Study Title: Developing Clinical Translational Tools to Communicate Genetic Risk among Individuals who are at Clinical High Risk for Psychosis

NCT Number: Not applicable

Date of Document: 12/19/2023

2. OBJECTIVES

Overview and Purpose:

This project seeks to understand how someone already in a high-risk state will interpret genetic information informing risk of 'conversion' to a full disorder. How people interpret this possibility carries important consequences for how they choose to respond, which may range from fatalistic acceptance of the disorder to proactive preventative behavior. With the aim to encourage an active pro-health response, we propose developing two tools for communicating genetic risk and evaluate them regarding their effectiveness in inducing a positive response to the risk of illness. The two tools will consist of: 1) a clinician manual, designed to be used by a PhD level clinician with some genetic counseling training to communicate risk to CHR youth; 2) a high-impact, computerized tutorial ('AutoTutor') that has been used to convey genetic risk for breast cancer (i.e. BRCA gene). To create these 2 tools, experts in psychiatric genetics and stigma will work to develop the 2 tools to convey genetic risk information to youth and young adults identified as in a 'clinical high-risk state' (CHR) for psychosis. We assess primary outcomes of increased intent to engage in treatment and healthy behaviors, and a secondary outcome of reduction in stigma. While specific genes for risk of psychosis are not yet used in diagnosis or treatment, a genetic malleability (GM) framing conforms to the known genetic risk for psychosis, and has a strong likelihood of being used in the not too distant future. Because of the relatively large innovation involved, we seek to establish initial acceptability, safety, and efficacy of each tool. We then use a nonrandomized, within-subject, pre- vs. post design to examine whether providing the genetic malleability framing via each tool (n=27 CHR youth per tool, N=54 total) leads to improved outcomes. For each tool, participants will be conveyed hypothetical information proposing being identified as having a substantially elevated, genetically-malleable risk for developing psychosis.

Specific Aims and Hypotheses:

Aim 1: To develop 2 translational tools to convey a genetic malleability framing for psychosis-risk, we develop a clinician manual and a computerized AutoTutor to undergo acceptability, safety, and initial efficacy testing.

> Rationale: We evaluate tools that provide a genetic malleable (GM)framing, which has been linked with: a) greater agency, hope and optimism about recovery (Dar-Nimrod et al., 2014; Farrell, Lee, & Deacon, 2015); b) greater perceived odds of recovery, mood regulation(Lebowitz & Ahn, 2018) and less hopelessness (Lebowitz, Ahn, & Nolen-Hoeksema, 2013) in 3 experimental studies for depression, which persisted at 6 month follow-up (Lebowitz & Ahn, 2015). While people with psychosis show benefit from psychiatric genetic counseling (Inglis et al., 2015), access to such counselors is rare. Creating tools to beneficially convey GM framing for CHR adds greatly to public health.

Aim 2: To test whether CHR youth, after being exposed to the genetic malleability framing via each tool, will show greater endorsement of increased intent to engage in treatment and healthy behaviors and less stigma when compared with pre-exposure to the tool.

> We predict that CHR youth, after receiving the GM framing via each tool, will show greater *intent to engage in treatment and healthy behaviors* and less *stigma* vs. pre-exposure.

-- As an exploratory analysis, we hypothesize that improvements in these outcomes will be associated with reductions in the mechanism of 'genetic essentialism'.

> Re: the *exploratory analysis,* GM may benefit outcomes by reducing the mechanism of genetic essentialism (Farrell, Lee, & Deacon, 2015; Lebowitz, Ahn, & Nolen-Hoeksema,

2013). Studies have not tested mediating mechanisms when examining effects of genetic framings (Anido, Carlson, & Sherman, 2007; Dunn et al., 2008; Heshka et al., 2008). We will use identified mechanisms to convey beneficial results (i.e. that genes do not imply a fixed future) via the tools.

3. BACKGROUND, SIGNIFICANCE, AND RATIONALE:

Great strides are being made in identifying new 'high-risk states' or early signs of elevated risk, for illnesses such as Alzheimer's disease, diabetes, and psychosis (Tabák et al., 2012; Wang et al., 2013). Those in a high-risk state are distinct from asymptomatic individuals and those with the disorder in that signs are present but the full disorder has not yet developed (Fusar-Poli et al., 2014; Miller et al., 2003). Early interventions for high-risk states show promise in averting the full disorder or reducing its impact (Bateman et al., 2012; Boraxbekk et al., 2015; Buysschaert et al., 2015; Dubois et al., 2007; Fonseca, 2007; Grant et al., 2013; Lin et al., 2017; McGorry et al., 2012; Sadeghi et al., 2015; Schellenberg et al., 2013). Best outcomes are more likely with increased intent to engage in treatment/healthy behaviors, which may be shaped by genetic information (van Rijn et al., 2011).

Rapid advances are being made in identifying genes associated with high-risk states. How those already in a high-risk state respond to genetic information regarding the risk of developing the full disorder may range from fatalistic acceptance to proactive preventative behavior. One specific genetic framing, hereafter called 'genetic malleability' (**GM**), has in itself been shown to promote engagement in pro-health behaviors across mental illness (Lebowitz, & Ahn, 2015; 2018; Lebowitz, Ahn, & Nolen-Hoeksema, 2013), Alzheimer's (Chao et al., 2008), and chronic diseases (Aspinwall et al., 2015; Jenkins et al., 2013; Kullo et al., 2016; Meisel & Wardle, 2014), including the uptake of treatment and positive health behaviors (improved diet, exercise, or use of medication. The GM framing involves a modifiable genetic risk that can be turned on or off based on environmental/behavioral factors (Hakak et al., 2001; Lebowitz, 2014; Van Os, Rutten, & Poulton, 2008). This framing applies to high-risk states because both genetic and environmental/behavioral factors influence illness trajectory (Bird et al., 2010; Stevens et al., 2015), and risk for developing the full disorder(Benros, Eaton, & Mortensen, 2014; Gebicke-Haerter, 2012; Oh & Petronis, 2008). Conveying genetic risk to those in high-risk states (Christensen et al., 2007; DiMillo et al., 2015; Lawrence et al., 2016; Meiser et al., 2005; Vähäsarja et al., 2015), has also been linked with higher stigma due to greater self-perceptions of differentness. The GM framing may help address this as it has been found to reduce stigma for heart disease (Robinson et al., 2016), obesity (Hilbert,2016), and Alzheimer's (Christensen et al., 2007), thus showing promise for high-risk states. Responding to this, we seek to develop tools to promote potential beneficial impacts of GM beliefs, which have been shown to exert change on the main psychosocial outcome of intent to engage in treatment and healthy behaviors (Aspinwall et al., 2015; Chao et al., 2008; Jenkins et al., 2013; Kullo et al., 2016; Meisel & Wardle, 2014), and the secondary outcome of stigma (Corrigan & Watson, 2002). Because tools that convey genetic framing for high-risk states do not exist and would comprise a sizeable advance by enabling dissemination of a potentially beneficial genetic framing, this proposal focuses on these tools' development and initial testing for safety, acceptability and efficacy. Confirming the tools' utility offers a strong basis to conduct future testing via a RCT.

