Predictors and Mechanisms of Conversion to Psychosis in At Risk Youth: Toward a Prevention Strategy

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Tyrone D. Cannon has no personal financial relationships with commercial interests relevant to this presentation.
3 Parts to Today’s Talk

• Prediction of Psychosis
  – How do we find people most at risk for imminent onset?

• Mechanisms of Onset of Psychosis
  – Is there neural deterioration before onset that could potentially be prevented

• Prevention of Psychosis
  – What approaches available now show promise for preventing onset and/or functional disability?
Prodromal Risk Approach to Psychosis

- SIPS/SOPS: Onset or worsening in past year of sub-psychotic intensity positive symptoms or genetic risk with recent functional decline
- Initial studies observed 50-60% conversions to psychosis within 1 year; most conversions are to schizophrenia and schizoaffective disorder, others to mood disorders with psychotic features
Example: Perceptual Abnormalities

**P. 4. **DESCRIPTION: PERCEPTUAL ABNORMALITIES/HALLUCINATIONS

a. Unusual perceptual experiences. Heightened or dulled perceptions, vivid sensory experiences, distortions, illusions.

b. Pseudo-hallucinations or hallucinations into which the subject has insight (i.e. is aware of their abnormal nature.)

c. Occasional frank hallucinations that may minimally influence thinking or behavior.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

### PERCEPTUAL ABNORMALITIES/HALLUCINATIONS

<table>
<thead>
<tr>
<th>Severity Scale (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Absent</td>
</tr>
<tr>
<td>1 Questionably Present</td>
</tr>
<tr>
<td>2 Mild</td>
</tr>
<tr>
<td>3 Moderate</td>
</tr>
<tr>
<td>4 Moderately Severe</td>
</tr>
<tr>
<td>5 Severe but Not Psychotic</td>
</tr>
<tr>
<td>6 Severe and Psychotic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>0 Absent</th>
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<th>4 Moderately Severe</th>
<th>5 Severe but Not Psychotic</th>
<th>6 Severe and Psychotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor, but noticeable perceptual sensitivity (e.g. heightened, dulled, distorted, etc.)</td>
<td>Unexpected, uniformed perceptual experiences/changes that are puzzling but are not considered to be significant.</td>
<td>Repeated, uniformed, images (e.g., shadows, trails, sounds, etc.), illusions, or persistent perceptual distortions that may be worrisome or experienced as unusual.</td>
<td>Recurrent illusions or momentary hallucinations that are recognized as not real yet can be frightening or captivating, and may affect behavior slightly. Not sure of source of experiences.</td>
<td>Hallucinations that occasionally affect thinking or behavior, that are experienced as possibly external to self or possibly real. Skepticism can be induced.</td>
<td>Recurrent hallucinations perceived as real and distinct from the person's thoughts. Clearly influence thinking, feeling, and/or behavior. Skepticism cannot be induced.</td>
<td></td>
</tr>
</tbody>
</table>
North American Prodrome Longitudinal Study (NAPLS)

Prediction of Psychosis in Youth at High Clinical Risk

A Multisite Longitudinal Study in North America

Tyrone D. Cannon, PhD; Kristin Cadenhead, MD; Barbara Cornblatt, PhD; Scott W. Woods, MD; Jean Addington, PhD; Elaine Walker, PhD; Larry J. Seidman, PhD; Diana Perkins, MD; Ming Tsuang, MD; Thomas McGlashan, MD; Robert Heinssen, PhD

Context: Early detection and prospective evaluation of individuals who will develop schizophrenia or other psychotic disorders are critical to efforts to isolate mechanisms underlying psychosis onset and to the testing of preventive interventions, but existing risk prediction approaches have achieved only modest predictive accuracy.

Objectives: To determine the risk of conversion to psychosis and to evaluate a set of prediction algorithms maximizing positive predictive power in a clinical high-risk sample.

