Funding from NIMH, NARSAD, AFSP, Beckwith Foundation
Royalties from Guilford, UpToDate
Consultation with HealthWise
Member, Scientific Board, Klingenstein Third Generation Foundation
Objectives

- To review limitations of current approaches to assessment and treatment of suicidal people
- To discuss advances in “objective” measures of suicidal risk
- To discuss advances in the treatment of suicidal adolescents
Limitations of Current Approaches

- Assessment of suicidal patients dependent on their self-report
- Patients do not always disclose suicidal risk
- Clinicians vary in their skills for assessing suicidal risk
- Patients who die by suicide are most often seen in non-mental health sectors
- Few risk factors for imminent risk for suicidal behavior
- Suicide is a rare outcome
Focus research on imminent suicidal risk
Need large samples given low rate of suicide
Identification of indicators of suicidal risk from existing data, like electronic medical records
Need for objective measures of suicidal risk that may be less sensitive to patient attempts for lack of disclosure
Limitations with Regard to Treatment

- Few evidence-based treatments for treatment of suicidal patients
- Treatments are often long, intensive, and require extensive training
- Therefore, hard to find qualified therapists
- Few objective measures of treatment targets, which impedes dissemination and quality control
- Treatments don’t provide intervention based on daily fluctuation in mood and circumstances
Possible Solutions

- Use of technology to provide decision and therapeutic support for clinicians
- Use of technology to expand reach of evidence-based care
- Convert evidence-based treatments to games or other accessible forms of online interventions
- Use technology to monitor patients and shape patient and clinician response
- Identify biological mechanisms of suicidal behavior and directly target these mechanisms
## Approaches to Assessment that Could Lead to Novel Interventions

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronic Health Record data mining</td>
<td>Clinician best practice alerts in real time</td>
</tr>
<tr>
<td>Passive cell phone data</td>
<td>Use information to alert clinicians, guide mobile interventions</td>
</tr>
<tr>
<td>Use of speech quality, language content, facial expression</td>
<td>Can alert clinicians and guide mobile interventions</td>
</tr>
<tr>
<td>Implicit Association Test for Suicide</td>
<td>Mobile app to target IAs</td>
</tr>
<tr>
<td>Neurosemantic Signatures for Suicidal Concepts</td>
<td>Direct Cranial Stimulation</td>
</tr>
<tr>
<td>Metabolomic Assessment of treatment-refractory, suicidal patients</td>
<td>Correction of metabolomics abnormalities</td>
</tr>
</tbody>
</table>
Use of Electronic Health Records to Identify Individuals at High Suicidal Risk

- Can get large samples
- Low cost
- Most at-risk patients present in medical health sector, where expertise in assessing suicidal risk not always readily available
- New techniques such as machine learning and natural language processing can to extract more useful data from electronic health records than previous approaches
Machine Learning is a Powerful Technique for Classification and Prediction

Machine Learning

- **Herbert Alexander Simon**: “Learning is any process by which a system improves performance from experience.”
- “Machine Learning is concerned with computer programs that automatically improve their performance through experience.”

Herbert Simon
- Turing Award 1975
- Nobel Prize in Economics 1978

https://www.slideshare.net/liorrokach/introduction-to-machine-learning-13809045
Training Data Set

Linear Classifiers

Email Length

New Recipients

Any of these would be fine...

...but which is best?

https://www.slideshare.net/liorrokach/introduction-to-machine-learning-13809045
Testing Different Algorithms

Which one?

Email Length

New Recipients

- 2 Errors
- Simple model

Email Length

New Recipients

- 0 Errors
- Complicated model

https://www.slideshare.net/liorrokach/introduction-to-machine-learning-13809045
Test Data Set

The Non-linearly separable case

https://www.slideshare.net/liorrokach/introduction-to-machine-learning-13809045
Non-linear Algorithm Will Perform Better

The Non-linearly separable case

The Non-linearly separable case

https://www.slideshare.net/liorrokach/introduction-to-machine-learning-13809045
Use of diagnoses and prescriptions to identify people who attempt or complete suicide (Barack-Cohen et al., 2017; Kan et al., 2012)

Natural language processing to identify individuals who made a suicide attempt or had suicidal ideation when not reflected in diagnoses (Anderson et al., 2015)

Use of content of natural language processing to identify those at risk for suicide ("positive valence" protective) (McCoy et al., 2016; Pestain et al., 2017)