Based on emerging studies (Beauchamp et al., 2011; Conrad, 2001; Dar-Nimrod et al., 2010; Einsiedel & Geransar, 2009; Schnittker, 2008; Wilde et al., 2010), we propose GM may impact outcomes by reducing the mechanism of genetic essentialism. The genetic essentialism mechanism consists of beliefs of permanence and inevitable development of the genetic condition (Beauchamp et al., 2011; Conrad, 2001; Dar-Nimrod et al., 2010; Einsiedel &

Geransar, 2009; Schnittker, 2008; Wilde et al., 2010). Those holding genetic essentialist views were less likely to adopt preventative behaviors across conditions (e.g. heart disease (Hardcastle et al., 2015; Hunt et al., 2000; Senior, Marteau, & Peters, 1999), obesity (Rodriguez & George, 2014). Our pilot work with CHR youth shows providing the GM framing is linked with lower genetic essentialism. Building on this work, we propose to develop 2 new tools to facilitate positive intent towards treatment by reducing genetic essentialist beliefs.

We assess our tools among CHR youth (16-30 yrs). Treatment of CHR, before 1st episode of psychosis shows promise in averting disorder onset (McGlashan et al., 2004; Morrison et al., 2006; Nordentoft et al., 2006; Phillips et al., 2007). The CHR shares features with high-risk states such as pre-type 2 Diabetes where both: a) may begin in adolescence; b) have identifiable genetic and behavioral risk factors; c) are in ~1/3 of cases likely to develop the full disorder without intervention (American Diabetes Association, 2010; Fonseca, 2009). While specific risk genes for psychosis are not yet used in diagnosis, genetic heritability is viewed as a key contributor for psychosis (i.e., schizophrenia [SCZ], the most studied psychotic disorder (Doherty, O'Donovan, & Owen, 2012; International SNP Map Working Group, 2001; Purcell et al., 2009; Santoro et al., 2015; Swami, 2011), with genetic risk ascribed to common and rare variants. For regular use of genetic testing in practice, more research confirming the predictive power of genetics for an individual's development of psychosis is required (DiMillo et al., 2015; Hakak et al., 2001), as there is no known single-gene form of SCZ. Notably, research has linked lifestyle/behavioral factors (stress, cannabis use) to developing SCZ (Caspi et al., 2005; Gallagher III & Jones, 2016; Miller et al., 2001; Smit, Bolier, & Cuijpers, 2004; Volkow et al., 2016), suggesting a gene-by-environment interaction (Furrow, Christiansen, & Feldman, 2011; Moffitt, Caspi, & Rutter, 2006). This is supported by findings of differentially methylated regions, a gene X environment mechanism, at the BDNF, serotonin transporter, and FKBP5 loci (Kular & Kular, 2018). A GM framing fits the known genetic risk for psychosis and is very likely to be used in the future.

Psychiatric genetic counseling to aid people adapt to the implications of genetic risk (Friesen et al., 2016; Resta et al., 2006), which occurs in 1 session and shows benefit even without genetic testing (Inglis et al., 2015), has led to more treatment engagement for people with psychosis (Costain et al., 2012 a, b,; Hippman et al., 2016). An individualized, interactive dialogue with an expert is key to address core misconceptions (Austin & Honer, 2007;), such as misinterpreting genetic risk probabilities (e.g. perceiving 1%-5% risk as 'high') (Austin, 2010). Yet because only 1% of 4,000 genetic counselors in North America work in psychiatry (Fusar-Poli et al., 2014) (a figure that will rise when specific psychosis risk genes are identified), tools providing genetic knowledge for CHR via an interactive exchange could greatly expand access to the benefits of psychiatric genetic counseling.

Tool #1-AutoTutor An interactive, automated tool that could convey genetic risk and increase intent to engage in treatment for CHR youth would be a major advance. Many CHR youth prefer technology (Alvarez-Jimenez et al., 2014; Lal et al., 2015), due to problems relating with others (Carrión et al., 2011; Liddle, 2000; van Rijn et al., 2011). AutoTutor, an intelligent system that simulates talking with a human tutor (Wolfe et al., 2015), has been effective in conveying genetic concepts and improving medical decision-making about genetic risk for breast cancer (Widmer et al., 2015; Wolfe et al., 2016). AutoTutor's efficacy as a communication tool is why we will use it to educate CHR youth about GM; we reason that changing beliefs about GM will initiate behavior change because beliefs about GM have shown to affect changes in pro-health behaviors (Aspinwall et al., 2015; Chao et al., 2008; Jenkins et al., 2013; Kullo et al., 2016; Meisel & Wardle, 2014). Using pre-existing software developed by co-I Dr. Hu, our AutoTutor,

PsyGist (**Psy**chosis **G**enetic-risk **I**ntelligent **S**emantic **T**utor) will convey genetic risk to CHR youth.

Tool #2-Clinician Manual A 2nd advance is to develop a manual for clinicians, to convey genetic risk to CHR youth. A standardized manual enables an interactive discussion of genetic risk, has been tested in people with SCZ (Costain et al., 2012a; Hippman et al., 2016) and suggests efficacy for high-risk states. Our expert co-I, Dr. Austin, has tested a protocol that provides a template for our work.

A distinct strength is that a GM framing has led to more pro-health behaviors across conditions (Aspinwall et al., 2015; Chao et al., 2008; Jenkins et al., 2013; Kullo et al., 2016; Meisel & Wardle, 2014). Weaknesses in the evidence base include this framing not being used with high-risk states and lack of tools to ease access, which are both addressed by our plan. **Impacts:** Future genetic risks for psychosis are likely to fit GM. We develop 2 tools to deliver this framing to increase pro-health behaviors in a high-risk state, expand access to genetic information, and to increase intent to use treatment and reduce stigma for CHR youth. PsyGist is one of the 1st intelligent systems to run from any computer with internet capabilities and promises to be scalable, cost-effective and high impact. The Manual offers a protocol for trained clinicians to convey genetic risk to CHR. Our study is among the few to attempt to modify genetic essentialism. Lastly, our study adds to the sparse data regarding genetic framings on youth.

4. METHODS

Study Design

The study will be rolled out in two phases:
(1) development of the translational tools; and
(2) assessment and evaluation of the safety, acceptability and effectiveness of tools using pre-post comparisons.

A sequential assignment procedure will be used to assign participants to first the Clinician Manual educational session and then the PsyGist educational session. Thus, the first 27 individuals enrolled in the study will be assigned to the Clinician Manual educational session, while the next 27 individuals will be assigned to the PsyGist educational session (Clinician Manual n=27; PsyGist n=27; Total N=54). Sequential assignment is being utilized in this protocol to ensure that the probability of contamination, resulting from participants sharing study information between educational session groups, is minimized.
All Assessments will be presented in two 2.5-hour visits, 1 week prior and immediately after exposure to each Tool (Clinician Manual or PsyGist) because it would be unethical not to debrief youth about the hypothetical framing immediately following the session. However, we will take as many brief breaks throughout the sessions as necessary to accommodate the participant. 'Acceptability' measures will be administered only once after post-test measures.

