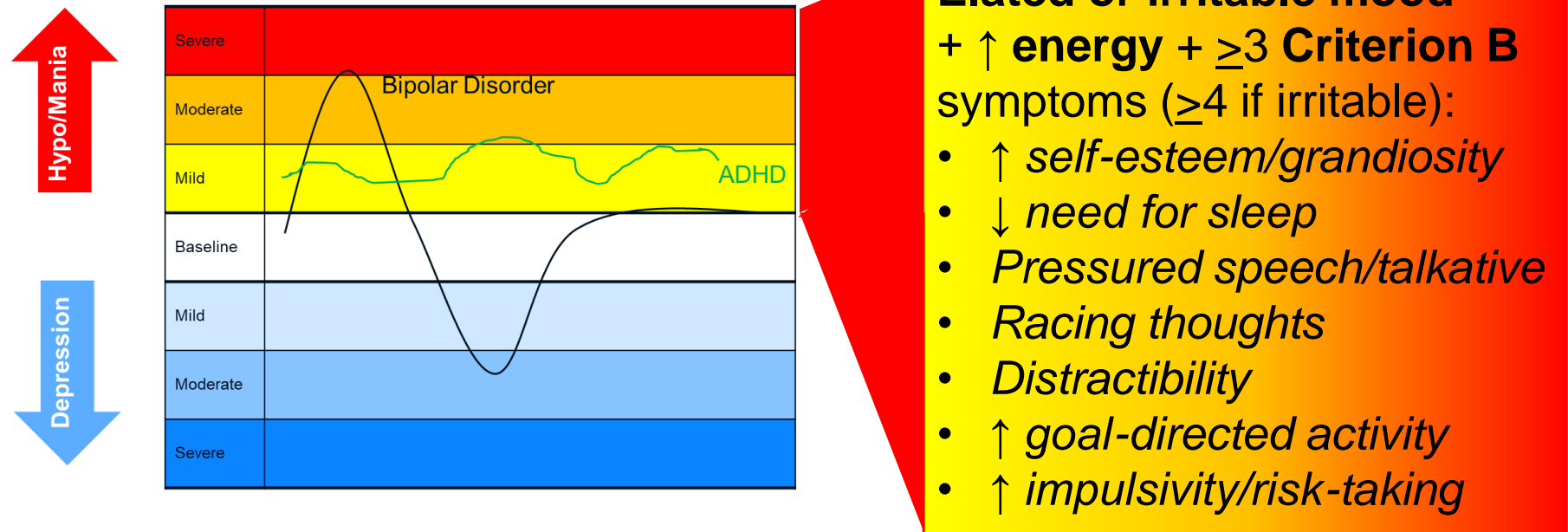
- Earlier onset associated w/ substance abuse, worse course, suicidal thoughts & behaviors

▶ Delays in diagnosis and treatment are common: average of 5.8 years (younger onset → greater delays)

Goal: To recognize BD earlier to avoid treatment delays during important developmental periods

BD in Youth: Scope of Diagnosis

- ▶ BD is defined by the *episodic* nature of symptoms



Question from early 2000s: Is *chronic* irritability, esp. if it is “explosive” and “energetic”, a symptom of BD?

Answer from the late 2000s: No.

Caveat: These children *may also* have BD, but key is *spontaneous episodicity* + *temporal clustering* of symptoms

BD in Youth: Spectrum of Disorder

- ▶ What if symptoms are clearly episodic, but they do not quite meet criteria for Bipolar-I/II?
- ▶ Other Specified Bipolar Disorder (OSBD)
 - This is not defined clearly in *DSM-IV* or *DSM-5*

Criteria from the COBY study:

- Occurs with ≥ 2 Criterion B symptoms (≥ 3 if only irritable)
- Last for the majority of the day (>4 hours in COBY)
- ≥ 4 lifetime days

OR

- Hypomania without a major depressive episode

Note: Most youth with OSBD have sufficient symptoms, but not duration criteria (hypomania < 4 days)

BD in Youth: Spectrum of Disorder

Why is it important to identify OSBD in youth

- ▶ Associated with poor psychosocial functioning, substance abuse and suicide attempts
- ▶ Informs treatment:
 - May be less responsive to SSRIs (although not always)
 - Data for efficacy of aripiprazole (if family history of BD)
- ▶ 50% go onto develop Bipolar-I/II within the next 5 years (COBY study)

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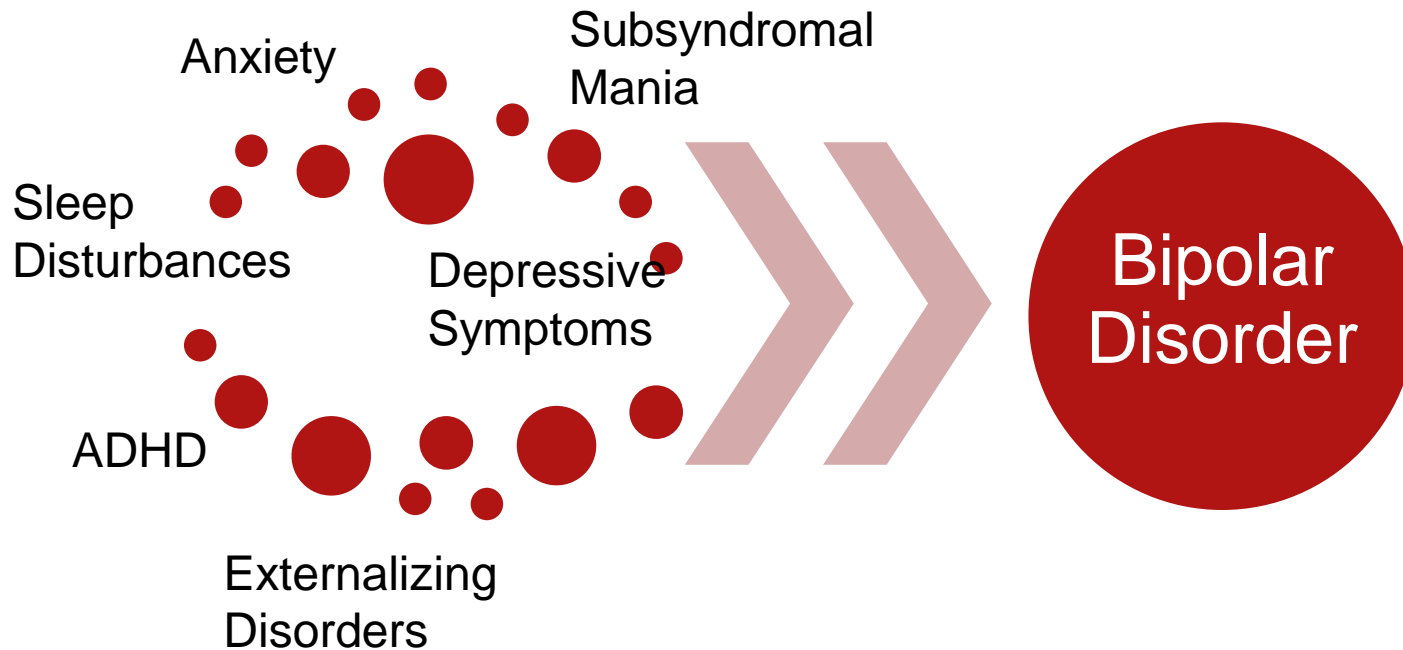
Motivating Clinical Case

▶ 10-year-old girl walks into your office, presenting with irritability and depressive symptoms. Her mother has a diagnosis of Bipolar I Disorder.