Could have the advantage of identifying people seen in primary care or ED who would benefit from mental health care and closer follow-up
Acoustic and Linguistic Aspects of Speech and Suicidality (Pestian et al., 2017)

- Analyzed linguistic and phonic quality of speech
- For adolescents, linguistic alone, 87% accurate; acoustic, 74%, combination, 93%
- Type of linguistic factors: less likely to laugh, get angry, express hope, more likely to sigh
- Adds to clinical data, and could be used to monitor clinical status and alert patient and clinician of status
Use of Passive Cell Phone Data to Monitor Clinical Status

- With passive cell phone data, can examine motion, number of locations visits, number and duration of conversations, circadian cycle, voice quality, facial expression
- Joshi et al., 2013: facial movement and speech quality, could classify depressives with 92% accuracy
- Saeb et al., 2015: found that depressive symptoms were correlated with location, mobility, number of conversations, circadian indices
- Used to monitor patients with schizophrenia and bipolar disorder
- Could alert patient and/or clinician and encourage changes in activity, sleep, and social activity
Use of Passive Cell Phone Data to Monitor Depressive Symptoms (Saeb et al., 2015)
Mobile Apps for Suicidal Individuals (Larsen et al., 2016)

- 123 phone apps of which 49 had suicide specific applications
- 27– support from friends and family
- 4– safety planning
- 17– facilitate connection with a crisis center
- Most had only 1 type of intervention, but Safety Planning apps had 4 on average
- No apps to help parents or clinicians respond
# As Safe As Possible (ASAP)

**PITTSBURGH**
- Tina Goldstein
- Antoine Douaihy
- Dana McMakin (now at FIU)
- Candice Biernessser
- Erin Wentroble
- Giovanna Porta
- Jamie Zelazny
- Satish Iyengar

**DALLAS**
- Betsy Kennard
- Aleksandra Foxwell
- Taryn Mayes
- Kristin Wolfe
- Alexandra Moorehead
- Victoria Owen
- Jessica Wiblin
- Lucas Zullo
- Jessica Jones
Period post-discharge from hospital the highest risk for repeat attempts and suicides

Often gap between discharge and first session

With outpatient treatment, suicidal events occur early in care, before have been able to teach much in the way of skills

Therefore, considered doing a brief intervention on the inpatient unit PRIOR to discharge

No treatment has used technology to augment and extend the impact of intervention
### Treatment As Usual (TAU)

- **Inpatient**
  - Standard safety plan
- **Outpatient**
  - most often IOP or Partial

### Added ASAP Components

- Chain analysis
- Safety Plan
  - Internal strategies
  - Interpersonal strategies
  - Clinical contact
- Distress Tolerance
- Emotion Regulation
- MI to encourage outpatient follow-up
Did first version that also including family, social support, and sleep that could not be completed on inpatient unit

Then streamlined to 6-8 hrs. plus coaching calls

App prototype developed and then got feedback from clinicians, parents, and patients

Current prototype: BRITE
- Personalized reminders daily to rate distress level

- Rating level of distress in real time:
- Savor, Distract, Soothe, Reasons to Live, Reaching out to Contacts – which all can be customized
How do you feel after completing the activity?

Better  Worse  Same

I didn't complete an activity.

You just rated your distress level as 3 😞. Do you want to enter a new rating?

Yes  No

- Rating the usefulness of the Activity
- Re-Rating of Distress Post Intervention
# Sample

<table>
<thead>
<tr>
<th></th>
<th>Pittsburgh</th>
<th>Dallas</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>29</td>
<td>37</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>15.7±1.1</td>
<td>14.6±1.7</td>
<td>15.1±1.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Caucasian Race</td>
<td>21 (72.4%)</td>
<td>30 (81.1%)</td>
<td>51 (77.3%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Female Sex</td>
<td>26 (89.7%)</td>
<td>33 (89.2%)</td>
<td>59 (89.4%)</td>
<td>&gt;0.99</td>
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<tr>
<td>SES</td>
<td>5.0±2.7</td>
<td>9.3±4.8</td>
<td>7.7±4.6</td>
<td>0.001</td>
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</tbody>
</table>
## Characteristics of Sample