Inclusion and Exclusion Criteria

All subjects will be drawn from the Center for Prevention and Evaluation Criteria (COPE's) Clinical High Risk for Psychosis (CHR) participants at the New York State Psychiatric Hospital (see protocol information below).

THE CENTER OF PREVENTION AND EVALUATION (COPE): A PROSPECTIVE STUDY OF SYMPTOMS AND COGNITION (FORMERLY 5567R) PI: Ragy Girgis (Protocol Number: 6654R)

Below are the overall inclusion criteria for the Center for Prevention and Evaluation Criteria (COPE), which is the recruitment site. Note that below we have specific recruitment criteria that identify a subset of the COPE respondents.

INCLUSION CRITERIA	METHOD OF ASCERTAINMENT
1. Male or females between the ages of 14-30	Phone screen and interview
2. Capacity to give informed consent for participants 18 and over OR participant's assent plus informed consent from parent for participants under the age of 18	Interview; assessment by clinician not involved in the study
3. English-speaking (for participants)	Phone screen and interview
4. Identified as at clinical high risk for psychosis as defined as a)attenuated positive symptoms b)brief intermittent positive symptoms c) schizotypal disorder or family history of psychotic disorder with recent decline in functioning (30 GAF points)	Structured Interview for Psychosis-Risk Syndromes (SIPS)/Scale of Psychosis-Risk Symptoms (SOPS)

The exclusion criteria for COPE below are as follows:

EXCLUSION CRITERIA	METHOD OF ASCERTAINMENT
1. Psychosis diagnosis	Clinical interview and Structured Interview for Psychosis-Risk Syndromes (SIPS)/Scale of Psychosis-Risk Symptoms (SOPS)
2. History of neurological, neuroendocrine or other medical conditions known to affect the brain	Clinical interview and collateral information from patient's treaters (with their authorization for release)
3. IQ < 70	WTAR < 6
4. Moderate or severe risk of harm to self or others	Clinical interview, and Columbia Suicide Severity Rating Scale

Below are the Specific Inclusion Criteria for this protocol:

INCLUSION CRITERIA	METHOD OF ASCERTAINMENT
1. Male or females between the ages of 16-30	Phone screen and interview
2. Enrolled in COPE	Enrollment record

3. Identified as at clinical high risk for psychosis as defined as having <u>at least one</u> of the following: a)attenuated positive symptoms b)brief intermittent positive symptoms	Structured Interview for Psychosis-Risk Syndromes (SIPS)/Scale of Psychosis-Risk Symptoms (SOPS)

Below are the Exclusion criteria for this protocol:

EXCLUSION CRITERIA	METHOD OF ASCERTAINMENT
1.Meeting CHR via <u>only</u> the Genetic risk and deterioration (GRD) syndrome. If the participant meets the GRD syndrome only, we *exclude* the rare Genetic risk + deterioration (GRD) syndrome (comprising <1% of CHR cases) because GRD requires having a 1st degree relative with any psychotic disorder, which may be linked with stronger reactions to genetic framings.	Clinical interview and Structured Interview for Psychosis-Risk Syndromes (SIPS)/Scale of Psychosis-Risk Symptoms (SOPS)
2. IQ < 80	The Test of Premorbid Functioning (TOPF)
3. Inability to adopt hypothetical situation	Hypothetical situation screener (see procedures section for description)

- Adults unable to consent (individuals with impaired decision making capacity)
  - <u>Will not</u> be included in this study
- Individuals who are not yet adults (infants, children, teenagers)
  - <u>Will be</u> included in this study (16-30 years old) (see inclusion/exclusion criteria)
- Pregnant women
  - <u>Will not</u> be included in this study
- Prisoners
  - <u>Will not</u> be included in this study

<u>Description of Subject Population:</u>
All subjects will be recruited from The Center for Prevention and Evaluation's (COPE) prodromal population at The New York State Psychiatric Institute (NYSPI).

Population to be Recruited: Individuals at Risk for Psychosis (CHR)

Number of completers required to accomplish study aims: *n*=27/tool (PsyGist & Clinician Manual); *N*=54 total participants between both groups (PsyGist & Clinician Manual)
Projected number of subjects who will be enrolled to obtain required number of completers: N=100

Age range of subject population: 16-30 years old

5. PROCEDURES

Study Timeline

Timeline	Month 0-2	Months 3-5	Months 6-22	Months 23-34
Task	Obtain IRB Approval	Develop 2 Tools	Test Tools (n=27 CHR youth/tool)	Refine Tools, Data Analysis + Manuscripts

Pre-Educational Session Protocol (Pre-Assessment):

Following successful enrollment into the study, and one-week prior to exposure to the educational session (either PsyGist or Clinician Manual), a trained research assistant will conduct pre- assessments. Participants will be assessed on: (1) covariates including socio-demographic variables, personality traits, exposure to genetic framing, barriers to mental health care, symptoms, cognition, quantification of perception of 'substantial psychosis risk' (0-100%) (2) 'genetic essentialism' (mechanism); (3) intent to engage in treatment and healthy behaviors (primary outcome); (4) stigma (secondary outcome). Data will be collected using REDCap with the exception of the following which may use an external site to collect data: (1) the Implicit Association Test for assessing stigma, and (2) the computerized behavioral task for assessing intent to engage in healthy behaviors. REDCap is a secure data collection tool that meets HIPAA compliance standards. REDCap will allow either the participant or the research assistant to fill out the measures being collected using this online tool.

Below is the information regarding the IAT and the new computerized behavioral tasks. We have updated the information concerning the administration of the website. While we don't plan to administer the IAT right now due to the study moving online, we may decide to administer this in the near future once we can better accommodate technical aspects of administration in an online format, while maintaining ethical standards.

Implicit Association Test (IAT): After completion of the pencil-and-paper stigma scale, participants will complete the IAT. The IAT will be administered on a secured and encrypted laptop. Research assistants will first review the instructions for the IAT, making certain that participants understand the process by which they must compete the task. Before starting the IAT, participants will be able to practice through the IAT's practice module.

Distress Protocol: Study staff will also be trained to administer a distress protocol (See description in "Post-Educational Session Protocol") throughout all phases of the study to monitor if participants exhibit signs of agitation, shaking or crying during or after exposure to the tool/ interview. The distress protocol will identify signs of distress, and prompt referral to the a clinician. A clinician, either Dr. Girgis (the director of COPE), Dr. Brucato (chief psychologist at COPE), or our clinician who is administering our clinician manual (Dr. Carol Cohen-Romano), will be available for participants who require referral to a clinician based on the distress protocol.