Design, Setting, and Participants: Longitudinal study with a 2 1/2-year follow-up of 291 prospectively identified treatment-seeking patients meeting Structured Interview for Prodromal Syndromes criteria. The patients were recruited and underwent evaluation across 8 clinical research centers as part of the North American Prodrome Longitudinal Study.

Main Outcome Measure: Time to conversion to a fully psychotic form of mental illness.

Arch Gen Psychiatry. 2008;65(1):28-37

Survival Distribution Function in NAPLS Consortium

<table>
<thead>
<tr>
<th>Follow-Up Epoch</th>
<th>NAPLS SIPS+ Sample</th>
<th>General Population</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-mo</td>
<td>35.3%</td>
<td>0.08%</td>
<td>405</td>
</tr>
<tr>
<td>6-mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-mo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---                           |----|------|-----|-------|-------|
Meets SIPS criteria for Prodrome | 291 | 35 |
Meets SIPS criteria AND
Any drug abuse            | 270 | .003 | 43  | 29    | 83    |
Social impairment (Mod-Severe) | 290 | .03 | 46  | 80    | 43    |
Suspicion (Mod-Severe)     | 291 | .006 | 43  | 79    | 37    |
Unusual thought content (Mod-Severe) | 291 | .002 | 48  | 56    | 62    |
Genetic Risk + Sign. Functional Decline | 291 | .001 | 52  | 66    | 59    |
SOC + UTC + GR/SFD         | 290 | .0001 | 81  | 30    | 90    |
Prediction of Psychosis in Adolescents and Young Adults at High Risk

Results From the Prospective European Prediction of Psychosis Study

Stephan Ruhrmann, MD; Frauke Schultz-Lutter, PhD; Raimo K. R. Salokangas, MD, PhD, MSc; Markus Heinimaa, MD; Don Linezen, MD; Peter Dinges, PhD; Max Birchwood, PhD; Paul Patterson, PhD; Georg Juchel, MD; Andreas Heitz, MD; Anthony Morrison, PhD; Shon Lewis, MD; Heinrich Graf von Reventlow, DiplPsych; Joachim Klosterkötter, MD

**Context:** Indicated prevention is currently regarded as the most promising strategy to attenuate, delay, or even avert psychoses. Existing criteria need improvement in terms of specificity and individual risk assessment to allow for better targeted and earlier interventions.

**Objective:** To develop a differential predictive clinical model of transition to first-episode psychosis.

**Design:** Prospective multicenter, naturalistic field study with a total follow-up time of 18 months.

**Setting:** Six early-detection outpatient centers in Germany, Finland, the Netherlands, and England.

**Participants:** Two hundred forty-five help-seeking patients in a putatively prodromal state of psychosis according to either ultra-high-risk (UHR) criteria or the basic symptom–based criterion cognitive disturbances (COGDIS).

**Main Outcome Measure:** Incidence of transition to psychosis.

**Results:** At 18-month follow-up, the incidence rate for transition to psychosis was 19%. Combining UHR and COGDIS yielded the best sensitivity. A prediction model was developed and included positive symptoms, bizarre thinking, sleep disturbances, a schizotypal disorder, level of functioning in the past year, and years of education. With a positive likelihood ratio of 19.9, an area under the curve of 80.8%, and a positive predictive value of 83.3%, diagnostic accuracy was excellent. A 4-level prognostic index further classifying the general risk of the whole sample predicted instantaneous incidence rates of up to 89% and allowed for an estimation of time to transition.

**Conclusions:** The prediction model identified an increased risk of psychosis with appropriate prognostic accuracy in our sample. A 2-step risk assessment is proposed, with UHR and cognitive disturbance criteria serving as first-step criteria for general risk and the prognostic index as a second-step tool for further risk classification of each patient. This strategy will allow clinicians to target preventive measures and will support efforts to unveil the biological and environmental mechanisms underlying progression to psychosis.