▶ Questions:

1. What are the risk factors for conversion to BD?
2. What is this girl's risk of conversion to BD?

Bipolar Disorder Prodrome



- Identification of a more specific prodrome is key step to timely diagnosis and early intervention

Pittsburgh Bipolar Offspring Study (BIOS)

PIs: Birmaher, Phillips

Design

- ▶ Case-control high-risk study with longitudinal follow-up (>10 years)

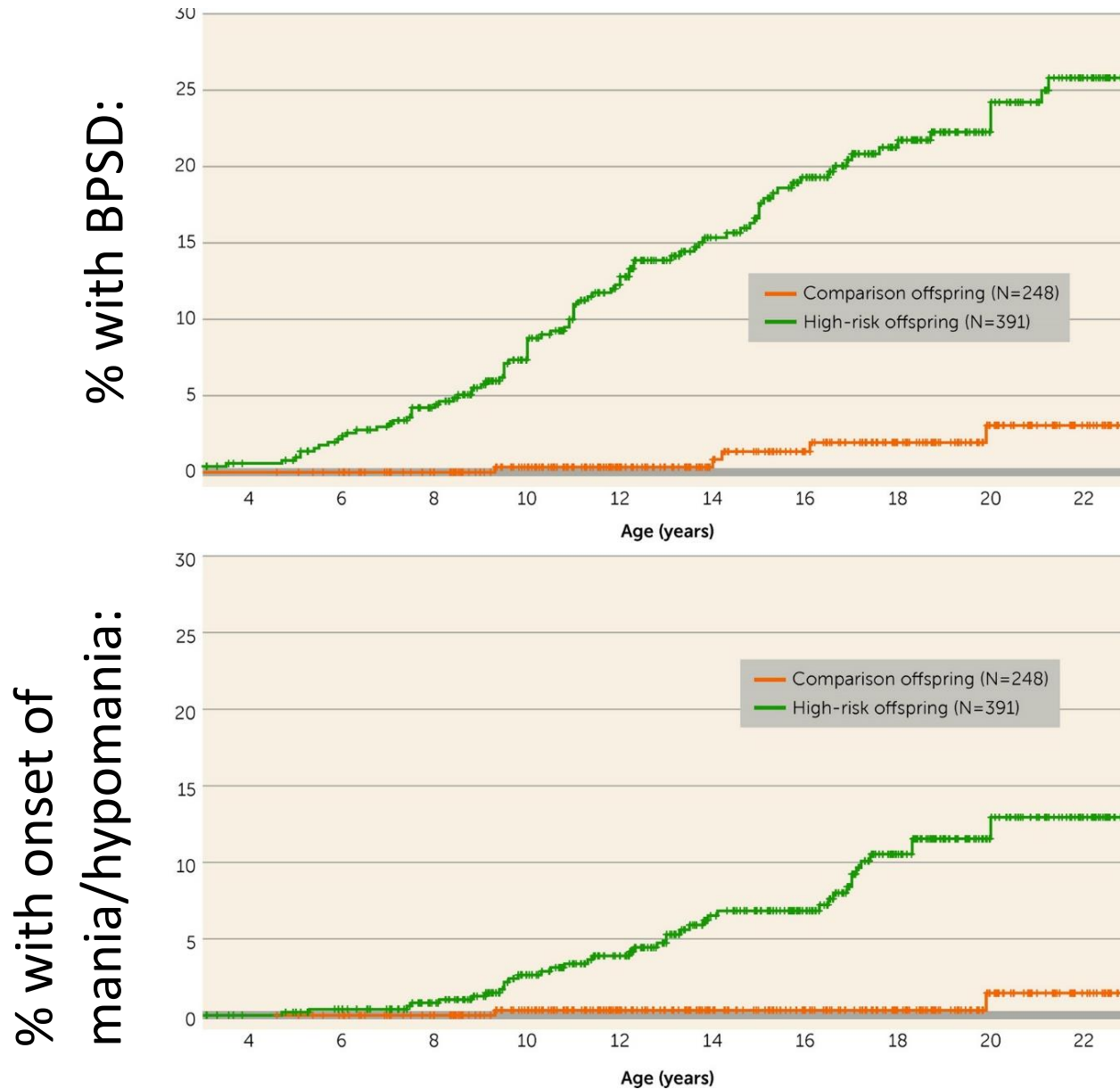
Participants

- ▶ 235 parents with BD I/II + offspring (6-18yo)
- ▶ 141 community control parents + offspring

Procedures

- ▶ Assess participants every 2 years

BD Onset in Offspring Groups



Which Symptoms Predict BD?

Parent Report

1. **Anxiety/Depression** (MFQ, SCARED, CBCL-anx/dep, etc.)
2. **Externalizing** (CHI, CBCL-externalizing, etc.)
3. **Inattention/Hyperactivity** (DBD-inattention/hyper, etc.)

Child Report

1. **Anxiety/Depression** (MFQ, SCARED)
2. **Externalizing** (CHI)
3. **Affective Lability** (CALS)

Depression Rating Scale

1. **Depression/Atypical** (Anhedonia, Fatigue, etc.)
2. **Sleep** (Insomnia, Circadian Reversal, etc.)
3. **Suicide/Weight Loss** (Suicidal Ideation, Lethality, etc.)