<table>
<thead>
<tr>
<th>Domain</th>
<th>Pittsburgh</th>
<th>Dallas</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Previous Attempts</td>
<td>23 (79.3%)</td>
<td>30 (81.1%)</td>
<td>53 (80.3%)</td>
<td>0.86</td>
</tr>
<tr>
<td>% Previous Attempts/SRB</td>
<td>29 (100%)</td>
<td>32 (86.5%)</td>
<td>61 (92.4%)</td>
<td>0.06</td>
</tr>
<tr>
<td>SIQ</td>
<td>71.3±20.3</td>
<td>63.0±22.9</td>
<td>66.6±22.0</td>
<td>0.13</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>19.1±5.0</td>
<td>17.8±5.5</td>
<td>18.4±5.3</td>
<td>0.30</td>
</tr>
<tr>
<td>SCARED</td>
<td>47.2±16.1</td>
<td>49.4±15.3</td>
<td>48.4±15.5</td>
<td>0.57</td>
</tr>
<tr>
<td>CRAFFT</td>
<td>1.6±1.6</td>
<td>1.4±1.7</td>
<td>1.5±1.7</td>
<td>0.52</td>
</tr>
</tbody>
</table>
## Suicidal and Treatment Outcomes

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>ASAP</th>
<th>p</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any suicidality*</td>
<td>80.8%</td>
<td>57.1%</td>
<td>0.06</td>
<td>-0.53</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>76.9%</td>
<td>57.1%</td>
<td>0.12</td>
<td>-0.43</td>
</tr>
<tr>
<td>Suicide attempt/SRB</td>
<td>26.9%</td>
<td>21.4%</td>
<td>0.64</td>
<td>-0.13</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>23.1%</td>
<td>14.3%</td>
<td>0.49</td>
<td>-0.23</td>
</tr>
<tr>
<td>NSSI</td>
<td>38.5%</td>
<td>39.3%</td>
<td>0.95</td>
<td>0.02</td>
</tr>
<tr>
<td>Engaged in treatment**</td>
<td>84.0%</td>
<td>78.6%</td>
<td>0.73</td>
<td>-0.14</td>
</tr>
</tbody>
</table>

*ideation/attempt/SRB
**defined as having attended ≥ 2 visits/days of partial, IOP, or outpatient program
Wilcoxon $\chi^2_1 = 1.19, p=0.28$

Log-rank $\chi^2_1 = 0.90, p=0.34$

$IRR=0.73$, 95% CI: 0.36, 1.49, $p=0.36$

Incident Suicidal Ideation

Months since Baseline

1-Survival

UC  ASAP
Incident Suicide Attempt

Wilcoxon $\chi^2_1 = 1.14, p = 0.29$
Log-rank $\chi^2_1 = 0.63, p = 0.43$

$IRR = 0.58$, 95% CI: $0.12, 2.46, p = 0.42$
70.6% participants viewed the App

75.0% added content

# times content was added: M=14.2, SD=11.0, median=9, range: 2-41

Which activity was added (% times)
- Savoring memories: 54.5%
- Memories: 21.2%
- Positive thoughts: 9.8%
- Reasons for living: 6.7%
- Contacts: 5.1%
- Journal: 1.6%
- Learning to savor: 1.2%

37.5% removed

# times content was removed: M=10.3, SD=5.6, median=9, range: 7-25

Which activity was removed (% times)
- Savoring memories: 82.8%
- Positive thoughts: 16.1%
- Reasons for living: 1.08%
### Relationship between Use of App and Suicidal Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Viewed the App</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>p</td>
<td>d</td>
</tr>
<tr>
<td>Any suicidality*</td>
<td>50.0%</td>
<td>59.1%</td>
<td>&gt;0.9</td>
<td>0.18</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>50.0%</td>
<td>59.1%</td>
<td>&gt;0.9</td>
<td>0.18</td>
</tr>
<tr>
<td>Suicide attempt/SRB</td>
<td>16.7%</td>
<td>22.7%</td>
<td>&gt;0.9</td>
<td>0.15</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>16.7%</td>
<td>13.6%</td>
<td>&gt;0.9</td>
<td>-0.09</td>
</tr>
<tr>
<td>NSSI</td>
<td>50.0%</td>
<td>36.4%</td>
<td>0.65</td>
<td>-0.28</td>
</tr>
</tbody>
</table>

*ideation/attempt/SRB
## Feedback about Intervention

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>ASAP</th>
<th>Total</th>
<th>p</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Client Satisfaction Questionnaire</td>
<td>24.1±5.2</td>
<td>26.6±3.8</td>
<td>25.5±4.7</td>
<td>0.07</td>
<td>0.58</td>
</tr>
</tbody>
</table>

*Higher score indicates better satisfaction
Possible total score: 8 to 32

### Participant Quotes:

- “It taught me how to better understand my emotions and see when I’m more likely to get more upset and when I’m not as upset...like your emotional thermometer – how upset you are.”