Arch Gen Psychiatry. 2010;67(3):241-251

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**Table 3. Cox Proportional Hazard Model**

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>p</th>
<th>SE</th>
<th>Wald</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIPS Positive subscale score &gt;16</td>
<td>1.571</td>
<td>0.428</td>
<td>13.46</td>
<td>4.81 (2.78-11.13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bizarre thinking score &gt;2</td>
<td>0.860</td>
<td>0.387</td>
<td>4.99</td>
<td>2.28 (1.12-5.01)</td>
<td>.03</td>
</tr>
<tr>
<td>Sleep disturbances score &gt;2 or SIPS</td>
<td>0.790</td>
<td>0.387</td>
<td>4.19</td>
<td>2.21 (1.34-4.37)</td>
<td>.04</td>
</tr>
<tr>
<td>Schizotypal personality disorder according to SIPS</td>
<td>1.000</td>
<td>0.423</td>
<td>6.01</td>
<td>2.83 (1.23-6.45)</td>
<td>.02</td>
</tr>
<tr>
<td>GAF-M score, highest in the past year²</td>
<td>0.000</td>
<td>0.016</td>
<td>0.00</td>
<td>1.00 (1.00-1.00)</td>
<td>.03</td>
</tr>
<tr>
<td>Years of education, including university²</td>
<td>0.250</td>
<td>0.086</td>
<td>8.36</td>
<td>1.28 (1.084-1.521)</td>
<td>.04</td>
</tr>
</tbody>
</table>

---

**Table 4. Classification of Predefined Risk**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic score³</td>
<td>&lt;3.00</td>
<td>3.00 to 3.99</td>
<td>4.00 to 4.99</td>
<td>&gt;5.00</td>
</tr>
<tr>
<td>No. of patients (%)⁴</td>
<td>32 (12.5)</td>
<td>99 (41.5)</td>
<td>72 (33.0)</td>
<td>25 (14.3)</td>
</tr>
<tr>
<td>Estimated time to transition, mean (SEM), d</td>
<td>637.1 (15.7)²</td>
<td>657.1 (10.3)²</td>
<td>654.6 (11.6)²</td>
<td>356.4 (35.0)²</td>
</tr>
<tr>
<td>Ill of transition to psychosis, %</td>
<td>3.5</td>
<td>4.3</td>
<td>7.8</td>
<td>48.0</td>
</tr>
<tr>
<td>At month 9</td>
<td>3.5</td>
<td>8.0</td>
<td>8.0</td>
<td>86.1</td>
</tr>
<tr>
<td>At month 12</td>
<td>3.5</td>
<td>8.0</td>
<td>8.0</td>
<td>86.1</td>
</tr>
<tr>
<td>At month 18²</td>
<td>3.5</td>
<td>8.0</td>
<td>8.0</td>
<td>86.1</td>
</tr>
<tr>
<td>Distribution of inclusion criteria, %</td>
<td>COGDIS</td>
<td>18.8</td>
<td>11.1</td>
<td>1.6</td>
</tr>
<tr>
<td>GAF-M</td>
<td>76.0</td>
<td>31.2</td>
<td>21.5</td>
<td>14.3</td>
</tr>
<tr>
<td>Both</td>
<td>16.3</td>
<td>54.5</td>
<td>54.9</td>
<td>82.9</td>
</tr>
</tbody>
</table>

---

**Figure 3. Kaplan-Meier survival analysis for risk classes of prognostic index (n=245).**
Implications

• Clinical and psychosocial measures easily implemented in community sites can achieve 80% positive prediction for psychosis
  – Enable more selective recruitment into prevention studies, avoiding exposure of false positives to potential adverse effects
  – Sensitivity can still be improved (perhaps w/ biological measures)

• Prodrome represents a critical period for studying changes in brain function associated with onset of psychosis
  – Fewer confounding influences than in first-episode patients
  – Can lead to elucidation of predictive biomarkers
Part II