Mania Rating Scale

1. **Total Score**

BIOS Participants - Offspring

Baseline:

Offspring of BD
Parents with BD
(n=33)
(BD-I/II:11, OSBD:22)

Offspring of BD
Parents without
BD (n=326)

Community
Control
Offspring(n=220)

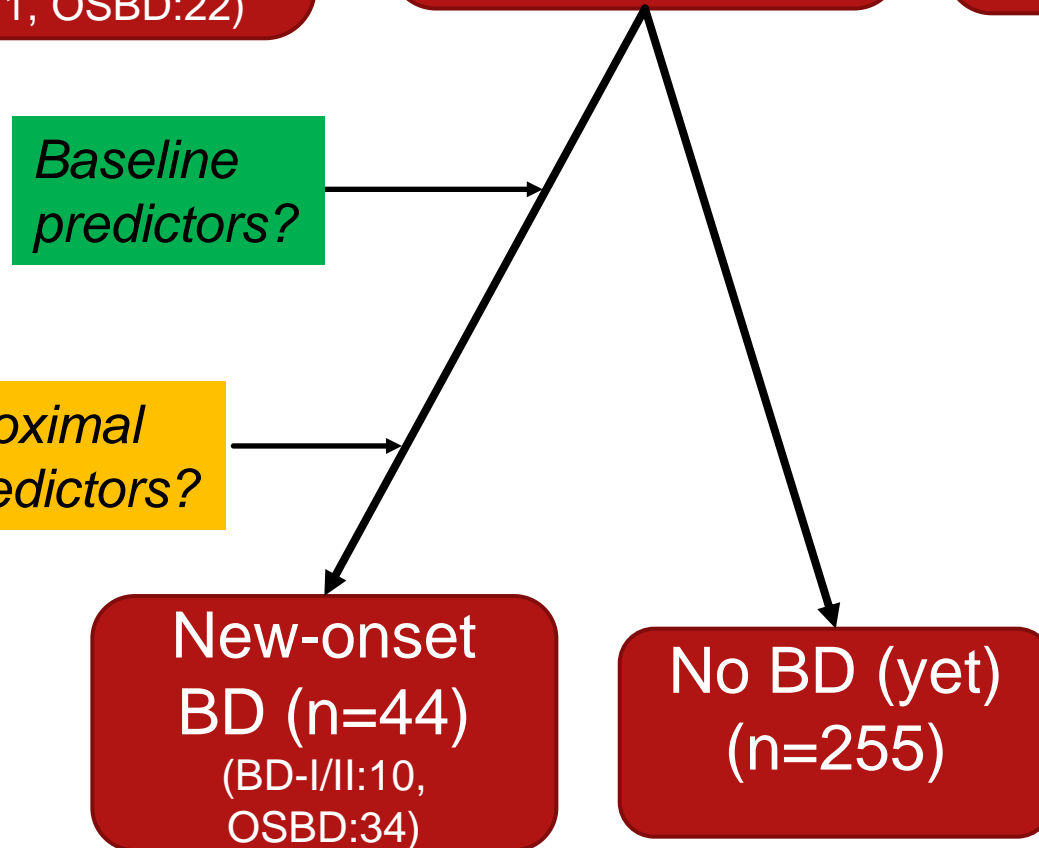
*Baseline
predictors?*

*Proximal
predictors?*

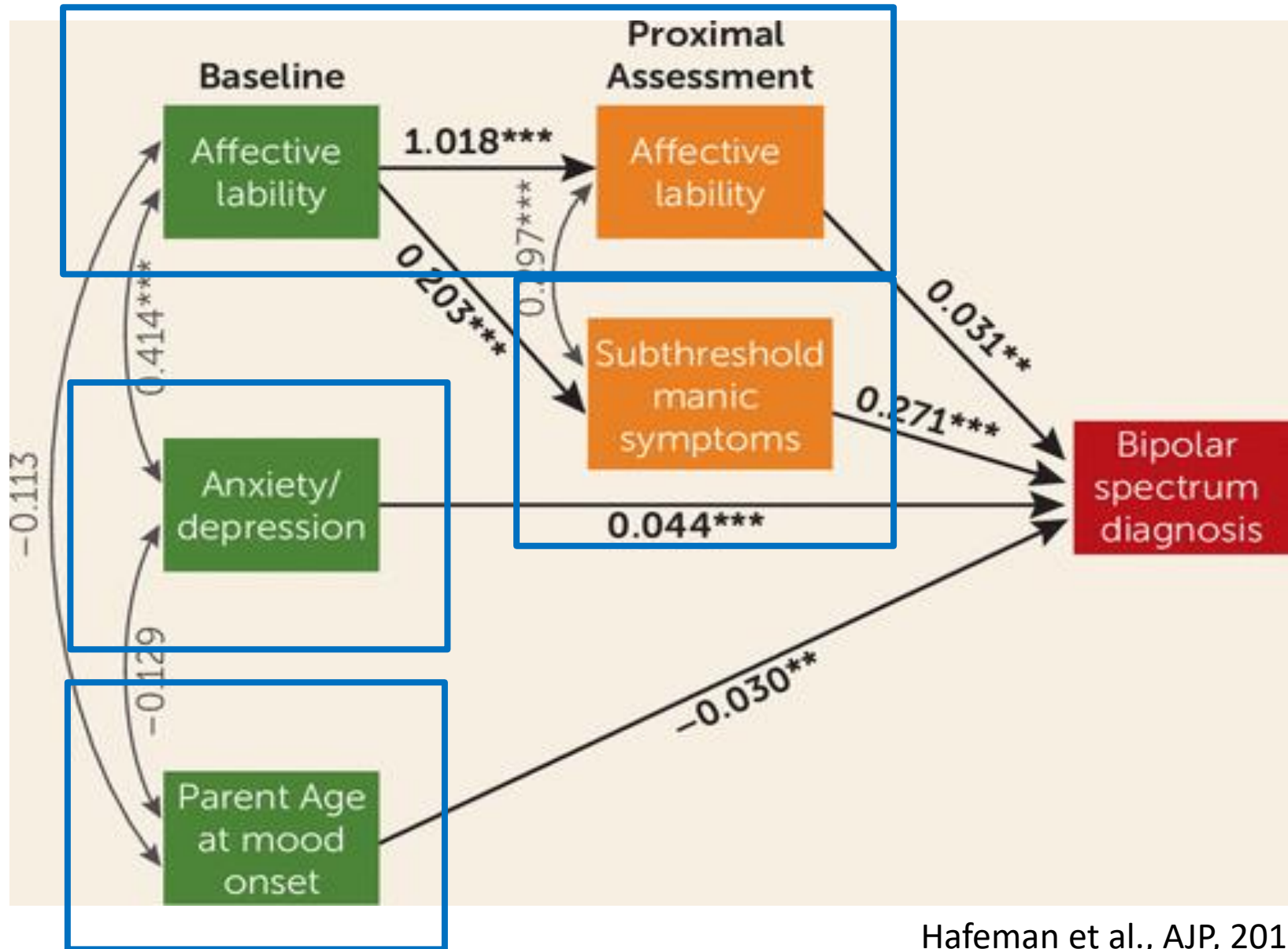
Follow-up
(mean 8.4 years):