Educational Session-specific Protocol:

PsyGist procedures. During online administration, PsyGist, will be accessed by participants via logging into a platform. Research assistants will provide detailed information to participants regarding basic use and guidelines for this program. PsyGist has 3 parts: (1) assessment of the youth's causal model for their high-risk state; (2) an individualized 'pre-tutorial' vignette matched to their causal model; (3) a 'tutorial' presenting the 'genetic malleability' framing. PsyGist will guide participants through its three components. First, PsyGist will assess the participant's causal model for their high-risk state by presenting a 1-item visual analog scale asking, 'Is your high-risk state caused by environmental factors, genetic factors, or both?' Then a slider on the scale will be used to assign youth to 1 of 3 individualized pre-tutorial vignettes developed from prior genetic counseling materials 'primarily genetic', 'primarily environmental' or 'combined'.

Identifying a user's causal model enables the Genetic Malleability framing conveyed via the interactive Tutorial to better fit pre-existing beliefs. Participants will interact with a PsyGist Genetic Malleability Tutorial, taking an anticipated 12 to 13 turns. PsyGist will propose a prompt (e.g. 'How do genes affect psychosis risk?') which youth will answer. The tutorial will impart key Genetic Malleability concepts, such as 'risk genes may be turned on or off by lifestyle factors. While CHR samples show some cognitive impairment, AutoTutor has been used in cognitively-impaired individuals and BRCA Gist has effectively increased genetic knowledge in lower-educated groups. Furthermore, PsyGist text is tailored to users' literacy as it uses variations of users own words. The Health Literacy Adviser software will also be used to rephrase PsyGist's text at an 8th grade level.

The research assistant will be present (online) throughout the presentation of PsyGist to answer any questions.

Clinician Manual Procedures. Participants in the Clinician Manual arm will be introduced to a trained Ph-D level clinician with some genetic counseling training and will complete one 60-minute session covering equivalent topics addressed in the PsyGist program. The manual will consist of: (1) a section exploring the youth's causal model for their high-risk state; (2) individualization per their causal model; and (3) tutorials that convey the main concepts of genetic malleability. Clinicians will assess individual causal models via discussion with CHR youth about their at-risk state. Individualization of genetic framing will occur using youths' causal models and will fall into 1 of 3 categories (per PsyGist): 'primarily genetic', 'primarily environmental' or 'combined'. Visual aids will be used to elicit discussion. The session between the clinician and the participant will be audio recorded with the participant's permission. Participants will be able to initial whether they agree to or do not agree to be audio recorded during their meeting with the clinician. This will allow respondents to consent to the study and decide whether or not they would like to be audio recorded. A participant deciding not to be audio recorded will not exclude them from participating.

To accommodate recording during our virtual session and ensure participant confidentiality, we will ensure that the video part of the meeting is not recorded (i.e. the recording will be audio only; this feature is available via HIPAA-compliant video teleconferencing) and the audio recording will be saved to a secured laptop.

The research assistant will not be present for the 60-minute session but will reconvene with the participant for post-educational session assessments.

Study staff will be trained to administer a distress protocol (See description in "Post-Educational Session Protocol") throughout all phases of the study to monitor if participants exhibit signs of agitation, shaking or crying during or after exposure to the tool/ interview. The distress protocol will identify signs of distress, and prompt referral to a clinician. A clinician, either Dr. Girgis (the director of COPE), Dr. Brucato (chief psychologist at COPE), or our clinician who is administering our clinician manual (Dr. Carol Cohen-Romano), will be available for participants who require referral to a clinician based on the distress protocol.

Post-Educational Session Protocol:

Post-educational assessment protocol will be equivalent to pre-educational session assessment protocol, with the addition afterwards of the new computerized behavioral task and an acceptability assessment, followed by debriefing. Additionally, the following measures will be administered only as part of the pre-education session protocol: demographics, barriers to mental healthcare, exposure to genetic framing, life orientation test, tolerance for uncertainty.

New Computerized Behavioral Task: Research assistants will administer a new computerized behavioral task to assess intent to engage in healthy behaviors via measurement of time spent by youth (in seconds) and engagement (measured in number of clicks) with a social media platform. During online administration the research assistant will send the participant a link to the website and ask the participant to share their screen while they are viewing the website. Unlike other measures, this computerized measure captures the amount of engagement with a health-promoting social media platform as our behavioral outcome. The interviewer will show the participant the website, developed by our team to be educational and interactive. The computerized behavioral task will be presented while participants are being asked to consider the hypothetical genetic malleability framing. The website has these sections: i) Information on ways to improve mental health; ii) Ways to find help; and iii) Social support blog, which offers access to an online support community of other youth with psychotic symptoms. Each section has options for the viewer to click and read. Using Google Analytics, a website feature, we will capture metrics for each participant such as: 1) the time in seconds the participant spends on each page, and; 2) the number of interactions with the website. This computerized measure promises to expand measurement of behavioral intention in a novel way, thus capturing an important new element of health-promoting behavioral change.

Acceptability assessment. Acceptability of each educational session will be assessed via audiotaped individual interviews wherein youth will be asked to "think aloud" about the content of the educational session. Youth will be queried regarding their cognitive processes about the educational session. Youth will be asked to report their understanding and any other cognitive process surrounding the overall content of the educational session. The following questions will be asked as part of the acceptability assessment.

Can you tell me what you think the educational session is about? (open ended question)
What did you learn? (open ended question)

What did you think about the educational session? (open ended question)
- Follow-up question: Were you able to understand it? (open ended question)
- Follow-up question: Was there anything that was confusing to you? (open ended question)
- Follow-up question: Is there anything you would change? (open ended question)

Did you understand that this session was about genetic malleability, or the idea that genes may put someone at risk to develop psychosis but there are environmental or lifestyle factors that can keep the gene from turning on? Answer choices: Yes/No

Further, participants will be asked to complete a brief usability questionnaire. If stress is indicated at any point regarding interacting with the tool or clinician, participants will be carefully probed for the source of any stress or adverse and serious adverse events, and will be immediately referred to a clinician, either Dr. Girgis (the director of COPE), Dr. Brucato (chief psychologist at COPE), or our clinician who is administering our clinician manual (Dr. Carol Cohen-Romano).
Debriefing: Immediately following completion of the post- educational session assessments, participants will be debriefed (1st debriefing) via: (1) discussing any concern about the genetic framing; (2) reinforcing that while researchers are beginning to identify genes that combine with each other to increase risk of development to psychosis, the genetic framing is hypothetical (that no clear genetic markers or biological tests yet exist for psychosis) followed by a True/False quiz testing knowledge of the current state of genetics in psychosis (described below); and (3) identifying distress via a distress protocol (see below) and an adverse and

serious adverse event (SAE) checklist (see below). To ensure that participants understand that the genetic framing is hypothetical, each participant will be asked 8 True/False questions following being told that the situation is hypothetical (e.g., “Currently, genes only suggest that a person may be at a higher risk of developing psychosis. It does not mean that he or she would definitely get the disorder”). Respondents will answer each question, and the interviewer will discuss any item that the respondent gets wrong to ensure understanding.

A second debriefing will occur 2-weeks after study completion, and again at 3-months after study completion. If any distress or adverse reaction is found, referral to Dr. Brucato, Dr. Girgis, or Dr. Cohen-Romano will occur immediately.

