

Advancing Discovery Summit 2018 Summary Report

Broad Institute, Cambridge, Massachusetts

March 21-22, 2018

Summit Overview

On March 21-22, 2018, the Stanley Center for Psychiatric Research at Broad Institute, the Psychiatric Genomics Consortium (PGC), and the National Alliance on Mental Illness (NAMI) hosted a day and a half summit with the goal of sparking truly innovative ideas and collaborations for making significant progress on the challenges of diagnosing and treating people with mental illness. This invitation-only event convened a diverse group of neuroscience thought leaders from academia and industry, leading advocates, and government and public policy experts. It also integrated the first-person and family experience of our current, imperfect treatment options.

Throughout the event, these representatives from key stakeholder groups shared perspectives from their areas of expertise and strategized together. The result was several concrete action plans that represent positive steps toward developing new and better treatments for schizophrenia and other serious mental illness.

These actions plans include:

- Create a public-private partnership
- Develop and execute a strategic communication plan
- Define the 50-100 targets/genes that are linked for schizophrenia
- Continue to engage key stakeholders
- Create a patient registry and hold a recruitment drive
- Define an advocacy role for NAMI consistent with this need
- Engage in data sharing
- Launch “All of Our Trials” to use data from existing clinical trials

See the end of the report for activities, milestones, and desired outcomes from these initiatives.

Summit Participants

Hosts

NAMI is the nation’s largest grassroots mental health organization. The organization brings the voice of the patient and their families to policymakers and researchers nationwide. NAMI has steadfastly supported resources for research; however, with the increasing recognition of the patient and family role in research, as well as changes in the rate of new treatments, NAMI is collaborating with the Broad Institute to convene leaders to promote acceleration of new discoveries and the sharing of information.

Psychiatric Genomics Consortium (PGC) unites investigators to conduct meta- and mega-analyses of genome-wide genomic data for psychiatric disorders. The PGC is the largest consortium and the largest biological experiment in the history of psychiatry. It includes more than 800 investigators from 38 countries. Samples from more than 900,000 individuals are currently in analysis, and this number is growing rapidly.

Broad Institute of MIT and Harvard is the world's leading biomedical research institute dedicated to the bold mission of using the full power of genomics to transform the understanding and treatment of disease. The Stanley Center for Psychiatric Research at Broad Institute aims to exploit the most advanced technologies for human genetic analysis to study psychiatric disorders in order to understand disease mechanisms, identify potential biomarkers, and ignite needed progress in therapeutics.

Individual Participants

Steering Committee members indicated by asterisk

- Anji Addington, Ph.D., Branch Chief of the Genomics Research Branch in the Division of Neuroscience and Basic Behavioral Science at NIMH
- Kathleen C. Anderson, Ph.D, Health Scientist Administrator at NIMH
- Linda Brady, Ph.D., Director of the Division of Neuroscience and Basic Behavioral Science at NIMH
- *Gerome Breen, Ph.D., Reader (Senior Associate Professor) In Translational and Neuropsychiatric Genetics at the Social, Genetic and Developmental Psychiatry Research Center at the Institute of Psychiatry, Psychology and Neuroscience at King's College London
- *Teri Brister, Ph.D., Director of Knowledge Integration at NAMI
- Tyler Brown, Ph.D., Program Manager at the Stanley Center for Psychiatric Research at the Broad Institute
- Steve Brunette, Ph.D., Associate Director, Patient Advocacy and Professional Relations, Boehringer Ingelheim Pharmaceuticals
- Sinéad Chapman, Associate Director of Genetic Project Management at the Stanley Center for Psychiatric Research at the Broad Institute
- *Guang Chen, M.D., Ph.D., Scientific Director on Translational Research, Mood Disease Area Stronghold, Neuroscience Therapeutic Area at Janssen R&D, LLC, Janssen Pharmaceutical Companies of Johnson & Johnson
- *David Collier, Ph.D., Research Fellow and Leader of the Psychiatric Genetics Group at Eli Lilly and Company
- Jeffrey Cottrell, Ph.D., Director of Translational Research at the Stanley Center for Psychiatric Research at the Broad Institute
- Patrick Cullinan, Ph.D., Leader of Scientific Advocacy at Takeda Pharmaceuticals
- *Ken Duckworth, M.D., Medical Director at NAMI
- Jessica Edwards, Senior Manager for External Relations at NAMI
- Andy Forbes, Ph.D., Senior Director for Global Clinical Development—CNS for Otsuka R&D

- Mary Giliberti, J.D., Chief Executive Officer at NAMI
- Joel Gelernter, M.D., Foundations Fund Professor of Psychiatry and Professor of Genetics and of Neuroscience; Director of Human Genetics (Psychiatry) at Yale University
- Joshua A. Gordon, M.D., Ph.D., Director of NIMH
- *Charles R. Harman, Chief Development Officer at NAMI
- Mona Hicks, Ph.D., Science and Technology Lead, One Mind
- Seth Hopkins, Ph.D., Executive Director Translational Medicine at Sunovion Pharmaceuticals, Inc.
- *Rosy Hosking, Ph.D., Manager of Scientific Communications and Outreach at the Stanley Center for Psychiatric Research at the Broad Institute
- *Steven E. Hyman, M.D., Harvard University Distinguished Service Professor of Stem Cell and Regenerative Biology and Director of the Stanley Center for Psychiatric Research at the Broad Institute
- Adrienne Kennedy, Executive Committee Secretary and Chair of Governance of the NAMI Board of Directors
- Kenneth Koblan, Ph.D., Head of Discovery and Global Translational Medicine and Early Development at Sunovion Pharmaceuticals Inc.
- Carlos Larrauri, M.S.N., A.R.N.P., F.N.P.-B.C., NAMI Board of Directors
- Mitchell Mathis, M.D., Director of the Division of Psychiatry Products at the Center for Drug Evaluation and Research of the US FDA
- Steven McCarroll, Ph.D., Dorothy and Milton Flier Associate Professor of Biomedical Sciences and Genetics at Harvard Medical School
- Venkatesha Murthy, M.D., Global Head of Psychiatry, Clinical Science, Takeda Neuroscience Therapeutic Area
- Keris Myrick, Director of the Office of Consumer Affairs for the Center for Mental Health Services of the Substance Abuse and Mental Health Services Administration
- Mark Namchuk, Ph.D., SVP of Research, Non-Clinical and Pharmaceutical Development, at Alkermes
- Benjamin Neale, Ph.D., Assistant Professor in the Analytic and Translational Genetics Unit at Massachusetts General Hospital, Assistant Professor in Medicine at Harvard Medical School, and Institute Member at the Broad Institute
- Mike Quirk, Ph.D., Vice President of Pharmacology at Sage Therapeutics
- Kanchan Relwani, M.D., Vice President of Medical Strategy, Medical Affairs, at Alkermes
- *Raymond Sanchez, Jr., M.D., Psychiatrist, PhRMA Biomedical Advisory Council Member and Trustee, and on the Board of Directors of the Connecticut Mental Health Center Foundation and Yale School of Medicine
- *Michael Sand, Ph.D., M.P.H., Senior Clinical Project Leader at Boehringer Ingelheim
- Eric Schaeffer, Ph.D., Senior Director of Neuroscience Innovation at Johnson & Johnson and Janssen Research & Development
- Andrew Sperling, Director of Federal Legislative Advocacy at NAMI
- *Paul Surgenor, Ph.D., National Director of Information, Support and Education at NAMI
- Howard Trachtman, Certified Psychosocial Rehabilitative Practitioner and Certified Peer

Specialist; Co-founder and President Emeritus of NAMI Greater Boston Consumer Advocacy Network

- Florence Wagner, Ph.D., Director of the Medicinal Chemistry Group in the Stanley Center for Psychiatric Research and the Center for the Development of Therapeutics at Broad Institute
- Brian Werneburg, Ph.D, Senior Medical Director at Sage Therapeutics

Facilitator

- John Griffin, Ph.D., Principal, Reos Partners

Report Writer

- Janice Molloy, Principal, Espira Editorial

Facilitation Process

The Summit organizers sought a facilitation approach that would challenge participants to go beyond business-as-usual and stimulate out-of-the-box thinking. To achieve this goal, NAMI contracted Dr. John Griffin from Reos Partners to facilitate the meeting.

Reos Partners specializes in bringing people together from different parts of a system to make meaningful progress together on complex, stuck challenges. The work they do with groups in complex systems is systematic, collaborative, and experimental. Reos Partners' facilitators seek *transformational* rather than *incremental* change—something NAMI and the Steering Committee members agreed is a desired outcome from this Summit and ongoing initiatives. Reos Partners also facilitated the inaugural Advancing Discovery Summit in 2016 and a preliminary Advancing Discovery gathering in September 2017, and worked with the Steering Committee to plan the current Summit.

Three-Step Process

Reos Partners bases much of its approach for making progress on complex problems on a methodology called "Theory U." As described by MIT lecturer Otto Scharmer, Theory U "enables leaders and organizations in all industries and sectors to shift awareness from ego to eco, to connect with the highest future possibilities, and to strengthen the capacity to realize those possibilities."

Theory U involves:

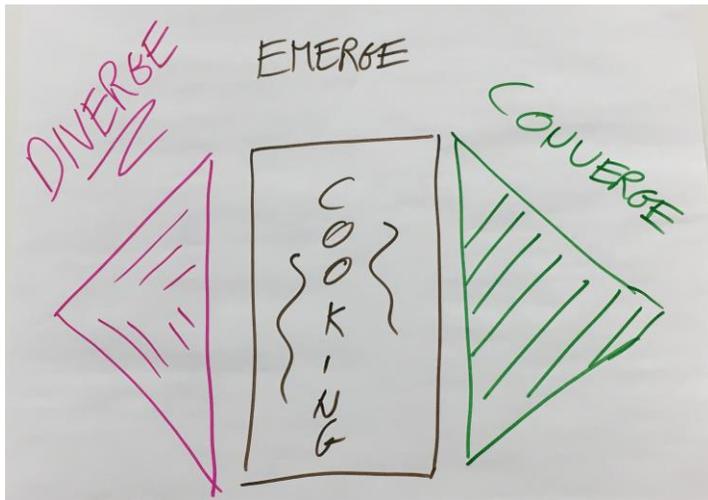
- *Co-Sensing*—so groups can get a shared sense of current reality
- *Co-Presencing*—so groups can generate deeper wisdom
- *Co-Creating*—so groups can create new possibilities together

Dialogue Interviews

As part of the preparation for the Summit, the Reos Partners' team worked with the Steering Committee to conduct and synthesize a series of "Dialogue Interviews." Details from these interviews are included below.