New-onset
BD (n=44)
(BD-I/II:10,
OSBD:34)

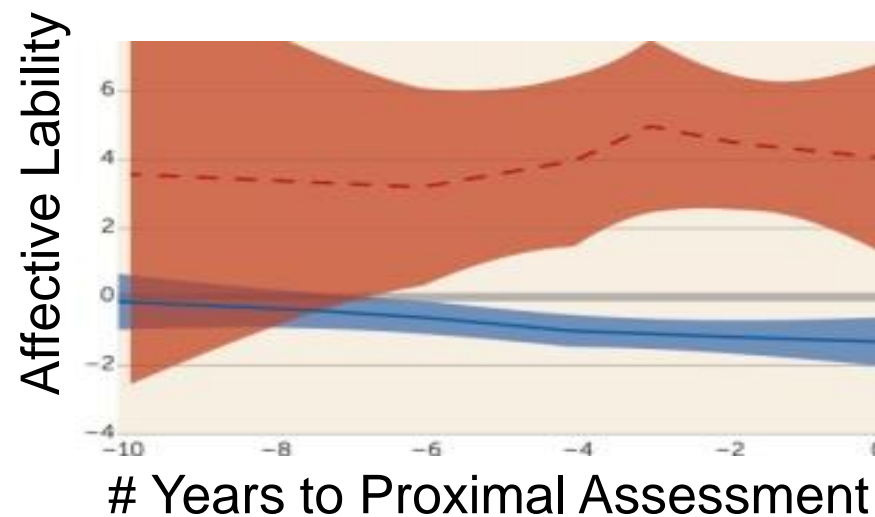
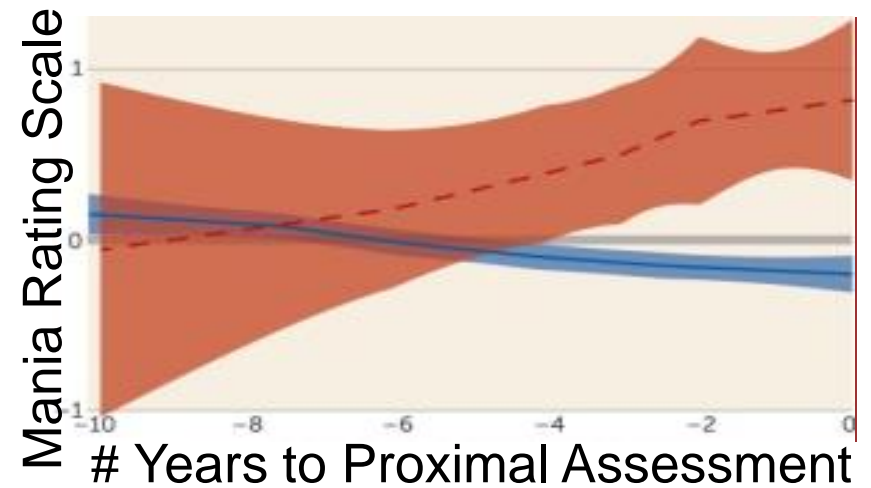
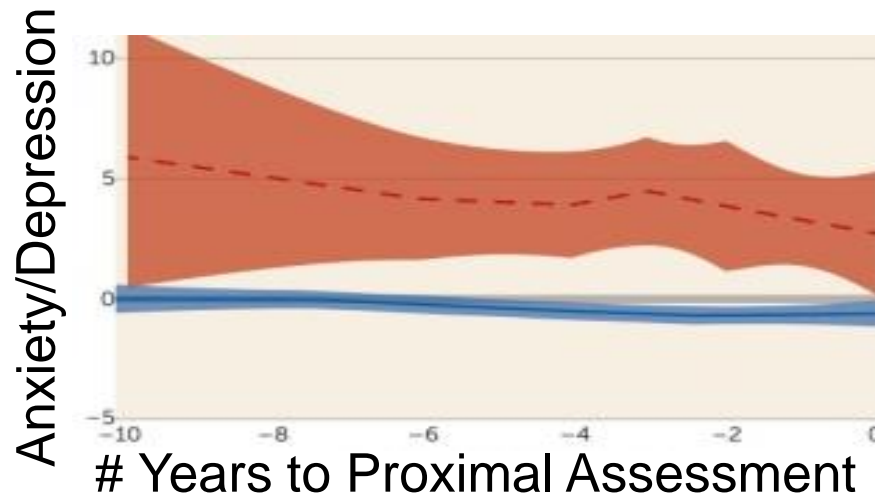
No BD (yet)
(n=255)