Debriefing for Behavioral, Computerized Measure of Intent to Engage in Treatment: After the post-assessment, participants are further debriefed about the computerized measure to assess intent to engage in treatment. Participants are told that this website is not a real website but that our study website was modeled after a real website entitled “Strong365.org”. During debriefing, participants are shown this real website, which offers similar up-to-date informational content and a blog where youth can interact and share personal stories.

Distress Protocol: Notably, to address potential distress, study staff will administer a “Distress protocol” to identify signs of distress and will be sensitive to the potential that distress may lead to an adverse event or serious adverse event. This will consist of the following steps and structured scales listed below.

1) First, the distress protocol consists of an adapted quantitative measure used to assess distressed mood and stress following the study procedures (3 subscales assessing Depression [8 items], Fatigue [4 items] and Stress [4 items] stemming from the study procedures on a 5-point scale; 0= not at all; 1=a little; 2=moderately; 3=quite a bit; 4=extremely) (see questions below). A positive quantitative rating of distress will be indicated by ≥2 items endorsed as “moderately” or more, and will trigger referral to a clinician.

Quantitative Distress Protocol Measures:
Due to your participation in this study, please answer the following questions.
Based on your meeting with the clinician or [interaction with AutoTutor], how [blank] do you feel?
Scale: 0= not at all; 1=a little; 2=moderately; 3=quite a bit; 4=extremely

1. Stressed (stress sub-scale)
2. Jittery (stress sub-scale)
3. Tense (stress sub-scale)
4. Overworked (stress sub-scale)
5. Unhappy (depression sub-scale)
6. Sad (depression sub-scale)
7. Blue (depression sub-scale)
8. Hopeless (depression sub-scale)
9. Discouraged (depression sub-scale)
10. Miserable (depression sub-scale)
11. Helpless (depression sub-scale)
12. Worthless (depression sub-scale)
13. Worn-out (fatigue sub-scale)
14. Fatigued (fatigue sub-scale)
15. Exhausted (fatigue sub-scale)
16. Weary (fatigue sub-scale)

Again, a positive quantitative rating of distress will be indicated by ≥2 items endorsed as

“moderately” or more, and will trigger referral to a clinician.

2) Second, interviewers will ask semi-structured, open-ended questions at the end of the interview to assess distress due to the study procedures (see below).
Due to your participation in this study, please answer “yes” or “no” the following questions.

1. Are you experiencing a high level of stress or emotional distress?
2. Are you currently having thoughts of harming yourself?
3. Are you currently having thoughts of harming someone else?

If participants answer “yes” to any of the above questions they will be referred to a clinician.
3) Third, interviewers will be trained to pay attention to crying, shaking, agitation (pacing, breaking away from the task) during the interview. RA’s will have completed or will be actively completing a clinical placement at COPE. If participants exhibit distress during exposure to the tool/interview, interviewers will stop the study procedures and ask if participants would like to discontinue the study. If so, the participant will be removed from the study and immediately referred to a clinician.

In sum, participants will indicate a “positive” distress rating on the “Distress Protocol” if they: 1) score “positive” on the quantitative items (see above); 2) respond affirmatively to the semi-structured, open-ended questions following all study procedures (see above); 3) exhibit distress during exposure to the tool/interview. If participants rate “negative” on all three components, participants will still be asked if they would like to check in with a clinician.

****All participants regardless of whether they demonstrate any distress during the protocol will also be asked the below questions after completion of all study procedures as part of the debriefing protocol:**

True/False Quiz Administered As Part of Debriefing Protocol
1) There currently exists a blood test to identify genetic risk for psychosis (F)
2) Scientists have identified genes that definitely cause psychosis (F)
3) Only genes determine one's chance of developing psychosis (F)
4) If you have a genetic risk for psychosis, this means that you will definitely develop psychosis (F).
5) Currently, genes only suggest that a person may be at a higher risk of developing psychosis. It does not mean that he or she would definitely get the disorder. (T)
6) The situation that we presented to you today about a blood test for psychosis was not real (T)
7) Psychosis may be caused by many factors, and genes could be one of them. (T)
8) Many other factors, for example, one’s environment and/or lifestyle, could impact how genes function. (T)

Assessment of Adverse Event. Unfavorable occurrences that may be related to participation in the study, including: (1) exacerbation of CHR symptoms; (2) distress or anxiety (see “Distress Protocol” above); and (3) suicidal ideation, will be reviewed by the PI, and scored based on: a) how attributable the event is to the study (from a scale of [1] “Unrelated” to [5] “Definitely related”) and b) the severity of the event (on a scale of [1] “No adverse event” to [5] “life-threatening/disabling/fatal)”. Adverse Events that are at least “somewhat attributable” and “somewhat severe” (i.e. marked and non-transient psychological distress greater than a few days) [3 or more on both scales] will be submitted to the NHGRI program Officer with the annual progress report and will also be submitted to the DSMB and IRB.

Serious Adverse Event (SAE). A Serious Adverse Event (SAE) will be one that results in death or the immediate risk of death, hospitalization, or persistent or significant disability/incapacity. These may include: (1) suicide attempt or completed suicide; (2) violent behaviors towards others; and (3) psychiatric hospitalization related to the study. In addition to immediately dealing with the event, the study PI will score adverse events based on: a) how attributable the event is to the study (from a scale of [1] "Unrelated" to [5] "Definitely related") and b) the severity of the event (on a scale of [1] "No adverse event" to [5] "life-threatening/disabling/fatal)". Serious Adverse Events that are at least "somewhat attributable" and "somewhat severe" (i.e. suicidal ideation) [3 or more on both scales] will be submitted to NHGRI's Program Officer, the DSMB, and the IRB within 10 business days of study team becoming aware of the event. Deaths will be reported within 5 days of the study team becoming aware of the event.

Adverse and Serious Adverse events will be reported according to the following NIH guidelines:

Reportable Event	**Timeline for Reporting**	**Reported by**
IRB/DSMB suspensions or terminations	Within 3 business days of receipt (to NHGRI)	DSMB and PI
Protocol violations	With the annual progress report (to NHGRI Program Officer, and DSMB)	PI
Unanticipated Problems, involving risks to subjects or others	Within 10 business days of study team becoming aware of the event (to NHGRI Program Officer, DSMB, and IRB)	PI
Adverse Events, expected and/or unrelated to study participation	With the annual progress report (to NHGRI Program Officer, DSMB, and IRB)	PI
Unexpected Serious Adverse Events (SAE) related to study participation	Within 10 business days of study team becoming aware of the SAE (to NHGRI Program Officer, DSMB, and IRB)	PI
Deaths related to study participation	Within 5 business days of PI first learning of event (to NHGRI Program Officer, DSMB, and IRB)	PI

6. STATISTICAL ANALYSIS PLAN

We will assess variables' distributions. We use bivariate tests to compare pre- vs post-intervention outcomes via paired t-test and Mann-Whitney Signed Rank tests. Primary and secondary outcomes will be assessed. We will stratify the sample by key covariates (e.g., IQ) and test for significant pre- vs post-mean difference scores by stratification.