Mechanisms of Conversion to Psychosis
Developmental Model

- Genomic
- Pre- & Perinatal Complications
  - Neural System Vulnerabilities (E.g., Frontal and Medial Temporal Lobe Systems, Mesolimbic DA System, HPA Axis)
- Synaptic Pruning, White Matter dev’t
- Neural System Vulnerabilities
- Social Environmental Factors (Stress)
- Psychosis Onset
  - Prodromal Symptoms
  - Functional Deterioration
  - Premorbid Behavior Disturbance
  - Deterioration
- Delayed Language
- Motor abnormalities

Conception | Birth | Infancy | Childhood | Adolescence | Adulthood
Adolescent Neurodevelopment: Gray Matter

• Typical Development
  – Synapses are overproduced early in development
  – During adolescence and early adulthood, normal pruning process occurs eliminating 40% of cortical synapses in frontal lobe (Huttenlocher, 1979)
  – Pruning results in fine tuning/increased efficiency of cortical networks

• Patients with schizophrenia have a ↓ dendritic spine density (Glantz & Lewis, 2000) but intact number of neurons (Selemon, 1995) potentially resulting from a disrupted pruning process
Adolescent Neurodevelopment: White Matter

• Typical Development
  – Oligodendrocyte (myelin sheath) surrounds axon, increasing conduction velocity
  – Hippocampus and frontal lobe undergo majority of myelination in adolescence and into early adulthood
  – DTI indices of myelination and axonal organization (e.g., fractional anisotropy) increase during this period

• Patients with schizophrenia show reductions in white matter volume and lower FA in key tracts
Based on McGlashan and Hoffman *Arch Gen Psychiatry* 2000
Anatomical Imaging Using Surface Based Algorithms

- Comparison of voxel intensities between scans at brain’s (or structure’s) edges
- Adjust cortical folding pattern using deformation-based approaches

Thompson et al, J Neurosci 2003
Steep rate of surface contraction in prefrontal cortex in youth with first-episode schizophrenia compared with healthy controls

Steeper rate of surface contraction in prefrontal cortex in prodromal youth who convert to psychosis compared with those who do not

Non-converters (n=23)

Converters (n=12)

Between-group Comparison (two-tailed t-tests)

Diffusion Imaging Using Tract Based Spatial Statistics

- Creates Mean FA (from all subjects)
- Creates skeleton based on regions of white matter shared between all subjects (center of tracts)
- Overlays skeleton with each subject’s FA map
- Selects voxels at center of the tracts (brightest voxels) and assigns that value to skeleton so that data is in same space but represents each subject's own center of the tract
DTI of Superior Longitudinal Fasciculus and Verbal Working Memory

FA predicted working memory performance
First Episode Patients: F(1,11)=6.28 p=.029
Controls: F(1,16)=8.55, p=.010
DTI-Based Assay of Medial Temporal Lobe White Matter Fails to Show Normal Increase with Age and Associates with Poorer Functional Outcome in UCLA Prodromal Patients

Potential Genomic Contributors

- **Gray Matter**
  - Sequence variations in DISC1, RGS4, AKT1
  
- **White Matter**
  - Sequence variations in Neuregulin 1 and its receptors (erbB)

- Altered expression of these genes + BDNF etc.

- Altered expression of oligodendrocyte genes

Li et al. *PNAS* 2007

Roy et al. *PNAS* 2007
NAPLS II Aims

1. Replicate clinical risk prediction algorithm in a new prospective sample and extend it by incorporating information on neurocognitive functioning
   - 720 prodromal patients, 240 demographically matched controls
   - Focus is on maximizing prediction (PPP and sensitivity) using measures easily implemented in community settings

2. Investigate a model of disrupted adolescent brain development resulting in dysconnectivity as the proximal mechanism underlying conversion to psychosis
   - Gray matter density, white matter integrity (FA), functional connectivity/coherence
# NAPLS II Enrollment (close to study midpoint)