Baseline and Proximal Predictors of BD

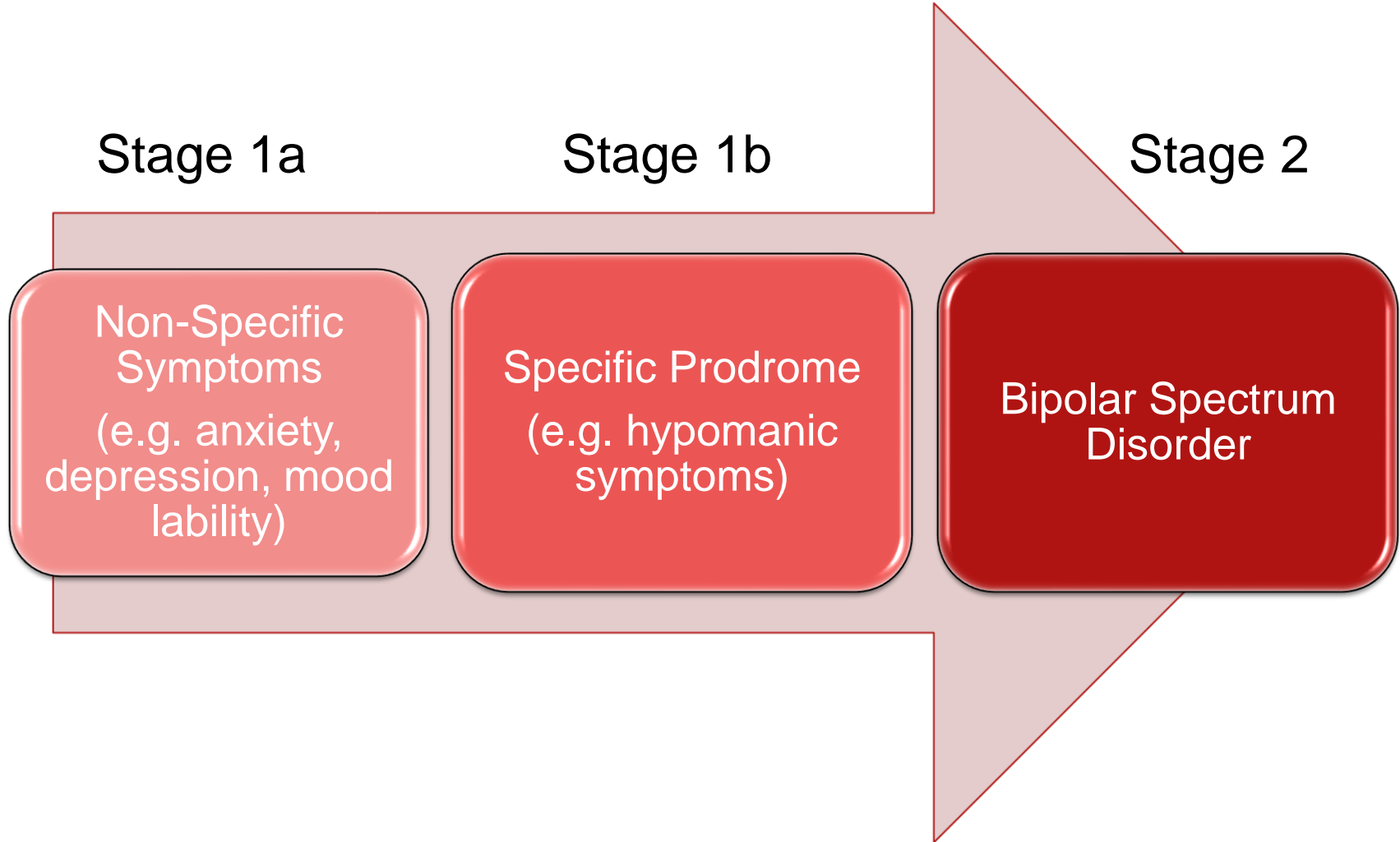


Symptom Time Course



New-onset BD:
NO ———
YES ———

Staged Model of the Bipolar Prodrome



(McGorry 2006; Duffy et al. 2014; Hafeman et al. 2016; Axelson et al. 2015; Van Meter et al 2016)

Clinical Implications

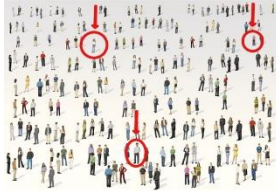
Back to the 10 year old girl... Which symptoms increase index of suspicion?

1. Early anxiety/depressive symptoms
 2. Mood lability
 3. Over time... subthreshold manic symptoms
- ... Especially if mother developed a mood disorder in childhood or adolescence

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Population-Level Vs. Person-Level



Population-Level

- ▶ Useful for identifying preventable causes of disorder, treatment targets
- ▶ Population work often necessary prior to individual-level prediction

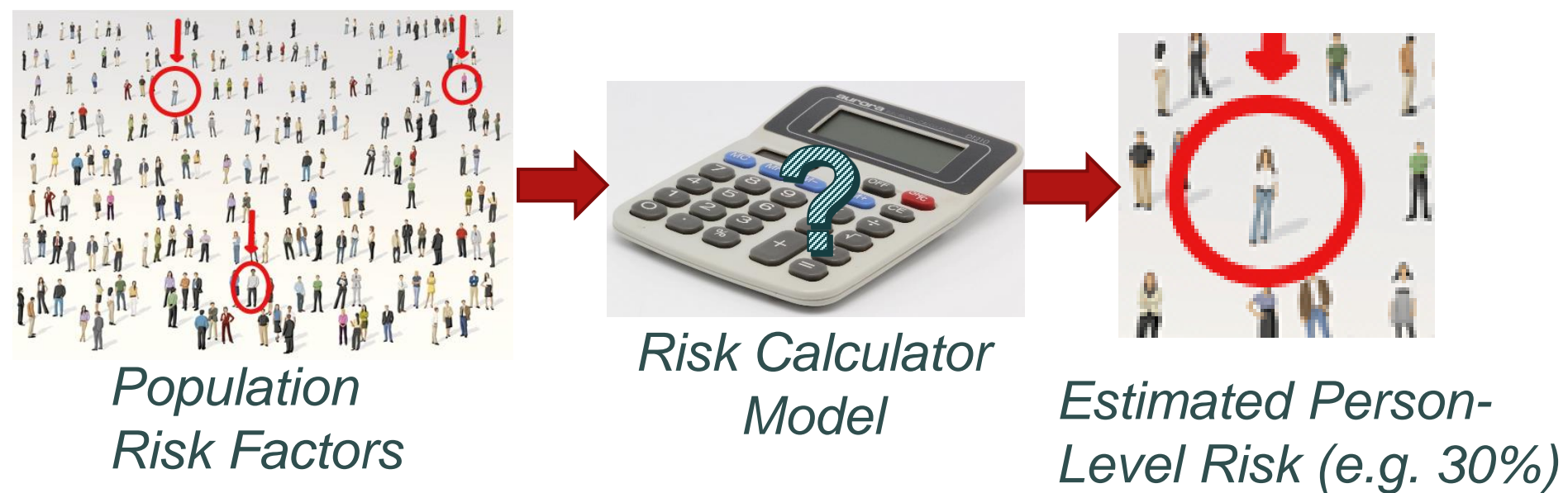


Person-Level

- ▶ Perhaps most important to a clinician: informing prognosis and treatment
- ▶ Given risk factors, what is this individual's risk of a given outcome?

Risk Calculator: Motivation

- ▶ *Question:* How likely is it that an individual child or adolescent with an affected parent will develop bipolar spectrum disorder (BSD)?



- ▶ Used in other areas of medicine, psychosis

Risk Calculator: Methods

- ▶ **Sample**: 412 at-risk offspring; 54 developed BD
- ▶ **Predictors**: Chosen based on meta-analysis

1. Modified KMRS (elation, irritability, decreased need for sleep, unusually energetic, increase in goal-directed activity, motor hyperactivity, grandiosity, accelerated speech, racing thoughts, poor judgment, inappropriate laughter, people seeking, increased productivity, distractibility, and mood lability)
2. Modified KDRS (depressed mood, irritability, negative self-image, fatigue, difficulty concentrating, psychomotor agitation, insomnia, daytime sleepiness, anorexia, weight loss, and suicidal ideation)
3. SCARED (child reported)
4. CALS (child reported)
5. CGAS
6. Offspring age at visit
7. Parental age at mood disorder onset

Risk Calculator: Predicting BD Onset

Accuracy: Good
(AUC=0.76)