- “I was having really bad anxiety. I was able to calm myself down, I used grounding and mindfulness.”

- “I know one of the skills was doing things that bring me joy, writing, painting, drawing, stuff like that. That helped me to tolerate distress.”
## Feedback about App

<table>
<thead>
<tr>
<th></th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computer Usability Satisfaction Questionnaire*</td>
<td>17.6±7.1</td>
<td>19.0±10.9</td>
<td>20.0±8.6</td>
</tr>
</tbody>
</table>

*Lower score indicates better satisfaction  
Possible total score: 10 to 70

---

### Participant Quotes:

- “I’ve used guided imagery…It’s really helpful for me when I can’t sleep or having a panic attack. It calms me down a lot, deep breathing. Those were the most helpful parts.”

- “It just helped me to focus on the good things, especially when I felt a little bit suicidal and I wasn’t really focusing on things that made me happy. Good things – the people in my life and my goals to become a nurse and help people”

- “I really liked how you check in with yourself, your temperature’s rising and you don’t even know it. You can stop and check in. I started doing it without even the app, it became natural to me. It helped a lot.”
Suggestions for Brite 2.0

- **Resources:** Teens wanted recommendations of possible resources and then wanted to personalize.
- **Functioning:** simple & straightforward means of interacting.
- **Customization:** additional ways to add color and personal preference.
- **Notification:** the key point is being prompted at the right time, some youth requested more notifications vs. less.
- **Accessibility:** need to use without wifi.
Next Steps

- Replicating ASAP/Brite in a larger sample
- Adapting Brite for a primary care setting
  - Use of passive data collection to identify the “right” time for notifications
  - Logic-driven “favoriting” to personalize intervention options
  - Additional feedback to streamline functioning, look & feel, & resource library
  - Improving accessibility through use without wifi
  - Adding parallel parent and clinician apps to support Brite
Conclusions

1. ASAP/Brite present a feasible combined treatment to bridge from inpatient to outpatient care
2. Both intervention and app were accepted by youth
3. Augmenting ASAP with the Brite app resulted in trends toward lower suicidal thoughts, attempts, and suicide-related behaviors
4. Our work is not done!
Matthew Nock, PhD
Professor of Psychology, Harvard University
MacArthur Fellow

http://nocklab.fas.harvard.edu/people/matthew-k-nock-phd
Suicide and Self-injury Implicit Association Test

- Show image and participant must either indicate that is “suicide/like me” or non-suicide/not like me
- Individuals with great attraction and less repulsion from self-injury and suicidal behavior will respond more quickly to suicide/like me, and non-suicidal individuals will respond more quickly to non-suicide/not like me
From: Assessment of Self-Injurious Thoughts Using a Behavioral Test
American Journal of Psychiatry

For each test block, the concept and attribute labels remain in the top corners of the screen and participants must classify each stimulus appearing in the center of the screen accordingly. In this example, the left key is the correct response because the image is of cut skin and the wording “Cutting” appears on the left side of the screen. Individuals who identify with self-injury (i.e., associate self-injury with the self) should perform more quickly on this test block because self-injury (i.e., “Cutting”) is paired with the self (i.e., “Me”). In contrast, noninjurers should perform more quickly on the test block in which “Cutting” is paired with “Not Me.” See https://implicit.harvard.edu/implicit/ for actual demonstration tests.
c This version measures the automatic association of self-injury with evaluative positivity. The difference between groups was significant (t=−4.66, df=87, d=1.00, p<0.001).
## SI-IAT (identification): Discriminant and Predictive Validity

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Sample</th>
<th>Outcome</th>
<th>AOR of SI-IAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nock &amp; Banaji, 2007</td>
<td>89</td>
<td>adolescents</td>
<td>Suicidal ideation</td>
<td>6</td>
</tr>
<tr>
<td>Nock et al., 2010</td>
<td>157</td>
<td>Adolescents &amp; young adults</td>
<td>Suicide attempt</td>
<td>10.9</td>
</tr>
<tr>
<td>Cha et al., 2016</td>
<td>123</td>
<td>adolescents</td>
<td>Self-injury</td>
<td>8.2</td>
</tr>
<tr>
<td>Glenn et al., 2015</td>
<td>662</td>
<td>13 yo</td>
<td>Self-injury</td>
<td>1.2-3.04</td>
</tr>
</tbody>
</table>
Interrelationship between SI-IAT and NSSI Frequency (Glenn et al., 2015)

Figure 2. Cross-lagged associations between nonsuicidal self-injury (NSSI) frequency and implicit associations with NSSI (SI-IAT) over 1 year (T2–T3). Unstandardized coefficients displayed. For clarity, disturbances are not displayed. Covariances involving exogenous variables are not estimated in count models.