7. DATA MANAGEMENT

Confidentiality of all participants will be preserved by coding all datasheets and other data sources and maintaining them in locked files/drawers in the study clinicians office/PI's office or will be kept on a secure computer by the study clinician/PI. ID numbers will be determined by order of participant entry into the study and will not be related in any way to participant

identifying data (i.e., the first participant who is recruited into the study will be subject #1, etc.). Data will be entered into a computerized database. The database is on a computer, which requires a password to access the data. Public dissemination of the results of this research will be reported on subjects collectively and will contain no identifying information about individual participants.

A deidentified dataset will be transmitted from Dr. Girgis to Dr. Yang (PI) at NYU only via encrypted, password protected files via secure email or an encrypted flashkey.

To accommodate the virtual administration of this protocol and ensure confidentiality, we will use a telephone or HIPAA-compliant video teleconferencing. We believe this will ensure that the virtual meeting is secure.

Protocol Violations

Any deviations from the IRB protocol will be first reviewed by BRANY's IRB and will subsequently be submitted in the annual progress report to NHGRI's Program Officer and to the DSMB.

Unanticipated Problems

Unexpected incidents, experiences or outcomes that are potentially related to participation and suggest that the research places the participants at a greater risk of harm than was previously known or recognized, will be reported to the NHGRI Program Officer, the DSMB, and the IRB within 10 business days of the study team becoming aware of the event.

Discontinuation criteria

Regarding discontinuation criteria and who will determine if a participant is too ill to continue to participate, a participant will discontinue the study under the following conditions: (1) if the participant decides not to continue the study for personal reasons; and (2) if the patient presents with acute or imminent harm to themselves or others, or suffers other incapacitating conditions (i.e., exacerbation of prodromal psychosis symptoms to the point of requiring in patient hospitalization) he or she may be removed from the study; and (3) if the participant develops full symptoms due to psychosis. In all cases, the participant's treating clinician will consult with the PI and be informed about the discontinuation of study participation.

Data Safety and Monitoring Board:

Given that the proposed study is an NIH-defined Phase I clinical trial, and that we are recruiting children, a Data and Safety Monitoring Board will be appointed. Members of the DSMB will include three established and well-recognized experts in stigma and psychosis/CHR who are doctoral-level clinicians and researchers who have had at least 5 years of clinical experience working with psychosis/CHR. The following members will comprise the DSMB, all of whom have no affiliation or role in the project: Phil Yanos, Kristen Woodberry, and Dan Shapiro. The DSMB will convene every six months and in the event of a serious adverse event.
Review/monitoring activities will include reviewing the protocol, risk-benefit considerations, informed consent documents and plans for data safety and monitoring; evaluating the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention; and other factors that can affect study outcomes; considering factors external to the study such as scientific or therapeutic developments that may have an impact on the safety of the participants; protecting the safety of the study participants and reporting on the safety and scientific progress of the trial. In addition to having the power to recommend to the PI that the study be stopped or modified, the DSMB can determine whether

any adverse event or serious adverse event affects the risk-benefit ratio of the study, and whether modifications to the protocol or consent forms are required.

REFERENCES:

Alvarez-Jimenez, M., Alcazar-Corcoles, M. A., Gonzalez-Blanch, C., Bendall, S., McGorry, P. D., & Gleeson, J. F. (2014). Online, social media and mobile technologies for psychosis treatment: a systematic review on novel user-led interventions. *Schizophrenia research*, *156*(1), 96-106.

American Diabetes Association. (2010). Diagnosis and classification of diabetes mellitus. *Diabetes care*, *33*(Supplement 1), S62-S69.

Anido, A., Carlson, L. M., & Sherman, S. L. (2007). Attitudes toward fragile X mutation carrier testing from women identified in a general population survey. *Journal of Genetic Counseling*, *16*(1), 97-104.

Aspinwall, L. G., Stump, T. K., Taber, J. M., Kohlmann, W., Leaf, S. L., & Leachman, S. A. (2015). Impact of melanoma genetic test reporting on perceived control over melanoma prevention. *Journal of behavioral medicine*, *38*(5), 754-765.

Austin, J. C. (2010). Re-conceptualizing risk in genetic counseling: implications for clinical practice. *Journal of genetic counseling*, *19*(3), 228-234.

Austin, J. C., & Honer, W. G. (2007). The genomic era and serious mental illness: a potential application for psychiatric genetic counseling. *Psychiatric Services*, *58*(2), 254-261.

Austin, J. C., Smith, G. N., & Honer, W. G. (2006). The genomic era and perceptions of psychotic disorders: genetic risk estimation, associations with reproductive decisions and views about predictive testing. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *141*(8), 926-928.

Bateman, R. J., Xiong, C., Benzinger, T. L., Fagan, A. M., Goate, A., Fox, N. C., ... & Holtzman, D. M. (2012). Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *New England Journal of Medicine*, *367*(9), 795-804.

Beauchamp, M. R., Rhodes, R. E., Kreutzer, C., & Rupert, J. L. (2011). Experiential versus genetic accounts of inactivity: implications for inactive individuals' self-efficacy beliefs and intentions to exercise. *Behavioral Medicine*, *37*(1), 8-14.

Benros, M. E., Eaton, W. W., & Mortensen, P. B. (2014). The epidemiologic evidence linking autoimmune diseases and psychosis. *Biological psychiatry*, *75*(4), 300-306.

Bird, V., Premkumar, P., Kendall, T., Whittington, C., Mitchell, J., & Kuipers, E. (2010). Early intervention services, cognitive–behavioural therapy and family intervention in early psychosis: systematic review. *The British Journal of Psychiatry*, *197*(5), 350-356.

Boraxbekk, C. J., Lundquist, A., Nordin, A., Nyberg, L., Nilsson, L. G., & Adolfsson, R. (2015). Free recall episodic memory performance predicts dementia ten years prior to clinical diagnosis: findings from the Betula longitudinal study. *Dementia and geriatric cognitive disorders extra*, *5*(2), 191-202.

Buysschaert, M., Medina, J. L., Bergman, M., Shah, A., & Lonier, J. (2015). Prediabetes and associated disorders. *Endocrine*, *48*(2), 371-393.

Cardno, A. G., Rijsdijk, F. V., Sham, P. C., Murray, R. M., & McGuffin, P. (2002). A twin study of genetic relationships between psychotic symptoms. *American Journal of Psychiatry*, *159*(4), 539-545.

Carrión, R. E., Goldberg, T. E., McLaughlin, D., Auther, A. M., Correll, C. U., & Cornblatt, B. A. (2011). Impact of neurocognition on social and role functioning in individuals at clinical high risk for psychosis. *American Journal of Psychiatry*, *168*(8), 806-813.

Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H., ... & Poulton, R. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biological psychiatry*, *57*(10), 1117-1127.

Chao, S., Roberts, J. S., Marteau, T. M., Silliman, R., Cupples, L. A., & Green, R. C. (2008). Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL Study. *Alzheimer disease and associated disorders*, *22*(1), 94.

Christensen, K. D., Roberts, J. S., Uhlmann, W. R., & Green, R. C. (2011). Changes to perceptions of the pros and cons of genetic susceptibility testing after APOE genotyping for Alzheimer disease risk. *Genetics in Medicine*, *13*(5), 409.