Dialogue Interviews are a key part of the co-sensing process. As described on the Reos Partners website, “Dialogue Interviews are in-depth conversations with concerned people throughout a complex system. Rarely do people feel so thoroughly heard. After conducting these conversations, we synthesize them and mirror them back, identifying common threads. The result is an unusually candid, reflective, and holistic assessment of the problem.... [Di]alogue Interviews provoke valuable thinking and discussion, but also create a platform for exploration and action.”

Diverge-Emerge-Converge



During the working session, Dr. Griffin introduced three steps for innovating:

- *Diverge*—explore new ideas and stimulate novel thinking
- *Emerge*—let ideas begin to form
- *Converge*—agree on actions for moving forward

The Summit design was intended to move participants through these phases.

Ground Rules

At the beginning of the working session, Dr. Griffin introduced simple ground rules for participants’ conduct during and after the session. These expectations encouraged attendees to participate in the discussion openly and fully:

- **Be present.** Rather than be distracted during the session, if you need to take a break for whatever reason, feel free to do so, and then come back to the room when you are ready to engage again.
- **Keep confidences.** You can say who was here, you can say what was said, but you can’t say who said what (without permission).
- **Practice democracy of time.** The summit isn’t based on an expert model. The more we can hear each other’s ideas, the better we can think together. Move from trying to

convince everyone else to adopt your ideas to hearing others' ideas. Pay attention to how much you are talking versus how much you are listening. Let people know if conversations that should be happening aren't taking place.

- **Have fun!**

Kinetic Activities

At two points in the program, Dr. Griffin had the participants get out of their seats and engage in brief movement-based activities. The purpose was to “break the ice” in this group of relative strangers from difference stakeholder groups and to create a sense of energy at moments when it might be lagging.

Wednesday Working Session

Opening

Dr. Rosy Hosking welcomed the group on behalf of the Broad Institute, where the Summit was being held. She said that Broad is thrilled to be in partnership with NAMI and PGC in hosting this event.

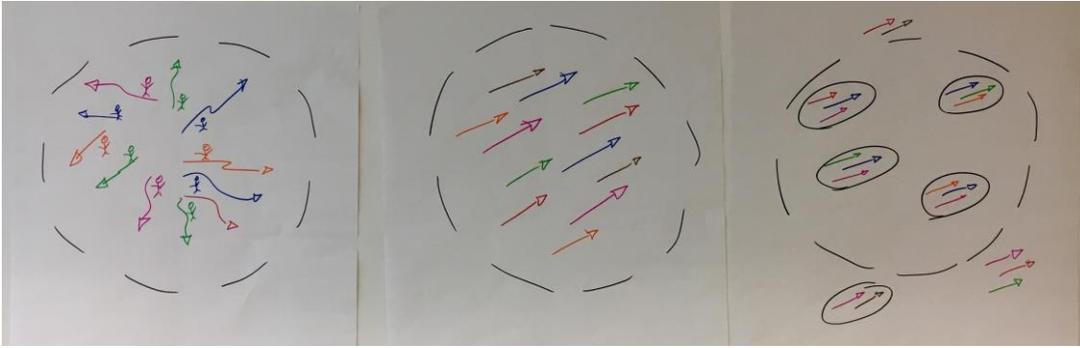
Adrienne Kennedy expressed the enthusiasm of the NAMI board of directors and staff in supporting robust conversations across silos. She noted that, as advances in mental health and brain health take place, we need to create cultures that can absorb these changes and cut the lag time between discovery and implementation.

Mary Giliberti welcomed the participants on behalf of NAMI and thanked the Broad Institute, the NAMI staff, and the event sponsors for their many contributions. She pointed out that, unlike aiming for the moon, where humans have already traveled, we need a “Mars shot” in order to make significant progress on helping people with mental illness. Current treatments often don't help or have significant side effects. We need more and better treatments and want to make the same kind of progress that has been made in combating diseases like HIV/AIDS.

Dr. Ken Duckworth welcomed participants to this important and compelling meeting, saying they represent the best chance for people with mental illness to have both “a mind and a body.” Current treatments can have significant side effects, such as weight gain, causing patients to go off their medications and suffer serious setbacks. Achieving mental health parity took tremendous effort, and we need the same level of activity around seeking better and new treatments for mental illness. Through the Dialogue Interviews, the Steering Committee identified 6-7 ideas that could help create momentum in this effort.

Process for Making Progress on Complex Issues

Dr. Griffin began by sharing three diagrams of the process through which people make progress on complex issues.



1. People are moving in all different directions. The ecosystem is contained by a porous boundary through which contributors enter and leave.
2. Over the last two years of meetings, participants have been working to align on a “North Star,” or a common direction and set of goals.
3. The goal of the 2018 Advancing Discovery Summit is for the group to identify specific nodes in which to conduct activities/pilot collaborative projects over the next two years. Some of these nodes may connect.

Check-In

At their tables, people shared their names and organizations and a brief statement about what excited them about participating in the event. Dr. Griffin then asked for participants to briefly share their comments and questions with the larger group. Comments included:

- Pleased that people with mental health issues have a voice at the table.
- People come to NAMI to look for information and hope.
- We need courage to try new things.
- It’s an opportunity to collaborate.
- How do we drive forward based on evidence?
- Genetics has taught us a lot about how different diseases overlap and that they are true biological phenomena.
- How can we move forward to a specific, biologically driven treatment path?
- NAMI is about building a movement.
- In updating NAMI’s Family-to-Family program, it became clear that not much has changed since 2014.

Report-Out from the Dialogue Interviews

The Steering Committee conducted Dialogue Interviews with 10 thought leaders, based on a series of questions they had generated in advance. (Some of the interviewees were also Summit participants). The goals of these 1- to 2-hour conversations were to:

- Start to break down the complex topic of brain research
- Identify ongoing areas of focus for the next two years
- Identify 6-7 ideas—or “podlets of work”—to focus on during the Summit

The facilitation team clustered quotes from the interviews to come up with common themes. Some of these were chosen as areas of focus for the Summit, while others will be examined at a future date:

1. Engagement of industry and academic for the long haul – overarching goal of the Summit
2. Stigma
3. Need for a Call to Action
4. Brain science is hard
 - Biomarkers
 - Data sharing
5. Translation gaps from bench to bedside and bedside to bench
6. Grants and transactional costs
7. Issues for patients and families—risks and benefits while waiting for better treatment options

Small-Group Conversations and Report-Outs

The participants then took part in small-group conversations based on the themes from the Dialogue Interviews. They discussed what surprised them, what didn't surprise them, what intrigued them, and what they thought was missing. The debrief covered the following:

General Discussion

There is a general need in the field to:

- Identify shared goals, even though we aren't a homogenized whole
- Identify targets
- De-risk pharma discovery and investment in neuroscience
- Deal with the placebo effect
- Use common language and practice honesty—can't obfuscate issues
- Shift away from single target stream?

Industry:

- What would the industry have to see to get really excited?
- Industry engagement—does the need for short-term wins justify staying in?
- Small biotech companies are being bought by large ones.
- Multilateral engagement—many companies engaging at once and with each other—is OK.

Progress:

- Progress is happening on depression—the momentum is starting to shift with the introduction of different compounds.

Cancer:

- What can mental illness researchers and advocates learn from cancer?
- How do we build the lexicon cancer has built—it's just "cancer"; people don't focus on the many variations.
- Private funding for mental illness isn't in the same ballpark.

Genetics is critical for:

- Identification of drug targets that are based on disease mechanisms rather than simply treating symptoms
- Destigmatization (though see later in the notes for the potential counter-productive effect of biology for stigma)

Science:

- The need for a bank of information from which to pull.
- What is the near-term use of scientific studies?
- There are fundamental misconceptions around brain health.
- How do we communicate cutting-edge science/give hope?
- How do we communicate scientific information in a way that's understandable?
- Why focus on one target? How can we diversify the risk, get more people involved?
- Animal behavioral model or cellular model; almost all current models are based on a mammalian model.
- Investigators don't have the right tools; we need a genuinely new approach.
- The first causal genes for schizophrenia from genome-wide association studies have been found, led by the open Psychiatric Genomics Consortium (PGC) which counts Broad scientists as founding members. The rate of discovery has not yet plateaued as we increase sample size, so there is definitely more to discover.
- Not enough new—companies offered things they weren't working on any more. The benefit and danger of repurposing:
 - If there's a new biological insight, great.
 - How many resources are wrapped up in repurposing versus in new research?

Clinical Trials:

- We need to address the issue that some people are so desperate, they are participating in multiple trials. Some aren't even diagnosed patients.
- Some people who don't have the illness are participating in clinical trials just to get paid; there are websites that tell them what to do.

Recap of the Dialogue Interview Findings

1. *Engagement for the long haul* (Dr. Ken Duckworth)

General comments:

- We live in a short-term world. How do we keep this engagement going until we reach new discoveries—in medical terminology, how do we "keep the vein open" (KVO)?

- The forces working against the effort include the complexity of finding biomarkers. How can Broad and NAMI keep this “dream team” engaged over the long term?
- What would it take for each of our teams/organizations to stay engaged over the long run? We need BOTH advocacy—short-term hand-to-hand “combat”—AND better treatments.
- Follow the example of the fight for mental health parity—lots of short-term battles while keeping the vein open over a decade.
- There’s a need to engage pharma and other professions, including anthropology, sociology, etc.