***p < .001; **p < .01; *p < .05
TEC is a game app that pairs self-injury with disgusting images, and self with positive images.

3 studies totaling 306 young adults recruited on-line with high rates of NSSI.

Over 1 month, use of TEC associated with declines in NSSI, suicide attempts, but not ideation.

In 2/3 studies, effects mediated by change in attitudes towards self-harm and by dose.

Effects faded in one month.
Figure 1. Screenshots of TEC screen types. TEC begins with a screen displaying matches, moves to a 2 x 2 grid for the first 15 trials; masks alternative options after the first pair member is selected for the second 15 trials; moves to a 3 x 3 grid for the third 15 trials; masks alternative options within this larger grid for the final 15 trials; and ends with a screen that displays positive (for active TEC) or neutral images (for control TEC), total trials correct, game and total points, and time elapsed for that instance of TEC. See the online article for the color version of this figure.
Figure 2. Effect of active TEC on NSSI-related outcomes. All comparisons controlled for several powerful covariates (see Supplemental Tables S2–S4); without these covariates, treatment effects tended to be stronger and there were significant treatment effects on overall NSSI outcomes in Study 3 (see Supplemental Table S1). Error bars = 95% confidence intervals. The upper-bound for the confidence intervals for self-cutting events in Study 2 and NSSI events from Studies 2 and 3 extend beyond the viewable area for the present graph (see Supplemental Tables S2–S4 for more information). Self-cutting events and NSSI events were not measured in Study 1. ***p<001
Change in Suicidal ideation, planning, and behaviors with TEC (Franklin et al., 2016)

Figure 3. Effect of active TEC on suicide-related outcomes. All comparisons controlled for several covariates (see Supplemental Tables S2–S4). Error bars = 95% confidence intervals. The upper-bound for the confidence intervals for suicide ideation outcomes extend beyond the viewable area for the present graph (see Supplemental Tables S2–S4 for more information). $\phi =$ no statistical tests were performed within individual studies for suicidal behavior outcomes; these were examined in aggregate within the text and the overall treatment effect was statistically significant. $^*p < .05; ^{**}p < .001$. 
One current interest is in identifying the neural basis of concept representations using fMRI in the new area of neurosemantics. In collaboration with colleagues in the School of Computer Science, we have developed experimental paradigms and machine-learning techniques (multi-voxel pattern analysis) that are being applied to the study of lexical, perceptual, and social concepts (identifying the neural signature of that object and the components of the signature). We can identify the thought of a concrete object, social interaction, and digit, and we are moving on to propositions. This is leading us to a specification of how simple thoughts are neurally coded. http://www.ccbi.cmu.edu/
17 pairs of young adults
Half with high ideation
Had them think about 30 words (10 suicide-related, 10 positive valence, 10 negative valence)
fMRI brain activation
Machine learning to classify patterns of activation
Discriminated ideators from healthy controls and ideators with and without a history of attempt by pattern of brain activation at greater than 90% accuracy
Differences in emotional valence of words part of the explanation
Direct Cranial Stimulation

Figure 2. Diagram of a typical tDCS setup for depression, with the anodal electrode over the left DLPFC (red) and cathodal electrode over the ipsilateral shoulder (blue). Note the direction of current towards the brain in the case of anodal stimulation, and outward in the case of cathodal stimulation. Insert: schematic illustration of neuronal resting membrane potential without tDCS, and after anodal (red) and cathodal (blue) tDCS.