<table>
<thead>
<tr>
<th>Site</th>
<th>Prodromal</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCLA</td>
<td>46</td>
<td>21</td>
<td>67</td>
</tr>
<tr>
<td>Emory</td>
<td>35</td>
<td>19</td>
<td>54</td>
</tr>
<tr>
<td>Harvard</td>
<td>15</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>Hillside</td>
<td>31</td>
<td>16</td>
<td>47</td>
</tr>
<tr>
<td>UNC</td>
<td>47</td>
<td>14</td>
<td>61</td>
</tr>
<tr>
<td>UCSD</td>
<td>33</td>
<td>25</td>
<td>58</td>
</tr>
<tr>
<td>Calgary</td>
<td>52</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>Yale</td>
<td>36</td>
<td>13</td>
<td>49</td>
</tr>
<tr>
<td><strong>TOTALS</strong></td>
<td><strong>295</strong></td>
<td><strong>163</strong></td>
<td><strong>458</strong></td>
</tr>
</tbody>
</table>

| Targeted, overall* | 305 | 103 | 408 |
| Targeted, by site* | 38  | 13  | 51  |

*Targeted enrollment from Feb 1, 2009, through Aug 30, 2010
Part III

Prevention of Psychosis
Drug Treatment of Schizophrenia
Factors Associated with Response

- Antipsychotic drugs produce (at least partial) relief of positive symptoms in most patients, but response is variable, and negative symptoms and cognitive and role functioning deficits largely refractory

- A longer duration of untreated psychosis (i.e., time between onset of symptoms and the initiation of treatment) is associated with:
  - Poorer drug response
  - Increased likelihood of relapse
  - Poorer long-term outcome

## Randomized Controlled Prevention Trials in Patients at Clinical High-Risk for Psychosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>McGorry</th>
<th>McGlashan</th>
<th>Amminger</th>
<th>Morrison</th>
<th>Addington</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active tx vs control condition</strong></td>
<td>Rispiradone + CBT vs Placebo + Support</td>
<td>Olanzapine vs Placebo</td>
<td>Omego 3 Fatty Acids vs Placebo, CBT for both</td>
<td>CBT vs Monitoring</td>
<td>CBT vs Supportive Therapy</td>
</tr>
<tr>
<td>N’s</td>
<td>31/28</td>
<td>31/29</td>
<td>41/40</td>
<td>35/23</td>
<td>27/24</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>![down pointing arrow]</td>
<td>![down pointing arrow]</td>
<td>![down pointing arrow]</td>
<td>![down pointing arrow]</td>
<td>![up pointing arrow]</td>
</tr>
<tr>
<td>Conversion to psychosis</td>
<td>![down pointing arrow] at end of tx; no diff. at f/u</td>
<td>![down pointing arrow] at end of tx; no diff. at f/u</td>
<td>![down pointing arrow] at end of tx; no diff. at f/u</td>
<td>![down pointing arrow] at end of tx; no diff. at f/u</td>
<td>![up pointing arrow] at end of tx; no diff. at f/u</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>No diff.</td>
<td>No diff.</td>
<td>![down pointing arrow]</td>
<td>No diff.</td>
<td>No diff.</td>
</tr>
<tr>
<td>Functioning</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>![down pointing arrow]</td>
<td>Not assessed</td>
<td>![up pointing arrow] Not assessed</td>
</tr>
<tr>
<td>Side effects</td>
<td>Significant weight gain</td>
<td>Significant weight gain</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

- **No diff.** indicates no statistically significant difference between groups.

---

**Parameter: Active tx vs control condition**

- **Rispiradone + CBT vs Placebo + Support**
- **Olanzapine vs Placebo**
- **Omego 3 Fatty Acids vs Placebo, CBT for both**
- **CBT vs Monitoring**
- **CBT vs Supportive Therapy**

---

**Parameter: Positive symptoms**

- **McGorry:** ![down pointing arrow]
- **McGlashan:** ![down pointing arrow]
- **Amminger:** ![down pointing arrow]
- **Morrison:** ![down pointing arrow]
- **Addington:** No diff.