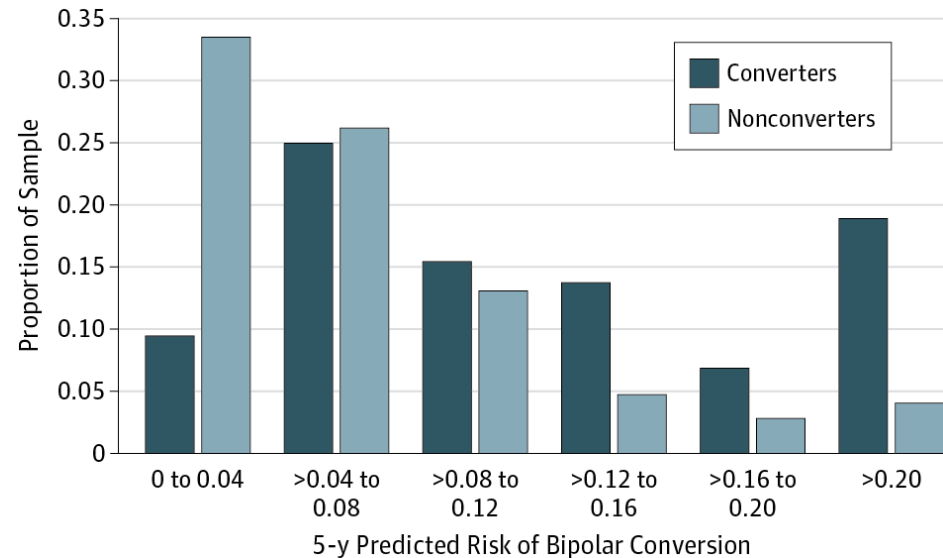


Table 1. Individual (Univariate) and Independent Predictive Value of Each Variable in the Risk Calculator

Predictor	Mean (SD)		AUC (95% CI)	
	Converting Visits	Nonconverting Visits	Univariate 5-y AUC	Decrement in AUC If Removed
Modified KDRS	21.3 (8.5)	17.1 (6.1)	0.68 (0.62 to 0.74) ^a	0.00 (−0.06 to 0.05)
Modified KMRS	20.8 (6.4)	17.8 (4.7)	0.70 (0.64 to 0.76) ^a	0.01 (−0.05 to 0.06)
CALS	19.5 (15.1)	12.0 (11.5)	0.66 (0.59 to 0.72) ^a	0.00 (−0.05 to 0.06)
SCARED	28.0 (15.5)	18.6 (13.0)	0.66 (0.60 to 0.72) ^a	−0.01 (−0.06 to 0.05)
CGAS	69.5 (13.0)	75.0 (12.9)	0.69 (0.63 to 0.76) ^a	0.01 (−0.05 to 0.06)
Parental age at mood disorder onset	15.9 (5.8)	20.1 (8.5)	0.68 (0.62 to 0.74) ^a	0.05 (−0.02 to 0.11)
Offspring age at visit	11.7 (3.2)	12.1 (3.5)	0.50 (0.44 to 0.55)	0.00 (−0.06 to 0.06)

Risk Calculator: Clinical Implications

Risk Calculator: Five-Year Risk to Develop Bipolar Disorder	
Modified Depression Rating Scale:(Instrument / All Instruments)	<input type="button" value="Click To Enter Score"/>
Modified Mania Rating Scale:(Instrument / All Instruments)	<input type="button" value="Click To Enter Score"/>
Children's Affective Lability Scale (Self-Report):(Instrument / All Instruments)	<input type="button" value="Click To Enter Score"/>
Screen for Child Anxiety Related Disorders (Self-Report):(Instrument / All Instruments)	<input type="button" value="Click To Enter Score"/>
Children's Global Assessment Scale:(Instrument / All Instruments)	<input type="button" value="Click To Enter Score"/>
Parent age of mood disorder onset:	<input type="button" value="Click To Enter Age"/>
Child's Age:	<input type="button" value="Click To Enter Age"/>
<input type="button" value="Click here for answer"/>	<input type="text"/>
<input type="button" value="Reset form"/>	
Back to CABS	

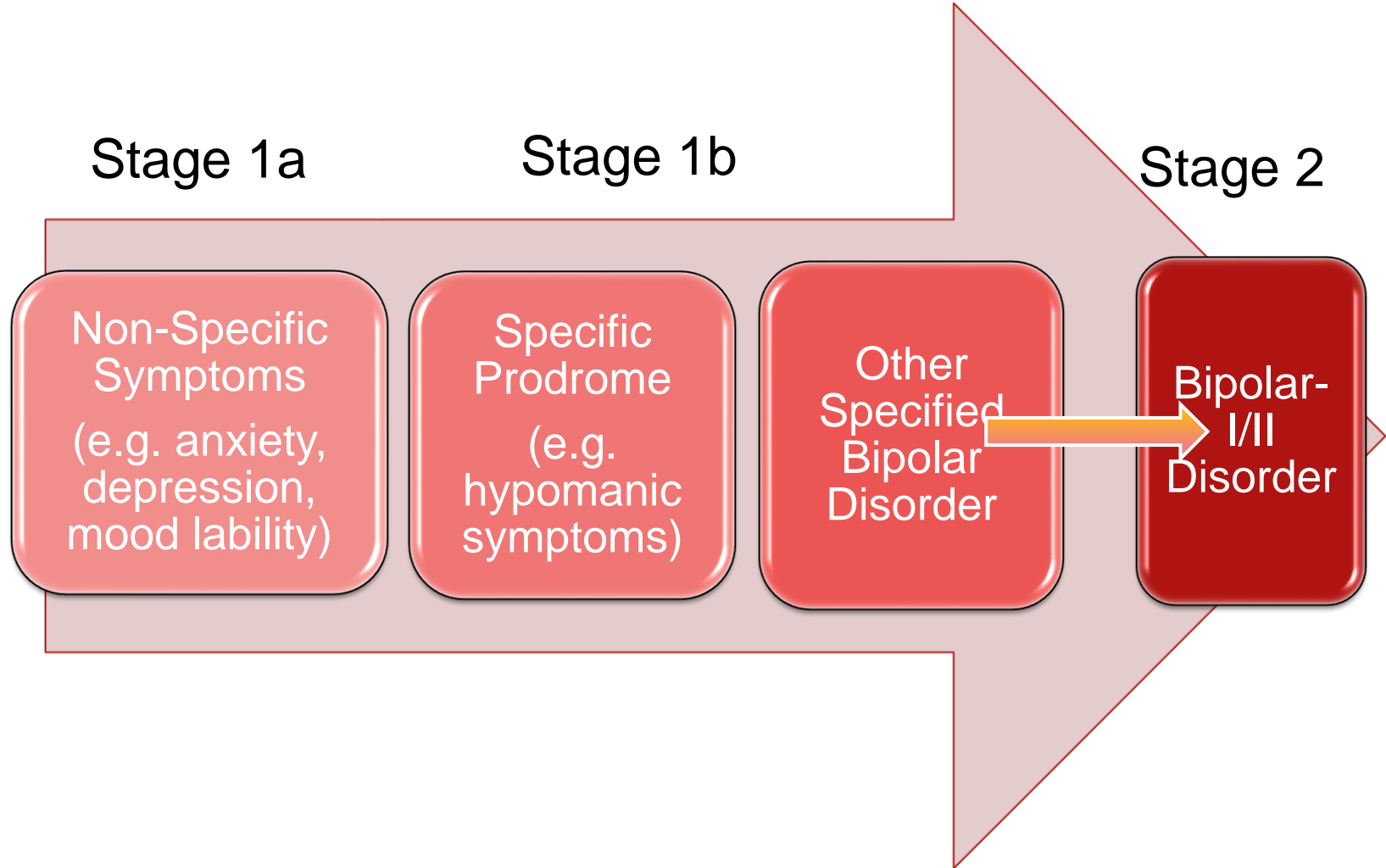
Note: Has not been externally validated (gold standard)