Impediments include:

- Infighting
- Lack of shared goals—not unified like other causes

Biggest fear:

- People will burn out and the industry won’t pursue breakthroughs on their own.

Need to:

- Get together and maintain a long-term focus.
- Achieve small successes to show we are heading in the right direction and provide support to people in treatment, even if those treatments aren’t optimal.
- Tolerate inevitable failures.
- Accept the reality that we may achieve monumental scientific achievement AND it’s not going to help anyone in your own family.

2. **Stigma** (Dr. Teri Brister)

Investment of Money and Energy in Mental Illness:

- Wall Street has enormous power over what people invest in; this could be one of the benefits of destigmatization.
- VCs must be willing to invest in MH—why are we segmenting brain disorder rather than rallying around?
- Name it, claim it, fund it.
- Funders/payers/people going into the field want to go where the attention is. Mental illness is “not a cool field to be in or where the smart kids go.”
- Healthcare professionals need better training in mental health issues.
- Because of the stigma attached to these illnesses, we’re losing people with both research and clinical experience.
- People in medical school are attracted to different areas.
- Stigma makes it harder to make the case for funding.
- Grant seeking takes a tremendous amount of time.

Destigmatization:

- HIV/AIDS moved past stigma.

- Destigmatize mental illness by focusing on the biology.
- Seek “balance” in the media and in public conversations about the social versus biological roots of mental illness.
- People fear discrimination—fear of taking medication, denial of treatment in ER.
- We do ourselves a disservice by not breaking stigma down; it includes misinformation, disinformation, bad information, mythology, family superstition, family lore, invisible illness.

3. ***Need for a Call to Action*** (Dr. Teri Brister)

NAMI:

- We’re a polarized and relatively young movement. We need to define a subset of common goals we can agree on.
- NAMI wants to hear what participants need from them.
- We have to keep stomping our feet—“How dare you get out of this space?” and “You guys all need to play together.”
- We will come out of this summit with a white paper/briefing report.

Creation of a Movement:

- We need a Warren Buffet or Michael J. Fox to help raise awareness. Mental health needs to be important to people, a community concern.
- We need a galvanizing force, like C. Everett Koop and HIV/AIDS.
- Examples of other movements/tipping points include the March on Washington. In that case, Malcolm X and Martin Luther King, Jr., agreed on jobs as a key issue.
- If not us, who; if not now, when?
- Who are we developing to break the stigma? Demi Lovato, a celebrity with bipolar disorder, has 56 million Twitter followers. Ken had lunch with her. She reported that, when she’s on tour, people line up to talk with her about mental health issues.

Progress:

- We are making progress—members of Congress are openly talking about family members with mental health issues.
- Need to make progress with Wall Street.

4. ***Brain Science Is Hard*** (Dr. Rosy Hosking)

Biomarkers:

- Number 1 wish is a biomarker.
- So far, no biomarkers have been identified like with Parkinson’s.
- Talk about ways to push on biomarkers.
- Subgroup of this group to work the biomarker issue?
- Have to know how to treat people with earlier diagnoses.
- Preventional or intersectional approach? How to use them? How much will they help?
- What biomarker?
- One kind is *surrogate endpoints*—what does this mean for psychiatry? The scales we use

to rate depression are 70-years old.

- You don't want to have to wait 20 years to know that X is a risk factor.
- Let's find something objective to indicate that a treatment will work.
- Good biomarkers come from a pathological chain of events from cause to effect.
- Implies there is one pathway.
- Very challenging—we don't know if there are 20,000 biomarkers or 1. Also, symptoms are so complex and varied.
- Another kind is *Diagnostic stratification biomarkers*.
- We want something you can use to diagnose pre-symptoms.
- It would be radical to test and treat 10-year-olds.
- Currently, the average length of time to diagnose bipolar disorder is 10 years.
- You could use the biomarker to reduce diagnostic uncertainty when the base rate is high.

Lack of Progress:

- It feels like we're 50 years behind the rest of medicine.
- A few pieces of the puzzle emerge every year.
- There are too few researchers/clinicians in the field.

Data sharing:

- Are companies willing to share?
- Open sourcing of data.
- Major barriers include short-term thinking, artificial barriers.
- Data is out there—people don't have the training to use it.
- There is reluctance to share genetic data because of privacy issues.
- Get samples out that are sitting in vaults.
- NAMI to work on FDA at future date.
- Genetics can help evaluate level of genetic risk; polygenetic risk scores.
- Phase 3 trials are beyond the scope of federal funding.
- Need more participants to have enough data. In some cases, data is available but DNA is needed.
- Retroactive consent—open old data sets
- Anonymized, certified researchers
- We shouldn't accept being denied access.
- Value of phase 3 datasets?
 - Look at the biology of responders
 - How valuable is that in moving the field forward? Are we advancing the field by looking at old data sets without the right structure?

Something this group could do soon is define the questions.

Could this group push the envelope to get beyond the consent issue?

Working Dinner

The group then adjourned and traveled to an offsite restaurant, where the conversations continued over dinner. With each course of the meal, participants moved to different tables, so they could meet and exchange ideas with different groups of people.

Thursday Working Session

Opening Remarks by Dr. Steve Hyman

- How do we bring treatments to people suffering from mental illness?
- How can we stem the exit of large pharma from this space?
- A closer partnership between NAMI and NIMH is important.
- The academic research community is largely dependent on NIMH.
- Patient groups haven't been as strong in mental health as they have with cancer.
- NAMI represents the voice of an honest broker and may be able to encourage pharma to reengage in this area.
- We also need to look beyond the traditional players to smaller biotech and venture capitalists, and convince them this is a timely, wise investment.
- This important conversation isn't easy, and we won't solve it all today, but it is a start.

Presentation by Dr. Joshua Gordon

NIMH is at the center of getting the science going by being funding research. As a peer research organization, it doesn't set policy or provide care.

His priorities:

- **Suicide prevention**—Identify implementable evidence-based practices and knowledge gaps
- **Computational psychiatry**—Develop computational perspectives and approaches to improve the understanding and treatment of mental health disorders
- **Translation of neural circuits**—Develop technologies to interrogate neural circuits, and ultimately improve the understanding and treatment of mental health disorders

The NIH BRAIN Initiative seeks to study the brain more deeply and try to understand genes' effect on brain function at the level of individual neurons. This requires tools that let us study in great detail. Broad/Stanley will feed what we can do in the next few years.

Public funders, academics, and the private sector envision that these technologies will accelerate discovery and increase targets for drug development.

Some biomarkers are closer to fruition than others. Stratification biomarkers may allow us to predict what treatment is going to help my patient best. Currently, there are often delays in finding the right medicine and right dose.

Depression Subtypes Study

A study captured images of more than 1,000 brains of people suffering from depression. It looked at nodes and connections between those nodes, which vary in strength and speed. In addition, activity varies over time and per node. The researchers found similarities and differences in these patterns, with some synchronized and others less so. Each individual has their own unique map. The study looked at the questions, How similar are any two maps? How many “kinds of brains” are there? Researchers came up with four (arbitrary) subtypes, based on fMRI imaging.

A few hundred of the subjects were then given experimental treatment—electrical stimulation to the medial prefrontal cortex. Some responded and some didn’t. The subjects were then separated by a clustering process of subtypes that responded to the treatment and those that didn’t.

It’s not a perfect study, in that it didn’t include more than one treatment, but it suggests the possibilities. (It may just indicate treatment responsiveness, rather than responsiveness to this treatment.) Clinicians need to know who is going to respond to which treatments. Various studies indicate the possibility that brain-based biomarkers may suggest how to treat certain patients.

We’re currently taking all people with one syndrome and giving one treatment. It would be useful to find treatments that are “great” for some people rather than “eh” for all.

Could it also be that people with different responses have different genetic profiles?

Dr. Gordon is not optimistic about blood-based biomarkers. In the big picture, MRI really is not that expensive now, and we are getting good at multi-site imaging.

For treatments like TMS (Transcranial magnetic stimulation) for treatment-resistance depression, the question is, how precise does it have to be? To be funded, we need individual-specific targeting to be able to demonstrate that are stimulating the right spot. Could lack of precision explain inconsistent efficacy? People in the field report that, correctly done, TMS is effective for some people.

Drug Development

To support the drug-development pipeline, NIMH is making resources available to researchers for free. They fund grants for up to phase 2 clinical trials.

NIMH has a program to support the development of assays and a psychoactive drug-screening program. Researchers target what you want to find a drug for, and robots test if the compound will affect your assay and vice versa (for more details, see <https://commonfund.nih.gov/molecularlibraries/index>).

NIHM will pay for this service for grantees in an effort to support people in developing

compounds to test and then provide the information to drug companies to take to phase 2 and 3 clinical trials.

Genetics

In terms of genetics:

Genes->Brain->Behavior

Genes code for molecules, which are assembled into neurons to form circuits. Circuits are assembled into neural systems (brains), which produce behavior.

But this isn't a linear process; it's more complex. There are many genes, many environmental factors, lots of difference phenotypes (at the cellular and circuit levels), and a variety of behaviors. We don't really know the relationships and need to fill in the map to understand how genes lead to behaviors.

We don't know how to do this, even though we can trace one gene across. Dr. Gordon is hoping to get creative ideas for funding. We need to study circuits, brains, and phenotypes in a large way. NIMH is creating an infrastructure for this to happen.

With the All of Us Research Program, NIMH is recruiting 1 million volunteers to be continually contacted to take a panel of behavioral tests. The goal is to sort them into different categories and determine how these categories relate to genetics. Of the 1 million people, 50% will be underrepresented minorities, to have a big enough sample size.

Research is looking from the cell level up and the behavioral level down. The neurobiological approach to genes seeks to determine how they affect brain function that leads to disease and then find what we can treat.