---

**Parameter: Conversion to psychosis**

- **McGorry:** ![down pointing arrow] at end of tx; no diff. at f/u
- **McGlashan:** ![down pointing arrow] at end of tx; no diff. at f/u
- **Amminger:** ![down pointing arrow]
- **Morrison:** ![down pointing arrow] at end of tx; no diff. at f/u
- **Addington:** No diff.

---

**Parameter: Negative symptoms**

- **McGorry:** No diff.
- **McGlashan:** No diff.
- **Amminger:** ![down pointing arrow]
- **Morrison:** No diff.
- **Addington:** No diff.

---

**Parameter: Functioning**

- **McGorry:** Not assessed
- **McGlashan:** Not assessed
- **Amminger:** ![down pointing arrow]
- **Morrison:** Not assessed
- **Addington:** No diff.

---

**Parameter: Side effects**

- **McGorry:** Significant weight gain
- **McGlashan:** Significant weight gain
- **Amminger:** None
- **Morrison:** None
- **Addington:** None
Psychoeducational multi-family group treatment with adolescents at high risk for developing psychosis

Mary P. O’Brien,1 Jamie L. Zinberg,2 Carrie E. Bearden,1 Melita Daley,1 Tara A. Niendam,2 Alex Kopelowicz1 and Tyrone D. Cannon1,2

Abstract

Aim: In this study, we investigate the feasibility and acceptability of a 9-month psychoeducational multi-family group (PMFG) intervention for adolescents who are at ultra-high-risk (UHR) for developing psychosis.

Methods: The treatment programme was adapted from those previously shown to be effective in patients with established psychotic illness, but emphasizes content relevant to adolescence and to a pre-onset phase of illness.

Results: Participants report that psychoeducational presentations are highly useful, they attend the PMFG group sessions regularly and report feeling comfortable in meetings and benefiting from them, and adolescents demonstrate improvement in symptoms and functional outcome.

Conclusions: This study was not a randomized controlled trial and multiple interventions were introduced simultaneously; thus, changes in outcome cannot be attributed to the PMFG intervention per se. Nonetheless, these results establish the acceptability of PMFG to adolescents and families, and encourage further research into the potential positive impact of PMFG with this at-risk population.
A Prevention Trial of Family-Focused Treatment (FFT) in Youth at Risk for Psychosis

- Random assignment to 18 sessions of manualized FFT provided over a 6-month period versus Enhanced Care (EC), consisting of 5 sessions of psychoeducation and diagnostic feedback for families
  - Best-practice pharmacotherapy and crisis management as needed in both arms
- Primary, secondary, and tertiary hypotheses, respectively, are that at-risk youth will respond better to FFT than EC at 6- and 12-month follow-ups in terms of:
  - school and social functioning, family functioning, and parental distress,
  - symptom trajectories (SIPS scores)
  - time to first onset of full psychosis

Supported by NIMH Challenge Grant and IMHRO
Conclusions

• Profile of clinical risk indicators and family history has 80% positive predictive power for conversion to psychosis
  – Working toward objective assays of biomarkers

• Altered profiles of adolescent brain development may participate in onset
  – Steeper than normal rate of gray matter loss (pruning) and absence of normal increase in white matter (myelination)
  – Risk genes may influence gray & white matter changes

• Prevention may be possible
  – Omega 3 fatty acids appear promising across all endpoints
  – Antipsychotics reduce symptom severity but do not appear preventive
  – Psychosocial interventions may better impact functioning/disability
  – Working toward novel molecular targets for intervention that may restore normal development & prevent onset
Acknowledgements

• National Institute of Mental Health
• Garen, Shari, Brandon & Shannon Staglin & Music Festival for Mental Health
• International Mental Health Research Organization (IMHRO) and NARSAD
• Numerous collaborators at UCLA, other NAPLS sites, and institutions worldwide (especially Univ of Melbourne, Karolinska Institute, Konsantervelaitos)
• Patients and families who have participated in our studies