Cohen, J. (2013). *Statistical power analysis for the behavioral sciences*. Routledge.

Conrad, P. (2001). Genetic optimism: Framing genes and mentalillness in the news. *Culture, medicine and psychiatry*, *25*(2), 225-247.

Corrigan, P. W., & Watson, A. C. (2002). The paradox of self-stigma and mental illness. *Clinical Psychology: Science and Practice*, *9*(1), 35-53.

Costain, G., Esplen, M. J., Toner, B., Hodgkinson, K. A., & Bassett, A. S. (2012a). Evaluating genetic counseling for family members of individuals with schizophrenia in the molecular age. *Schizophrenia bulletin*, *40*(1), 88-99.

Costain, G., Esplen, M. J., Toner, B., Scherer, S. W., Meschino, W. S., Hodgkinson, K. A., & Bassett, A. S. (2012b). Evaluating genetic counseling for individuals with schizophrenia in the molecular age. *Schizophrenia bulletin*, *40*(1), 78-87.

Dar-Nimrod, I., Cheung, B. Y., Ruby, M. B., & Heine, S. J. (2014). Can merely learning about obesity genes affect eating behavior?. *Appetite*, *81*, 269-276.

DiMillo, J., Samson, A., Thériault, A., Lowry, S., Corsini, L., Verma, S., & Tomiak, E. (2015). Genetic testing: when prediction generates stigmatization. *Journal of health psychology*, *20*(4), 393-400.

Doherty, J. L., O'Donovan, M. C., & Owen, M. J. (2012). Recent genomic advances in schizophrenia. *Clinical genetics*, *81*(2), 103-109.

Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J., ... & Meguro, K. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria. *The Lancet Neurology*, *6*(8), 734-746.

Dunn, N. F., Miller, R., Griffioen, A., & Lee, C. A. (2008). Carrier testing in haemophilia A and B: adult carriers' and their partners' experiences and their views on the testing of young females. *Haemophilia*, *14*(3), 584-592.

Einsiedel, E. F., & Geransar, R. (2009). Framing genetic risk: trust and credibility markers in online direct-to-consumer advertising for genetic testing. *New Genetics and Society*, *28*(4), 339-362.

Farrell, N. R., Lee, A. A., & Deacon, B. J. (2015). Biological or psychological? Effects of eating disorder psychoeducation on self-blame and recovery expectations among symptomatic individuals. *Behaviour research and therapy*, *74*, 32-37.

Friesen, P., Lawrence, R. E., Brucato, G., Girgis, R. R., & Dixon, L. (2016). Hopes and expectations regarding genetic testing for schizophrenia among young adults at clinical high-risk for psychosis. *Journal of psychiatric practice*, *22*(6), 442.

Fonseca, V. A. (2007). Early identification and treatment of insulin resistance: impact on subsequent prediabetes and type 2 diabetes. *Clinical cornerstone*, *8*, S7-S18.

Fonseca, V. A. (2009). Defining and characterizing the progression of type 2 diabetes. *Diabetes care*, *32*(suppl 2), S151-S156.

Furrow, R. E., Christiansen, F. B., & Feldman, M. W. (2011). Environment-sensitive epigenetics and the heritability of complex diseases. *Genetics*, *189*(4), 1377-1387.

Fusar-Poli, P., Yung, A. R., McGorry, P., & Van Os, J. (2014). Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention. *Psychological medicine*, *44*(1), 17-24.

Gallagher III, B. J., & Jones, B. J. (2016). Neglect and hereditary risk: Their relative contribution to schizophrenia with negative symptomatology. *International Journal of Social Psychiatry*, *62*(3), 235-242.

Gebicke-Haerter, P. J. (2012). Epigenetics of schizophrenia. *Pharmacopsychiatry*, *45*(S 01), S42-S48.

Grant, R. W., O'brien, K. E., Waxler, J. L., Vassy, J. L., Delahanty, L. M., Bissett, L. G., ... & Florez, J. C. (2013). Personalized genetic risk counseling to motivate diabetes prevention: a randomized trial. *Diabetes care*, *36*(1), 13-19.

Hakak, Y., Walker, J. R., Li, C., Wong, W. H., Davis, K. L., Buxbaum, J. D., ... & Fienberg, A. A. (2001). Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proceedings of the National Academy of Sciences*, *98*(8), 4746-4751.

Hardcastle, S. J., Legge, E., Laundy, C. S., Egan, S. J., French, R., Watts, G. F., & Hagger, M. S. (2015). Patients' perceptions and experiences of familial hypercholesterolemia, cascade genetic screening and treatment. *International journal of behavioral medicine*, *22*(1), 92-100.

Heshka, J. T., Palleschi, C., Howley, H., Wilson, B., & Wells, P. S. (2008). A systematic review of perceived risks, psychological and behavioral impacts of genetic testing. *Genetics in Medicine*, *10*(1), 19.

Hilbert, A. (2016). Weight stigma reduction and genetic determinism. *PloS one*, *11*(9), e0162993.

Hippman, C., Ringrose, A., Inglis, A., Cheek, J., Albert, A. Y., Remick, R., ... & Austin, J. C. (2016). A pilot randomized clinical trial evaluating the impact of genetic counseling for serious mental illnesses. *The Journal of clinical psychiatry*, *77*(2), e190.

Hughes, R., & Huby, M. (2012). The construction and interpretation of vignettes in social research. *Social Work and Social Sciences Review*, *11*(1), 36-51.

Hunt, K., Davison, C., Emslie, C., & Ford, G. (2000). Are perceptions of a family history of heart disease related to health-related attitudes and behaviour?. *Health Education Research*, *15*(2), 131-143.

Inglis, A., Koehn, D., McGillivray, B., Stewart, S. E., & Austin, J. (2015). Evaluating a unique, specialist psychiatric genetic counseling clinic: uptake and impact. *Clinical Genetics*, *87*(3), 218-224.

International SNP Map Working Group. (2001). A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature*, *409*(6822), 928.

Jacobsen, P. B., Valdimarsdottir, H. B., Brown, K. L., & Offit, K. (1997). Decision-making about genetic testing among women at familial risk for breast cancer. *Psychosomatic Medicine*, *59*(5), 459-466.

Jenkins, N., Lawton, J., Douglas, M., Walker, S., Finnie, R., Porteous, M., & Hallowell, N. (2013). How do index patients participating in genetic screening programmes for familial hypercholesterolemia (FH) interpret their DNA results? A UK-based qualitative interview study. *Patient education and counseling*, *90*(3), 372-377.

Kular, L., & Kular, S. (2018). Epigenetics applied to psychiatry: Clinical opportunities and future challenges. *Psychiatry and clinical neurosciences*, *72*(4), 195-211.

Kullo, I. J., Jouni, H., Austin, E. E., Brown, S. A., Kruisselbrink, T. M., Isseh, I. N., ... & Broeckel, U. (2016). Incorporating a genetic risk score into coronary heart disease risk estimates: effect on low-density lipoprotein cholesterol levels (the MI-GENES Clinical Trial). *Circulation*, *133*(12), 1181-1188.