Another possibility: Ignore all of this knowledge and stick with genes. Identify which of the 250 loci identified thus far (which may translate to hits in ~50 genes) produce schizophrenia. Then make compounds that affect these genes and start testing (or test other treatments). The hope would be that this approach would lead to effective treatments, both novel and traditional. Dr. Gordon guesses this will be rare, but if it works, it could speed drug discovery.

Another issue is what model or combination of models to use? We have tools for studying neurons, we have animal models—none are great. We're going to have to take risks and test multiple compounds in multiple models.

Some questions include:

- What level of evidence is required to justify human trials?
- What questions can we sensibly ask about models (instead of which model)?

Accelerating Medicines Partnership

The Accelerating Medicines Partnership (AMP):

- A major public-private partnership involving NIH and 10 pharmaceutical companies
- Aims to distinguish targets of disease most likely to respond to new therapies
- Partners have developed research plans; are sharing costs, expertise, resources
- NIH and private sector have so far invested ~\$187M over five years on projects in three major disease areas

There's a competition for AMP resources. Currently, funding is being provided for research on:

- Alzheimer's Disease
- Parkinson's Disease
- Type 2 Diabetes
- Rheumatoid Arthritis and Lupus

For each project, scientists from NIH and industry developed research plans aimed at characterizing effective biomarkers and distinguishing biological targets most likely to respond to new therapies.

Could there be public-private partnerships in the mental health space? Could we design a cooperative effort to look at genes? We need to agree on a set of genes, some panel of tests, and develop and characterize biomarkers (cells in a dish and in humans).

How did Parkinson's stakeholders decide they were ready for this process? Their major drug was approved in 1960, and there are rare monogenetic forms that aren't helpful.

Schizophrenia was up for consideration 3-4 years ago and not selected. There's not one biological mechanism for schizophrenia. Possible approaches could be to look at neurobiological mechanisms—synaptic pruning etc. Also, there's a richness of genetic data around 50 targets. We throw away money on projects with much less evidence.

Our next at bat is as early as 2019. We have been explicitly asked to make a proposal. The president has expressed interest in serious mental illness and public-private partnerships.

Alzheimer's PPPs have been invigorated by funds from Congress; they now receive more than \$1.2 billion/year. They had a plan and the confidence they are on the right track, through major advances in imaging and biomarkers.

Questions/comments:

- There needs to be a holistic approach. It takes years to rewire the brain. In the meantime, people also need housing, psycho-social support, and so on. Also, it may take a multi-pharmaceutical approach.
- One participant said she is heartened by the array of complexity involved; it gives dignity, honor, and respect to those struggling. They don't feel as much like failures or "I

didn't do it right.”

- In the past, researchers have been forced to simplify to ask clever scientific questions. Now, we can broaden our approaches to take advantage of the complexity rather than reduce it. We should also take advantage of growing interest in this area. It's helpful to have interest from the private sector and pressure from advocacy groups.
- Politicians are listening, and we have more ideas to bring to the table. We need to flesh out something with sufficient momentum to move to the next phase. It was a blow that schizophrenia didn't previously make the list. We now have more to offer and need to be clear about mechanisms and theories.

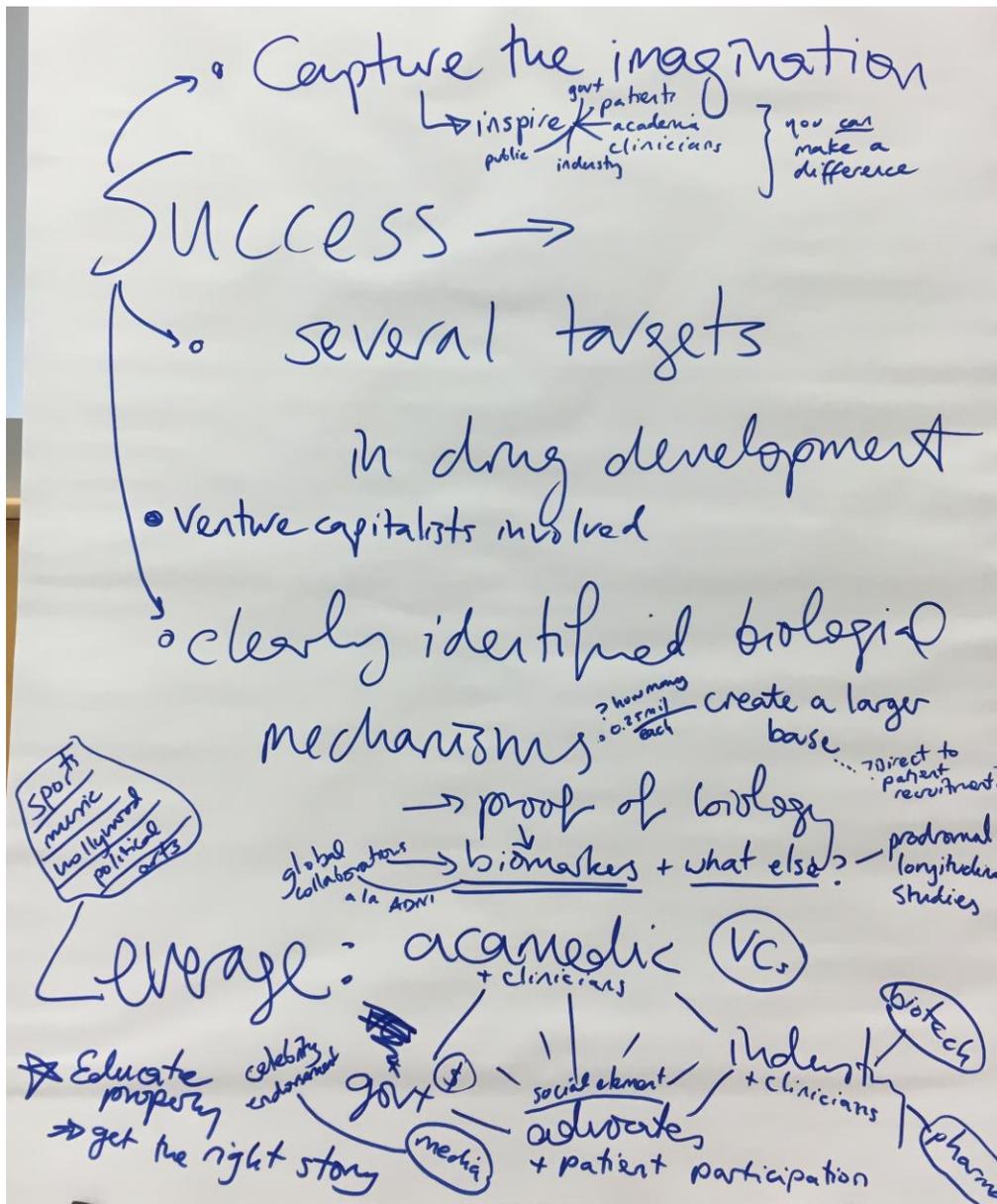
Small-Group Brainstorming and Report-Outs

At their tables, participants discussed:

- What are the opportunities going forward?
- What does success look like?
- How would the world be different?
- What are possible leverage points?
- What forces could support/hinder success?

Dr. Griffin instructed individuals to listen for what really excited or challenged them.

Group 1 Report-Out



Success:

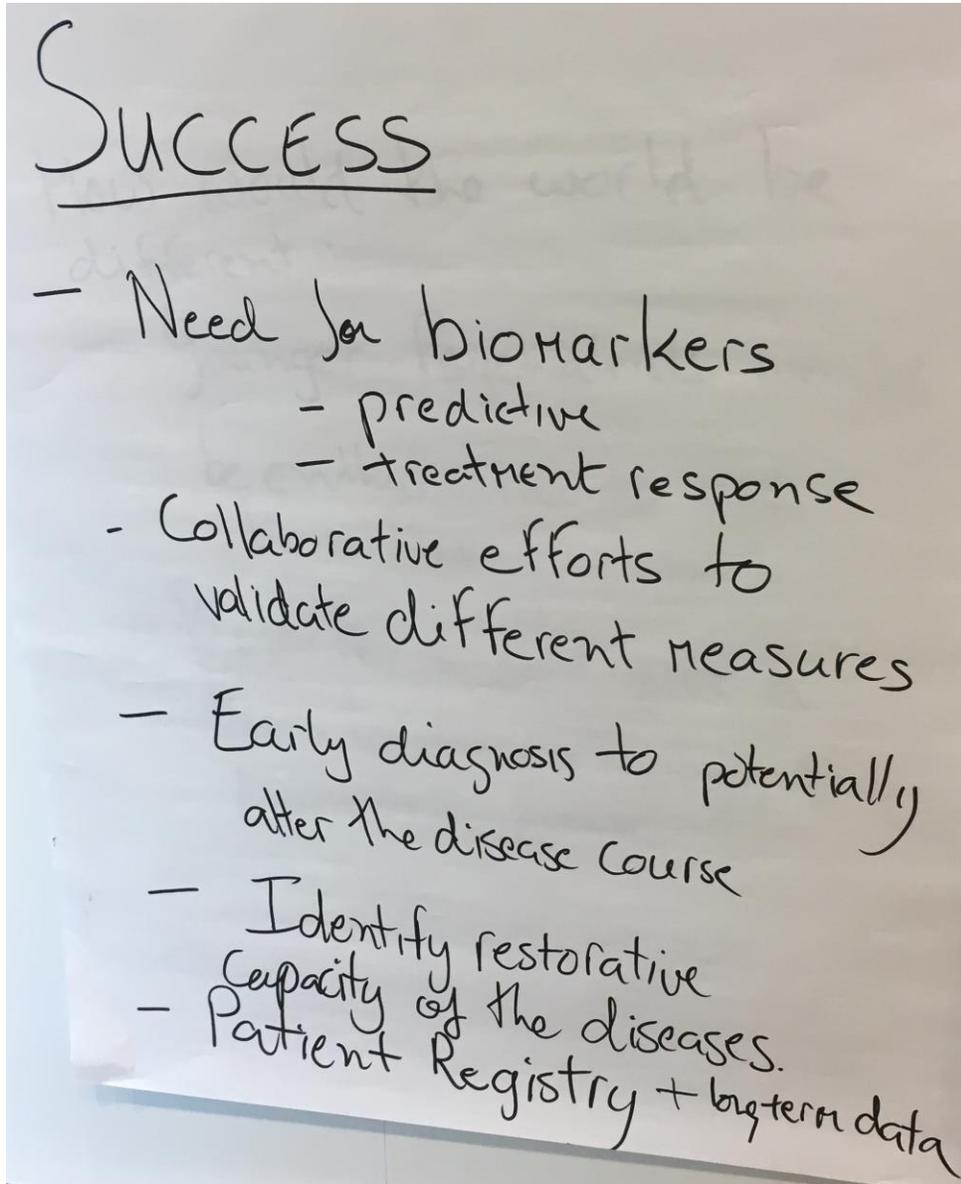
- Identification of multiple drug targets, causal chain mechanisms, surrogate endpoints.
- Inspiring and capturing people's imagination around making a difference.