A battery-powered device delivers a direct current of 2mA for 30 minutes.
Direct Cranial Stimulation

- Effective for treatment resistant depression (Brunoni et al., 2014)
- Targets impulsivity, decision making which are impaired in suicide attempts with same neurocircuitry involved (Ouellet et al., 2015)
- Not been carefully studied in reduction of suicidal ideation or prevention of suicidal behavior
Enhancing decision-making and cognitive impulse control with transcranial direct current stimulation (tDCS) applied over the orbitofrontal cortex (OFC): A randomized and sham-controlled exploratory study (Ouellet et al., 2015)

Fig. 1. Net score in the Iowa Gambling Task before and after active or sham tDCS. A significant tDCS intervention*time interaction was found (p = 0.04) after controlling for the main effect of time (p = 0.02).
Fig. 2. “Interference index” in the Stroop Colour-Word Task before and after active or sham tDCS. A significant tDCS intervention*time interaction was found ($p = 0.007$) after controlling for the main effect of time ($p = 0.01$).
Patient with treatment refractory depression and suicidal behavior

- Depression and self injury, age 11
- Suicide attempt age 14
- Age 15 suicide attempt 80 pills, discovered by chance, ICU stay
- No response to available medications
- Age 18, ECT with one week of response
- Refused ECT due to non-response, 49 day hospital stay due to continued suicidality

Lisa Pan, MD
Identified deficiencies circled in yellow.

<table>
<thead>
<tr>
<th>CSF Studies</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HIAA</td>
<td>38</td>
</tr>
<tr>
<td>HVA</td>
<td>116</td>
</tr>
<tr>
<td>Neopterin</td>
<td>&lt;5</td>
</tr>
<tr>
<td>BH4</td>
<td>10</td>
</tr>
</tbody>
</table>
Function of BH4

- Cofactor for phenylalanine-4-hydroxylase (PAH), tyrosine-3-hydroxylase, and tryptophan-5-hydroxylase; the latter two are key enzymes in the biosynthesis of biogenic amines.
  - BH4 serves as the cofactor for nitric oxide synthase2.

This patient was treated with sapropterin (Kuvan) and recovered (Pan et al., 2011)
Recruitment

- Age 14-40 years
- Failure of at least three full dose and adequate duration medication trials
- Study requires testing of cerebrospinal fluid, blood, and urine samples
- N = 50 affected and 18 controls
# IEMs and Treatment Refractory Depression

<table>
<thead>
<tr>
<th>Finding</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=50)</td>
<td>(N=18)</td>
</tr>
<tr>
<td>Low CSF 5MTHF</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Low CSF tetrahydrobiopterin</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal Acylcarnitine Profile</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Low Guanidinoacetate/Creatinine &amp; Creatine/Creatinine</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fabry Disease</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total with Metabolic Findings</strong></td>
<td><strong>30</strong></td>
<td><strong>0</strong></td>
</tr>
</tbody>
</table>
Cerebral Folate Deficiency (CFD)

- CFD is caused by inefficient folate transport across the blood brain barrier
- In health, folate is de-conjugated and carried across the blood-brain barrier as 5-MTHF
- CFD has low 5-MTHF in CSF and normal folate in plasma
- Therefore, diagnosis of CFD requires CSF
- Low 5-MTHF may also contribute to impaired BH4 synthesis, impairing serotonin, norepinephrine, and dopamine synthesis
Folate Metabolism (simplified). DHFR dihydrofolate reductase  SHMT serine hydromethyltransferase  MTHFR methylenetetrahydrofolate reductase
Folinic Acid

- Folinic acid bypasses de-conjugation and reduction steps for folic acid metabolism, i.e. deconjugation to 5-MTHF occurs without dihydrofolate reductase.
- 5-MTHF is then available for transport across the blood brain barrier.
- Dosing may be titrated to 1-2 mg/kg or higher.
Clinical Implications

- Treatment with folinic acid has resulted in sustained improvement of depressive symptoms in 7/9 (1 lost to follow-up).
- Depression: BDI: 28.4 (17-43) to 15.0 (6-36)
- Suicidal ideation: SIQ: 28.9 (8-70) to 17.7 (4-58)
Depression outcomes after treatment with folinic acid

Beck Depression Inventory (BDI)

Baseline BDI vs. Follow-up BDI

- Line 1
- Line 2
- Line 3
- Line 4
- Line 5
- Line 6
- Line 7
- Line 8
- Line 9-BH4&CFD
- Line 10-CFD&Abnormal Acylcarnitine
Tina Goldstein, PhD
Co-Director, Services for Teens at Risk

Associate Professor, Psychiatry and Psychology
Director, Psychology Internship and T32 postdoctoral training program
Director, Psychosocial treatment in Mood Disorders
Winner, Klerman Award for Early Investigators in Mood Disorders
2016, Recognized with a Presidential Early-Career Award for Scientists and Engineers
We acknowledge with gratitude the Pennsylvania Legislature for its support of the STAR-Center and our outreach efforts.
Thank you for your attention

- For copies of these slides, please email Joe Park at parkj5@upmc.edu