www.pediatricbipolar.pitt.edu

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Staged Model of the Bipolar Prodrome

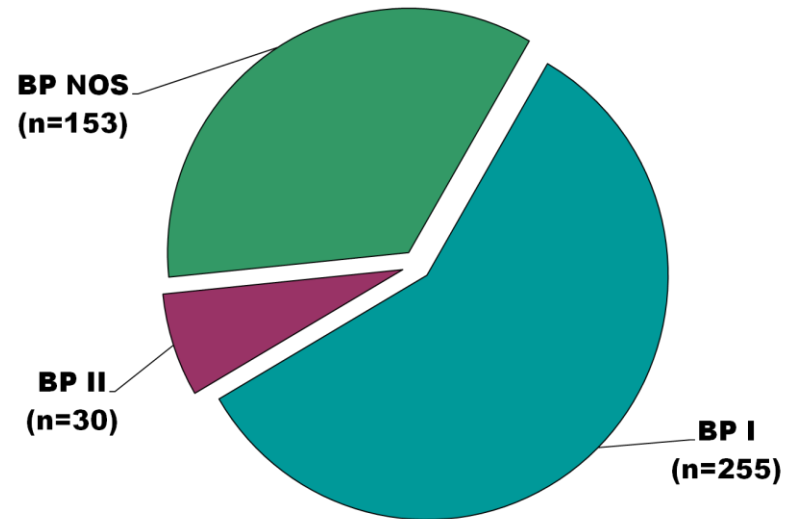


(McGorry 2006; Duffy et al. 2014; Hafeman et al. 2016; Axelson et al. 2015; Van Meter et al 2016)

Course and Outcome of Bipolar Youth (COBY)

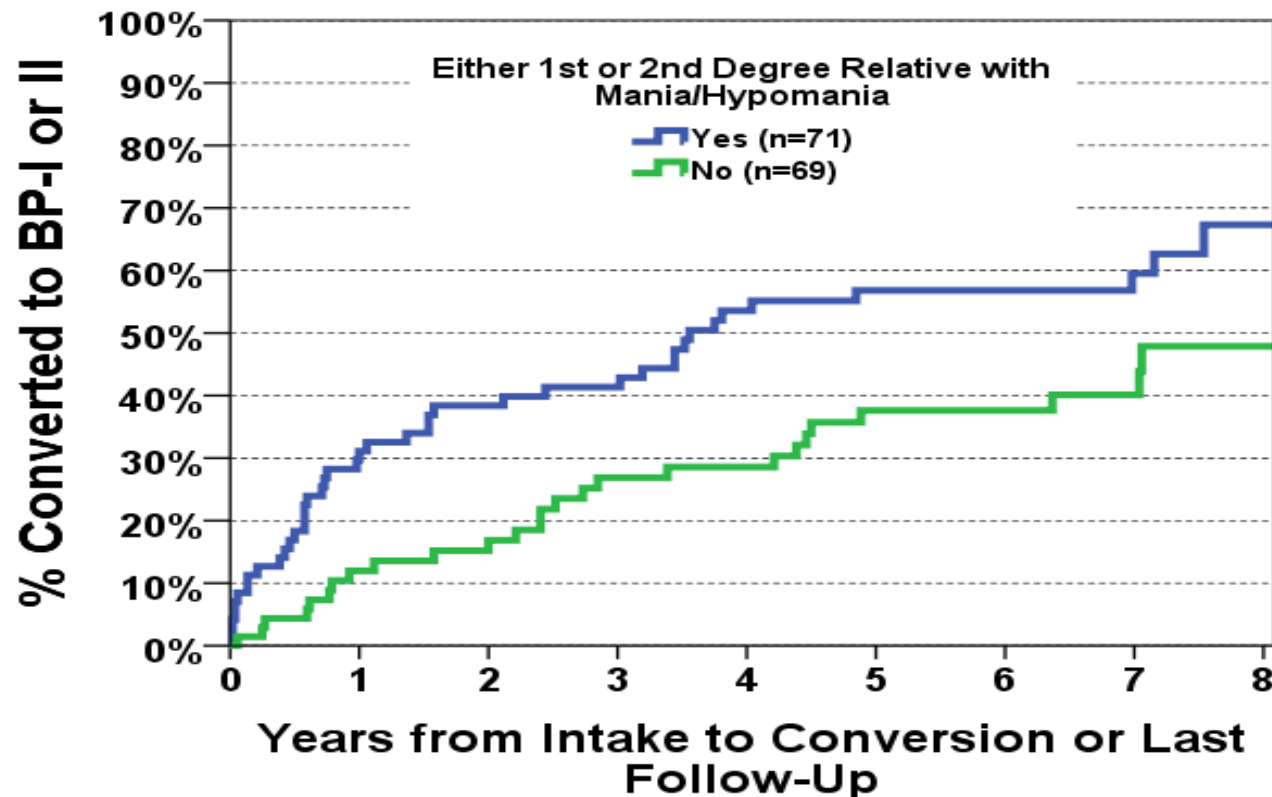
Pls: Birmaher, Keller, Yen, Strober

- ▶ Multicenter Study (Brown, UCLA, UPMC)
- ▶ Children and adolescents (8-17 years old at intake) with BD- I, II or NOS
- ▶ Follow-up every 6 months for a mean of >12 y
- ▶ Interviews with youth and parents about: mood, behavior, life events, treatment, cognition, school and family functioning



Diagnostic Progression From OSBD → BD-I/II

- ▶ BD-NOS → 45% BD-I and/or BD-II (by 2011)
- ▶ Main Predictor: Family history of bipolar disorder