Leverage Points:

- Education.
- Linking of academic, clinical, industry (bio tech, pharma, VC), government, social (advocacy and patient groups).
- National recruitment strategy—what would it look like? People could share their stories;

it would produce scientific deliverables; it would help raise compassion and combat stigma.

Group 2 Report-Out



Success:

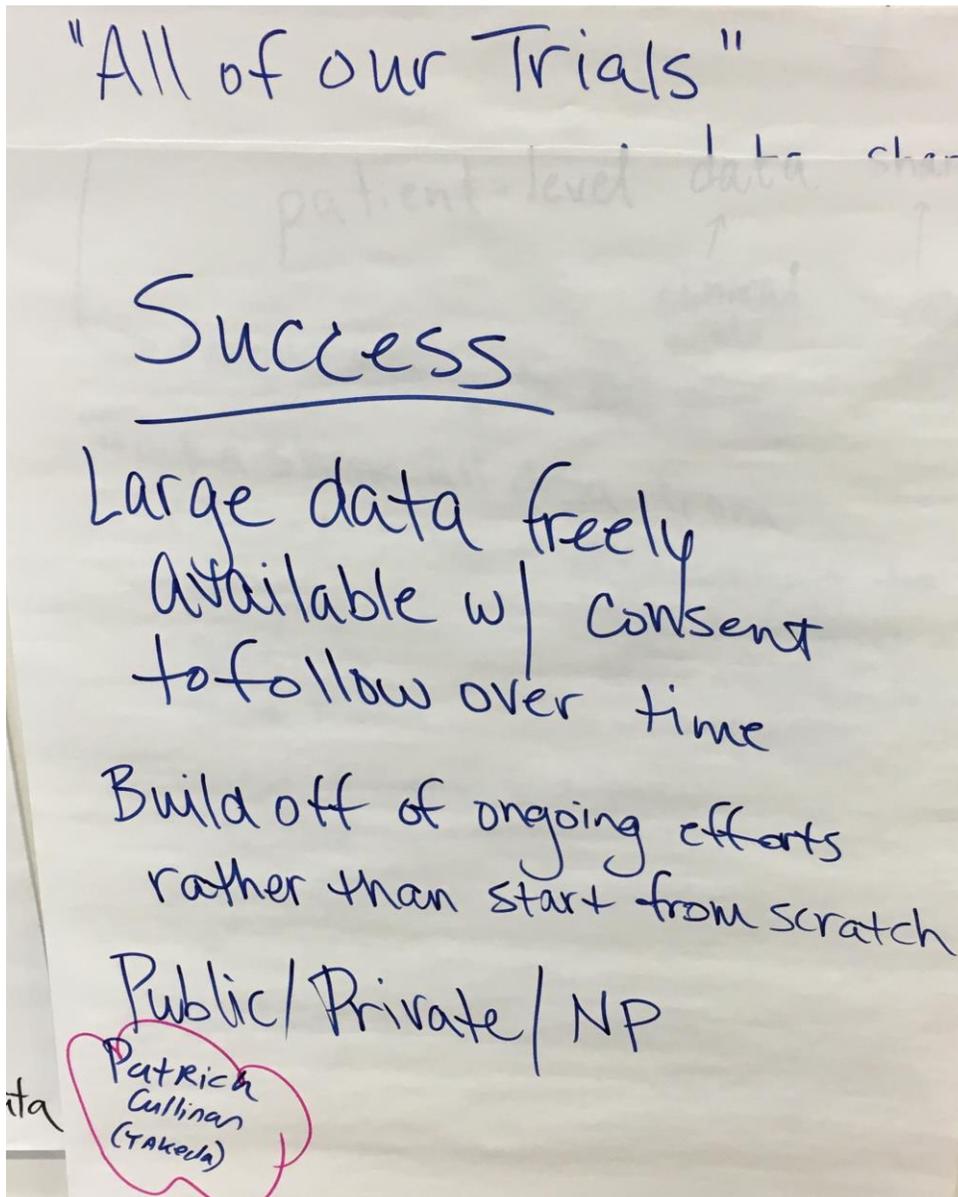
- Biomarkers—something that will allow us to predict that someone might develop schizophrenia and allow for earlier intervention.
- Collaborative efforts to validate different measures.
- Early diagnosis—more of a chemotherapeutic approach to prevent changes in brain architecture that lead to more significant disease.
- Restorative capacity—in neurodegenerative disease, there have been few effective

treatments, but some successes.

- Register people early in the illness, assign a unique identifier, do retrospective analyses.

What kind of global coalitions would be necessary to make these things happen?

Group 3 Report-Out

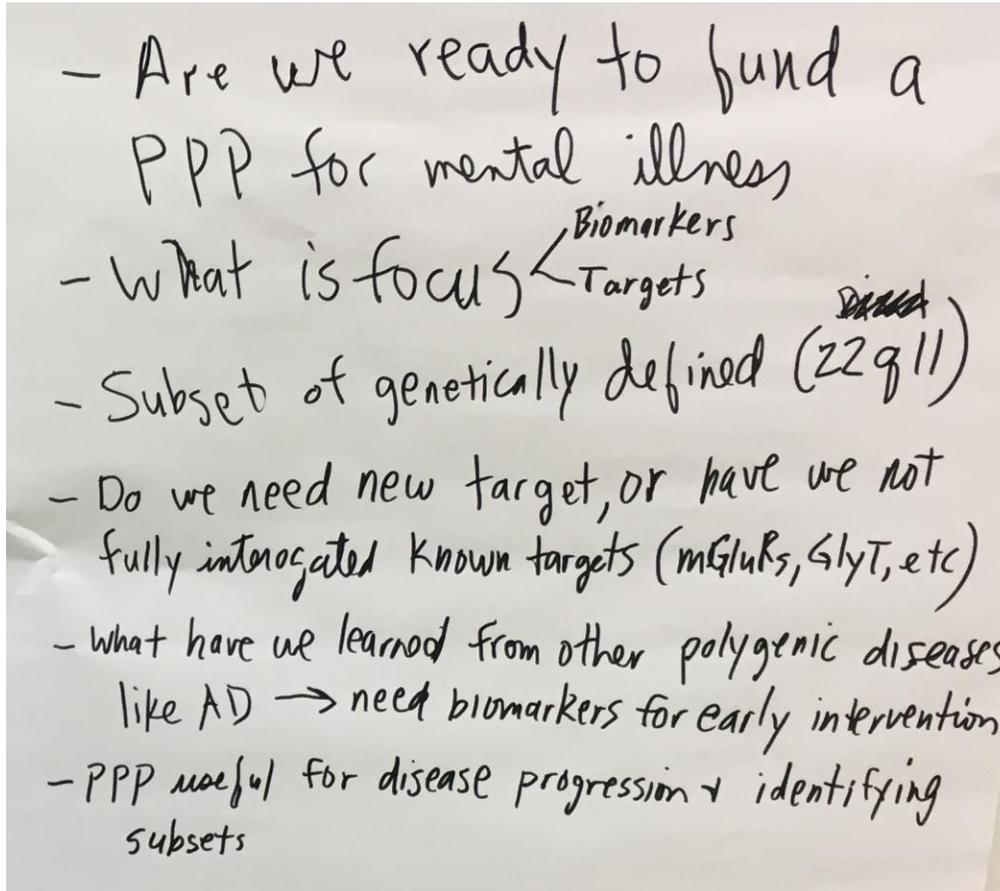


"All of Our Trials"—alumni of clinical trials can donate imaging etc.
Create a community for brain disease; NAMI gets patients, pharma donates data.
Could start now.

Success:

- Large pool of data freely available and with patients' consent to follow over time
- Building off of existing efforts
- Public, private, and not-for-profit partnerships

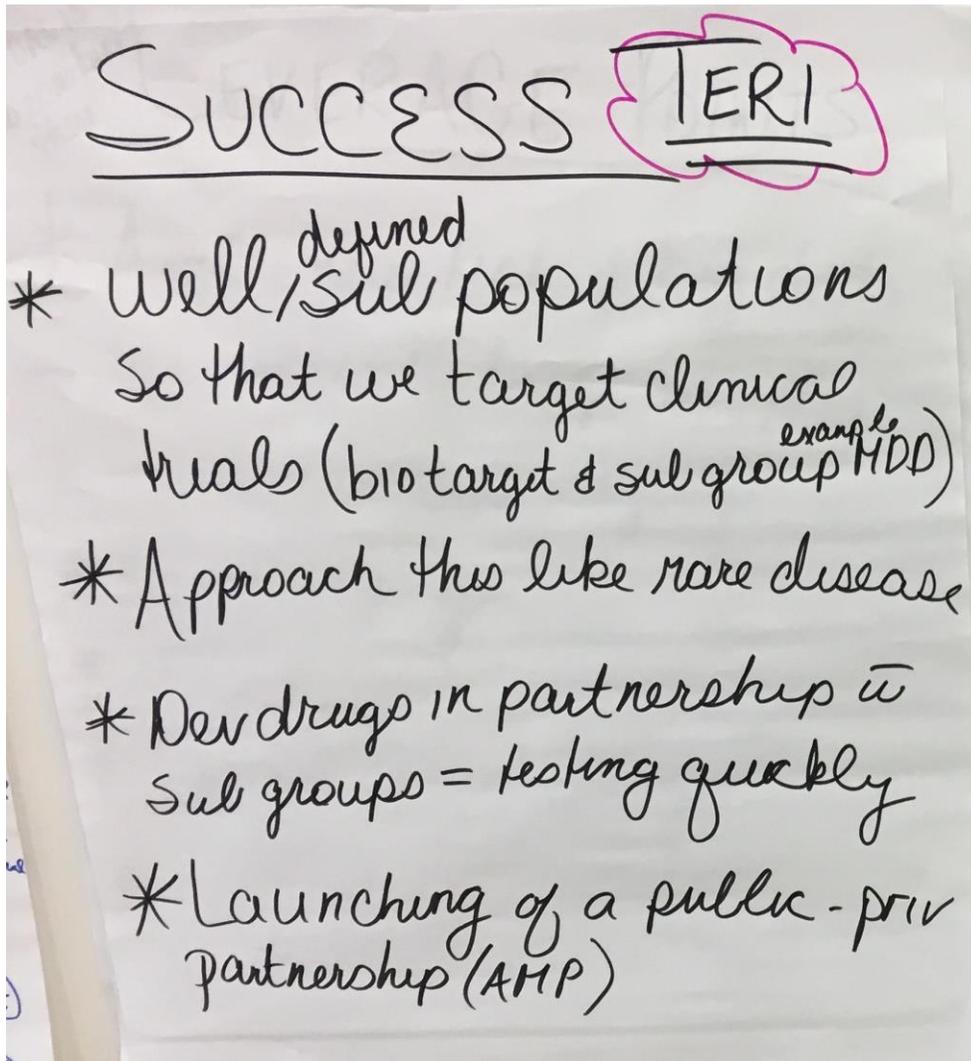
Group 4 Report-Out



Key Questions:

- Are we ready to fund a PPP?
- What would the focus of our PPP be? Biomarkers or new targets?
- Do we need new targets or do we need to fully integrate existing ones?
- What have we learned from other polygenetic diseases like Alzheimer's? Are we intervening too late?
- Should we be thinking of disease subpopulations that are more homogeneous and then use that as a stepping stone?

Group 5 Report-Out



Success:

- Define sub populations so we can target clinical trials.
- Approach this like with rare diseases.
- Develop drugs in partnership with subgroups and test quickly.
- Launch a PPP through AMP.

Support	Hinder
<ul style="list-style-type: none">• Data sharing• Communicating to general public the good things and collaborations that are happening (NIMH and NAMI to work on developing a fact sheet)	<ul style="list-style-type: none">• Data sharing—we aren't good at it• Projects close and data sits—build follow-up plan into grants

Podlets of Work

Next, Dr. Griffin introduced the idea of “Open Space,” or a marketplace of ideas. He encouraged participants with topics they would like to discuss with a subset of colleagues to write their topic on a piece of paper and post it on the wall. Others in the group then joined the topic they wanted to explore; they could also switch groups partway through the conversation if they chose to. Eight topics emerged; the first four were discussed in round 1, and the second four in round 2.

Round 1 Topics

1. National recruitment drive (collect genetic and clinical information, reduce stigma) and registry (how do we get buy-in funding and infrastructure for schizophrenia/bipolar?)
2. PPP goals: what should they be? (drug targets, biomarkers, AMP, cell models)
3. Therapeutic models
4. Biomarkers and subpopulations

Round 2 Topics (time ran out on the morning session before the groups could present their summaries)

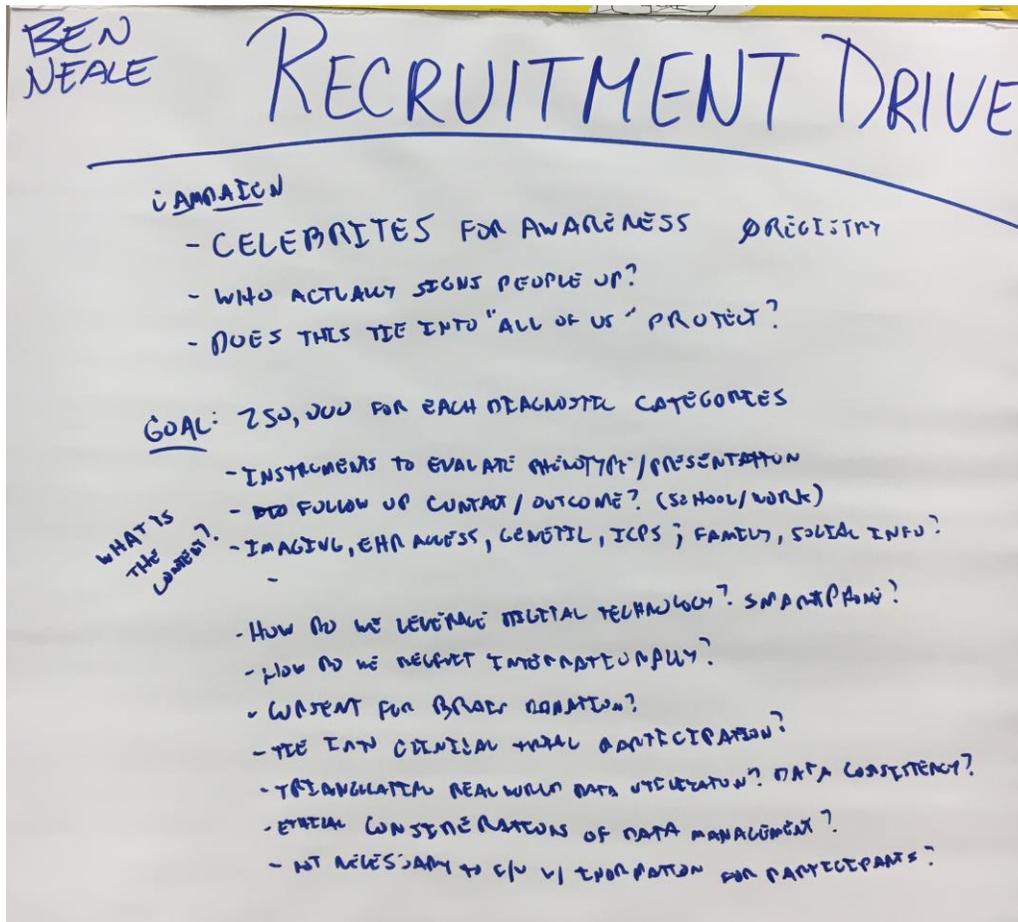
5. Data sharing—how can barriers be overcome?
6. Early shared PPP—precompetitive consortium on target identification; validate and develop pathways
7. Tracing and characterizing exceptional responders and nonresponders (identify pathways/what is it about this group of people?; identify subpopulations; biomarkers)
8. How can NAMI provide support/keep up momentum (NIMH, PPP, Data, AMP)?

Comments:

- Destigmatization requires more effective treatments. For example, with HIV/AIDS, having effective treatments lead to less stigma.
- Note that having biomarkers may increase helplessness, otherness.

Round 1

1. National Recruitment Drive/Registry



Campaign:

- Involve celebrities in the campaign.
- Avoid the word "registry."
- Contact existing initiatives.
- Who signs people up?
- How does it tie in with the All of Us project?

Goal:

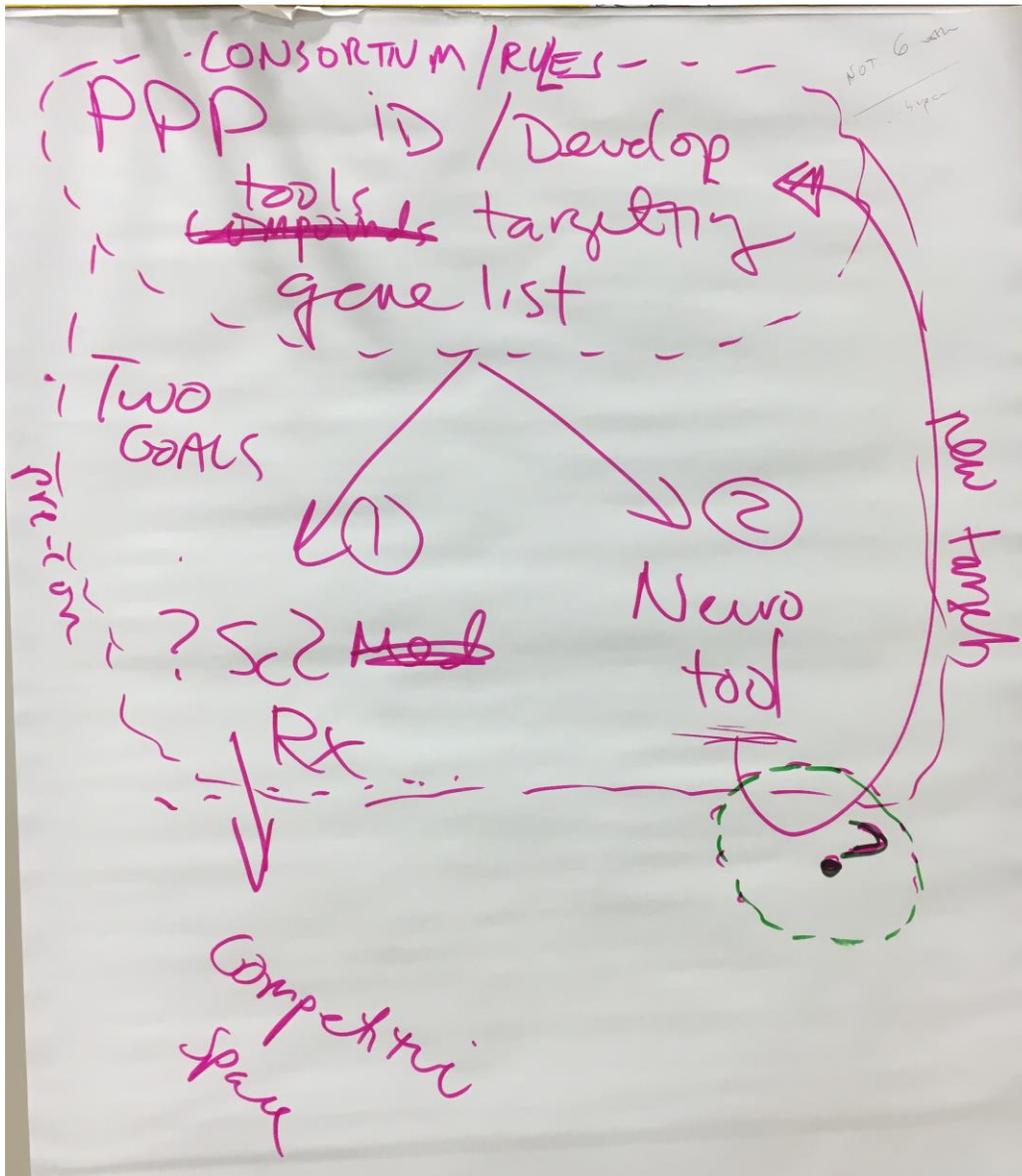
- 250,000 people for each diagnostic category.
- Instruments to evaluate phenotype/presentation.
- Follow-up contact so project can evolve; inform participants of outcomes.
- Determine type of data and how to collect. Clinical participation? Brain donation? Real-world data from insurance companies, Ancestry.com.