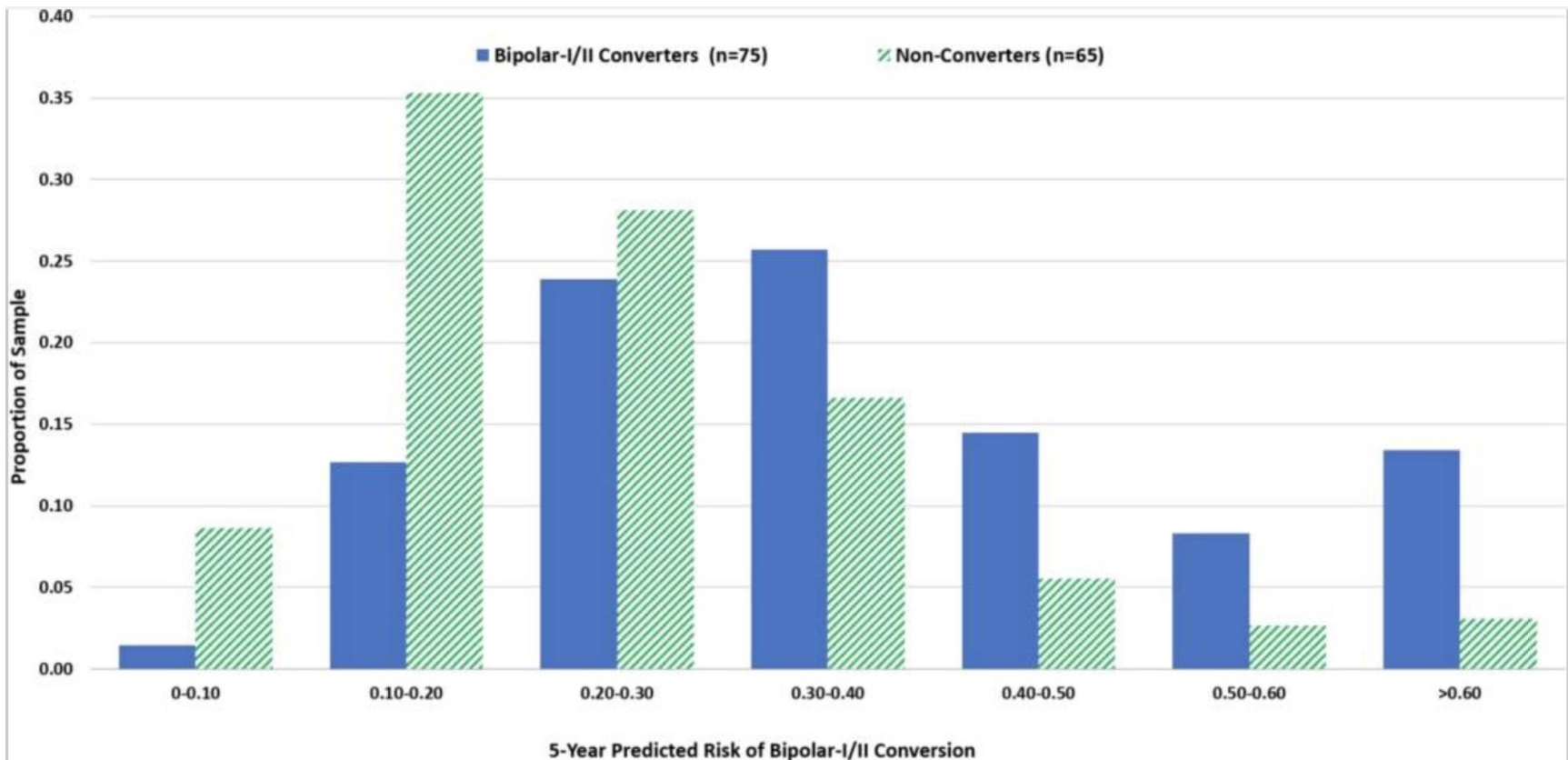


Risk Calculator: Methods

- ▶ Can a risk calculator predict (person-level) who will progress from BD-NOS to BD-I/II?
- ▶ Predictors chosen based on previous literature:
 - *KDRS Symptoms*
 - *KMRS Symptoms*
 - *Mood Lability*
 - *Anxiety (SCARED)*
 - *Functioning (CGAS)*
 - *Family History of Mania*
 - *Age*
 - *Race*
 - *Gender*
 - *Duration of BD Illness*

Results: Discrimination

763 index visits, 75 converted to BD-I/II in next 5 years
AUC= 0.71 in COBY; 0.75 in BIOS



Risk Calculator: Clinical Implications

Risk Calculator: Five-Year Risk to Develop Bipolar-I/II	
Modified Depression Rating Scale:(Instrument / All Instruments)	<input type="button" value="Click To Enter Score"/>
Modified Mania Rating Scale:(Instrument / All Instruments)	<input type="button" value="Click To Enter Score"/>
Behavior Control Scale – Lability (Self-Report):(Instrument / All Instruments)	<input type="button" value="Click To Enter Score"/>
Screen for Child Anxiety Related Disorders (Self-Report):(Instrument / All Instruments)	<input type="button" value="Click To Enter Score"/>
Children's Global Assessment Scale:(Instrument / All Instruments)	<input type="button" value="Click To Enter Score"/>
Duration of Bipolar Illness (Years):	<input type="button" value="Click To Enter Years"/>
Child's Age:	<input type="button" value="Click To Enter Age"/>
Race:	<input type="button" value="Click To Enter Race"/>
Family History of Mania?	<input type="button" value="Click To Enter Yes/No"/>
Gender:	<input type="button" value="Select Gender"/>
<input type="button" value="Click here for answer"/>	<input type="text"/>
	<input type="button" value="Reset form"/>
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Take Home Messages

- ▶ It is important to assess for BD in youth, and only diagnose youth who show *spontaneous episodicity* and *clustering* of manic symptoms.
- ▶ Important predictors of BD in at-risk youth are anxiety/depression, mood lability, and, closer to onset, subthreshold manic symptoms.
- ▶ We have built two risk calculators to predict, on the individual level, who will progress along the bipolar trajectory.

Questions/Next Steps

- ▶ Necessary steps prior to implementation in clinical practice
 - External validation by an independent group
 - Assess performance in a clinical setting
- ▶ What is the best way to use risk calculators in clinical practice?
 - Do you/your patient want to know the estimated risk of a particular outcome?
 - How will this impact treatment decisions?
- ▶ How can risk calculators be used as a research tool?
 - Identify a particularly high-risk group for an intervention
 - Assess biomarkers of risk – do they correlate with risk score? Do they add to clinical risk score to improve risk prediction?

Acknowledgements

- Patients and Families
- CABS Team
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