Questions:

- How do we leverage digital technology?

- How do we recruit internationally?
- What are the ethical considerations of data management?
- Where is the funding coming from? [Funding just awarded in UK.]

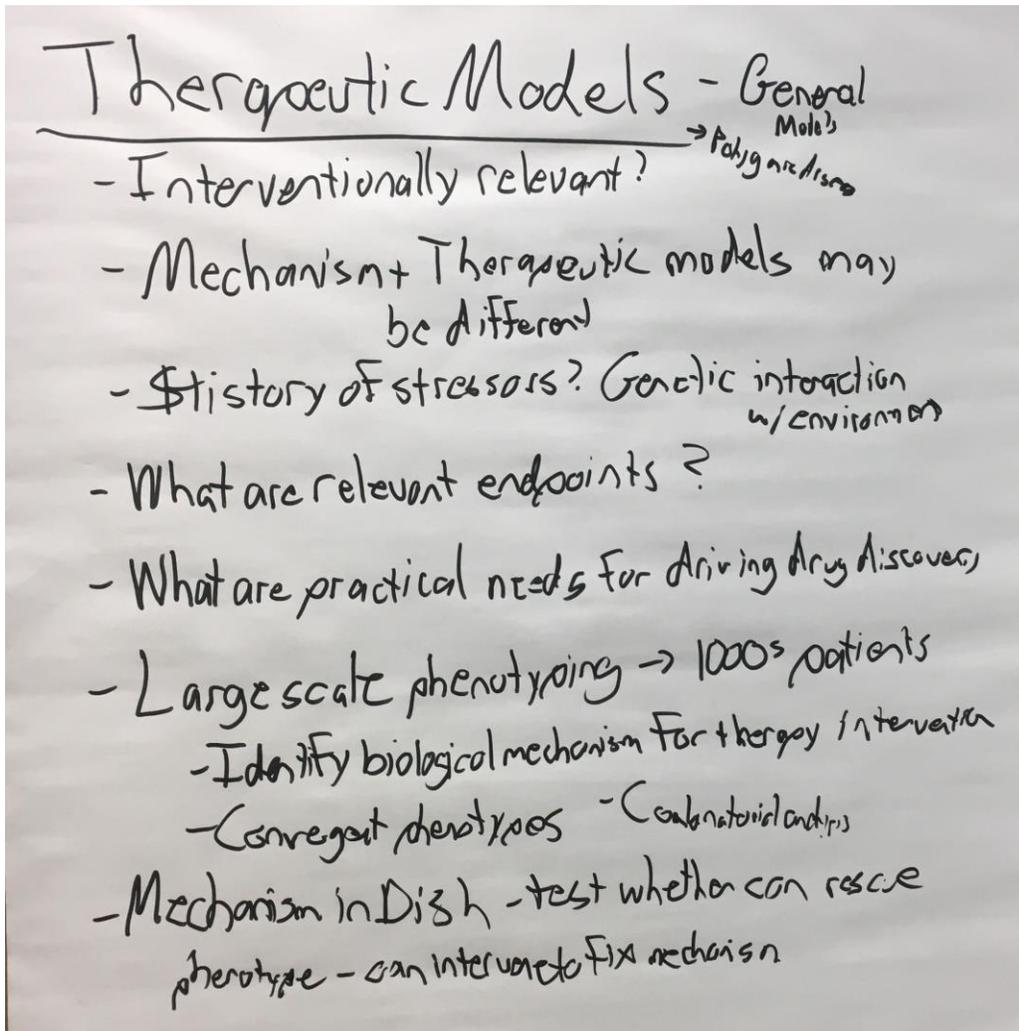
2. PPP for Target Exploitation



- Identify and develop tools that would target genomes in the pre-competitive space
 - To develop therapeutics
 - To develop new tools to explore neurobiology
- Develop actual drugs in the competitive space
- Consortium—is it open source or do members have first access?

- NIH—AMP is totally shared data, all done publicly
- AMP—people who bought into the process
- Engage biotech, VC groups—“This will help you in commercialization”—not-for-profit sector
- Organizations can fund projects that don’t get funded by NIH.

3. Therapeutic Models



Key questions:

- Are they interventionally relevant?
- Are the mechanism and the therapeutic models different?
- What is the role of the genetic interaction with the environment, for example, a history of stressors?
- What are the relevant endpoints? Can we use them to drive drug discoveries?
- Can we conduct large-scale phenotyping of 1,000s of patients in order to identify biological mechanisms for therapy and intervention?

- Can we test the mechanism in a dish and intervene to fix it?
- Is there a potential biospecimen sharing initiative?
- Need to work on the problem of risk of discrimination.
- Need to be credible.

4. Biomarkers and Subpopulations

Biomarkers 10-15 years old
 Prodromal, pre-schizophrenia

Polygenic scores

Cog testing, behavior

PET (SU2, etc.)

CSF (complement, etc.)

EEG/ERP - turn key systems)

APPs, digital tools

Current studies

- Harmony international consortium for some ~~bit~~ data (retrofit)
- ABCD study (prospective)

Gaps + Opportunities

- Data sharing ~~is~~ +
more open access

- Clinical data, e.g. Kaiser +
Geisinger

x- CSF → blood-based
correlates

x- PET

- EEG →

- Genetics

- Behavior

need:

1. Standardization

2. ↑ "n"

Can we intervene in the prodromal/pre-schizophrenia phase?

- Polygenetic scores
- Cognitive and behavioral testing
- PET
- CSF
- EEG/ERP
- Apps, digital tools

Current Studies:

- Harmony International Consortium (retrofit)

- ABCD Study (prospective)

Gaps and Opportunities:

- Data sharing and more open access
- Clinical data, for example, from EHRs/health plans
- CSF—blood-based correlates
- PET
- EEG
- Genetics
- Behavior

Need standardization and consensus.

Midday Check-Out

Before the group broke for lunch, Dr. Griffin asked participants to share a word or phrase, if they chose, to summarize their feelings after the morning session. The results are displayed in this piece of word art:



Planning Exercise

The final afternoon was spent turning all of the work from the previous sessions into activities and milestones leading to concrete outcomes over the next 12-18 months. The goal was to drill down into practical things we can do soon. Activities should include dates and people, either in this room or others—if they aren't concrete and people don't commit, they won't happen.

Notes:

- Might be an infusion of resources from NIMH
- Scope depends on resources
- Get pharma involved

The initiatives defined were:

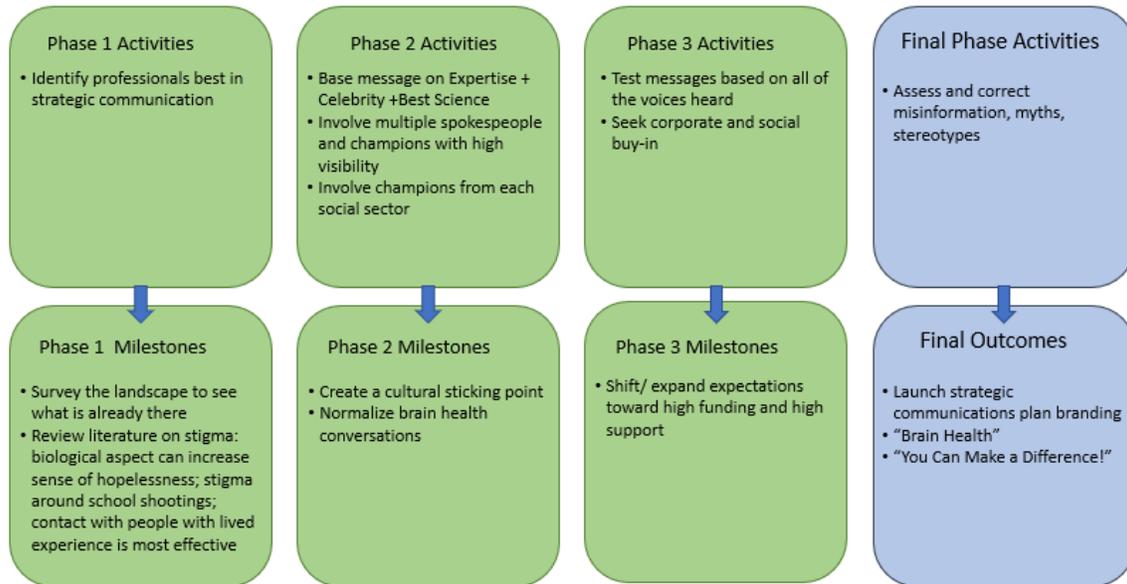
1. Create a public-private partnership
2. Develop and execute a strategic communication plan
3. Define the 50-100 targets/genes that are linked for schizophrenia
4. Continue to engage key stakeholders
5. Create a patient registry and hold a recruitment drive
6. Define an advocacy role for NAMI consistent with this need
7. Engage in data sharing
8. Launch “All of Our Trials” to use data from existing clinical trials

Process Flow Charts for the Initiatives

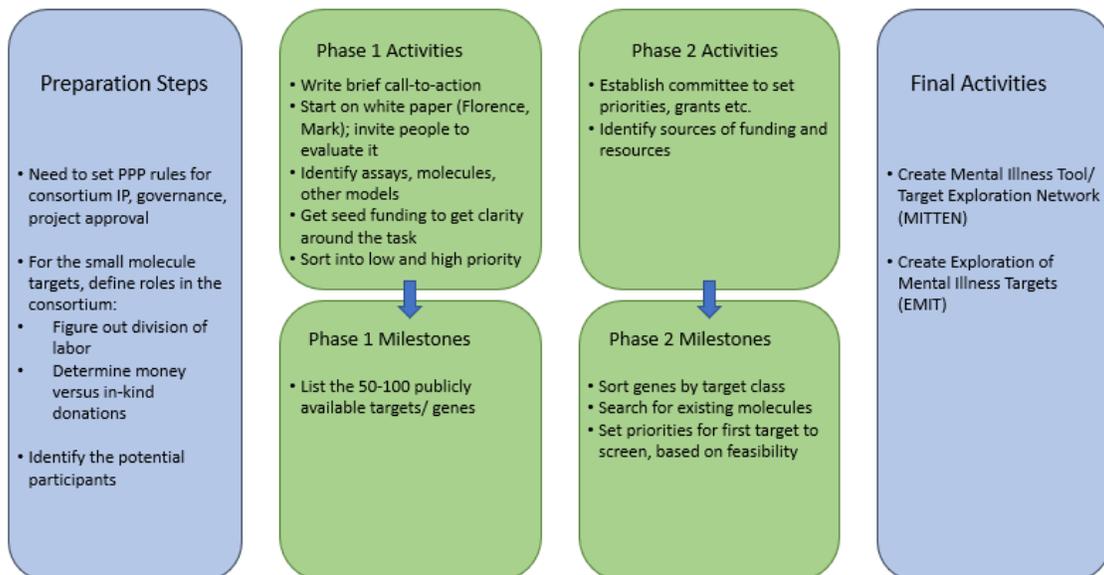
Create a Public-Private Partnership



Develop and Execute a Strategic Communication Plan



Define the 50-100 Targets/Genes that are Linked for Schizophrenia



Continue to Engage Key Stakeholders

Activities

- Meet again together or in parts
- Produce a white paper
- Include new players, including data mining, diagnostics, Asha Nayak from Intel (on the Sage Board of Directors)
- Identify (non-snow) locations and dates (DC, Boston)
- Compile a list of companies working in this space
- Determine how to include and best use advocacy
- Steering Committee (Teri and Rosy) to ask for reports, keep the groups accountable, and coordinate activities
- Plan a plenary session for leaders from each work stream to present progress to date
- Connect with the strategic communication plan work stream

Create a Patient Registry and Hold a Recruitment Drive

Phase 1 Activities

- Identify “what’s in it for me?” (contributing to our understanding and helping your family)
- Determine: which illnesses to collect/start with; how to recruit families; how to deal with phenotyping
- Consider: cost-effectiveness; expense of imaging
- Create: broad consent for data sharing; online portal
- Collect data:
 - Active: clinical data, DNA samples
 - Passive: EHRs (Epic) and EMRs (PCORI)
- Contact Jordan Smoller regarding public campaign for serious mental illness in All of Us
- Align with or be part of All of Us, National Mental Health Bioresource in UK (or similar in US), Genetics of Depression study in UK and Australia

6-Month Milestones

- Align with Strategic Communication Plan
- Decide goals:
 - Build data set (re-contactable, clinical trial quality)
 - Tackle stigma through understanding of mental illness
- NAMI engage celebrity / high profile campaign
- Define outputs: how to communicate findings to public, participants, and researchers

Final Outcomes

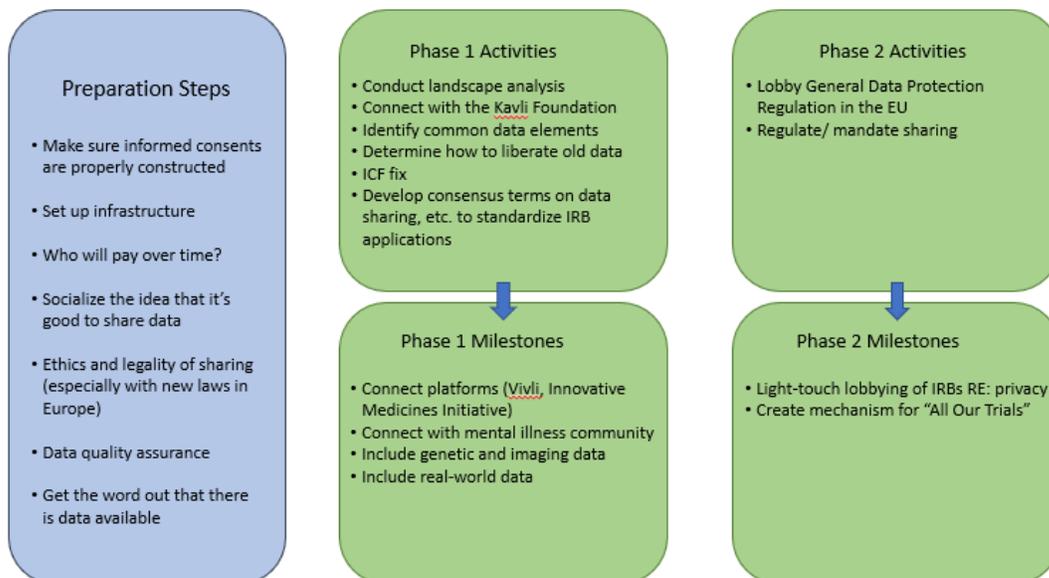
- Start collection: spit kits in doctors’ offices, hospitals, online
- App for mood and recruitment
- Genotyping at Broad
- Get DNA data from 23&Me

Define an Advocacy Role for NAMI Consistent with this Need

Activities

- Engage in conversation with FDA on patient-focused drug development for schizophrenia, as did with DBSA on major depression
 - Next PDUFA – breakthrough new treatments
 - PFDD – schizophrenia
 - Guidance/inclusion in drug development
- Assist in development of input to FDA on regulatory guidance for NIMH
 - Comments on papers and best practices
- Reengage societies, for example APA
 - Share science
- Advocate with companies and incentivize them to invest in mental illness, remind them that 20% of their employees have MI
- Mobilize grassroots army when ready
 - Include other advocacy organizations, such as One Mind, MHA, BDSA
 - Encourage people to write letters to the editor, use social media, meet with Members of Congress
- Continue to build awareness/ fight stigma/ increase education
 - Science = hope
 - Science kills stigma
 - Create a grand challenge, like an “X Prize”
- Engage with APA; partner with Rare Diseases groups
- Publicize and recruit people to join All of Us

Engage in Data Sharing



Launch “All of Our Trials” to Use Data from Existing Clinical Trials

Notes

- Goal is to “liberate” existing data from clinical trials
- Create a mechanism for people to sign up and release their data; if they are already willing to participate in a study, this is a small additional ask
- 23andMe – people can currently download their own data; encourage them to upload it to NIMH?
- Need to be aware of who is willing to share and who isn’t – is it based on the severity of their condition?

Check-Out

The group went around and did a final check-out; those who chose to mention a word or phrase that represented their overall thoughts or feelings at the end of the Summit.



Concluding Comments

- Dr. Duckworth pointed out that this is a marathon, and NAMI will be there along the way.
- Dr. Hyman noted that this is a powerful coalition, and many of the important people in this work were involved in this Summit.
- Dr. Gordon commented that NAMI and Broad made this event happen. Things are possible now that weren't three weeks earlier. He will get the ball rolling and keep people posted.

Next Steps

- Share report with participants for their feedback and input toward a peer reviewed paper.
- Follow up on potential PPP opportunities with NIMH and Josh Gordon (and other collaborations/partnerships mentioned).
- Organizing Committee to meet to:
 - plan future for reconvening this brain trust
 - decide which ideas from the report could be taken forward
 - investigate next steps

One suggested approach was to approach the eight initiatives as two major projects: Public-Private Partnerships and Data Collection and Sharing. The initiatives associated with each of the two projects are listed below for consideration.

Public-Private Partnerships

- Create a public-private partnership
- Define the 50-100 targets/genes that are linked for schizophrenia
- Develop and execute a strategic communication plan
- Continue to engage key stakeholders
- Define an advocacy role for NAMI consistent with this need

Data Collection & Sharing

- Create a patient registry and hold a recruitment drive
- Launch “All of Our Trials” to use data from existing clinical trials
- Engage in data sharing

Need to:

- Confirm “who’s in” and what this entails.
- Identify the short-, medium-, and longer-term goals.
- Clarify current resources to achieve goals (what we have and what we need).
- Confirm objectives and timelines, and develop strategies to achieve these.
- One short-term goal is the white paper discussion – what/how many/priorities/authors.