Lal, S., Dell'Elce, J., Tucci, N., Fuhrer, R., Tamblyn, R., & Malla, A. (2015). Preferences of young adults with first-episode psychosis for receiving specialized mental health services using technology: a survey study. *JMIR mental health*, *2*(2), e18.

Lawrence, R. E., Friesen, P., Brucato, G., Girgis, R. R., & Dixon, L. (2016). Concerns about genetic testing for schizophrenia among young adults at clinical high risk for psychosis. *AJOB empirical bioethics*, *7*(3), 193-198.

Lebowitz, M. S. (2014). Biological conceptualizations of mental disorders among affected individuals: A review of correlates and consequences. *Clinical Psychology: Science and Practice*, *21*(1), 67-83.

Lebowitz, M. S., & Ahn, W. K. (2015). Emphasizing malleability in the biology of depression: Durable effects on perceived agency and prognostic pessimism. *Behaviour research and therapy*, *71*, 125-130.

Lebowitz, M. S., & Ahn, W. K. (2018). Blue genes? Understanding and mitigating negative consequences of personalized information about genetic risk for depression. *Journal of genetic counseling*, *27*(1), 204-216.

Lebowitz, M. S., Ahn, W. K., & Nolen-Hoeksema, S. (2013). Fixable or fate? Perceptions of the biology of depression. *Journal of consulting and clinical psychology*, *81*(3), 518.

Liddle, P. F. (2000). Cognitive impairment in schizophrenia: its impact on social functioning. *Acta Psychiatrica Scandinavica*, *101*(400), 11-16.

Lin, A. L., Jahrling, J. B., Zhang, W., DeRosa, N., Bakshi, V., Romero, P., ... & Richardson, A. (2017). Rapamycin rescues vascular, metabolic and learning deficits in apolipoprotein E4 transgenic mice with pre-symptomatic Alzheimer's disease. *Journal of Cerebral Blood Flow & Metabolism*, *37*(1), 217-226.

McGlashan, T. H., Zipursky, R. B., Perkins, D. O., Addington, J., Woods, S. W., Miller, T. J., ... & Breier, A. (2004, April). Olanzapine for treatment of the schizophrenia prodrome: 2-year results of a randomized placebo-controlled study. In *Biological Psychiatry* (Vol. 55, pp. 226S-226S). 360 PARK AVE SOUTH, NEW YORK, NY 10010-1710 USA: ELSEVIER SCIENCE INC.

McGorry, P. D., Yung, A. R., Phillips, L. J., Yuen, H. P., Francey, S., Cosgrave, E. M., ... & Adlard, S. (2002). Randomized controlled trial of interventions designed to reduce the

risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Archives of general psychiatry*, *59*(10), 921-928.

McVay, M. A., Beadles, C., Wu, R., Grubber, J., Coffman, C. J., Yancy, W. S., ... & Voils, C. I. (2015). Effects of provision of type 2 diabetes genetic risk feedback on patient perceptions of diabetes control and diet and physical activity self-efficacy. *Patient education and counseling*, *98*(12), 1600-1607.

Meisel, S. F., & Wardle, J. (2014). 'Battling my biology': psychological effects of genetic testing for risk of weight gain. *Journal of genetic counseling*, *23*(2), 179-186.

Meiser, B., Mitchell, P. B., McGirr, H., Van Herten, M., & Schofield, P. R. (2005). Implications of genetic risk information in families with a high density of bipolar disorder: an exploratory study. *Social science & medicine*, *60*(1), 109-118.

Miller, P., Lawrie, S. M., Hodges, A., Clafferty, R., Cosway, R., & Johnstone, E. C. (2001). Genetic liability, illicit drug use, life stress and psychotic symptoms: preliminary findings from the Edinburgh study of people at high risk for schizophrenia. *Social Psychiatry and Psychiatric Epidemiology*, *36*(7), 338-342.

Miller, T. J., McGlashan, T. H., Rosen, J. L., Cadenhead, K., Ventura, J., McFarlane, W., ... & Woods, S. W. (2003). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophrenia bulletin*, *29*(4), 703-715.

Moffitt, T. E., Caspi, A., & Rutter, M. (2006). Measured gene-environment interactions in psychopathology: Concepts, research strategies, and implications for research, intervention, and public understanding of genetics. *Perspectives on Psychological science*, *1*(1), 5-27.

Morrison, A. P., French, P., Parker, S., Roberts, M., Stevens, H., Bentall, R. P., & Lewis, S. W. (2006). Three-year follow-up of a randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultrahigh risk. *Schizophrenia bulletin*, *33*(3),682-687.

Nordentoft, M., Thorup, A., Petersen, L., Øhlenschlæger, J., Melau, M., Christensen, T. Ø., ... & Jeppesen, P. (2006). Transition rates from schizotypal disorder to psychotic disorder for first-contact patients included in the OPUS trial. A randomized clinical trial of integrated treatment and standard treatment. *Schizophrenia Research*, *83*(1), 29-40.

Oh, G., & Petronis, A. (2008). Environmental studies of schizophrenia through the prism of epigenetics. *Schizophrenia bulletin*, *34*(6), 1122-1129.

Perkins, D. O., Olde Loohuis, L., Barbee, J., Ford, J., Jeffries, C. D., Addington, J., . . . Cornblatt, B. A. (2019). Polygenic Risk Score Contribution to Psychosis Prediction in a

Target Population of Persons at Clinical High Risk. *American Journal of Psychiatry*, appi. ajp. 2019.18060721.

Phillips, L. J., McGorry, P. D., Yuen, H. P., Ward, J., Donovan, K., Kelly, D., ... & Yung, A. R. (2007). Medium term follow-up of a randomized controlled trial of interventions for young people at ultra high risk of psychosis. *Schizophrenia Research*, *96*(1-3), 25-33.

Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'donovan, M. C., Sullivan, P. F., & Sklar, P. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, *460*(7256), 748-752.

Resta, R., Biesecker, B. B., Bennett, R. L., Blum, S., Estabrooks Hahn, S., Strecker, M. N., & Williams, J. L. (2006). A new definition of genetic counseling: National Society of Genetic Counselors' task force report. *Journal of genetic counseling*, *15*(2), 77-83.

Robinson, C. L., Jouni, H., Kruisselbrink, T. M., Austin, E. E., Christensen, K. D., Green, R. C., & Kullo, I. J. (2016). Disclosing genetic risk for coronary heart disease: effects on perceived personal control and genetic counseling satisfaction. *Clinical genetics*, *89*(2), 251-257.

Rodriguez, L., & George, J. R. (2014). Is Genetic Labeling of" Risk" Related to Obesity Contributing to Resistance and Fatalism in Polynesian Communities?. *the contemporary pacific*, 65-93.

Sadeghi, M., Talaei, M., Parvaresh Rizi, E., Dianatkhah, M., Oveisgharan, S., & Sarrafzadegan, N. (2015). Determinants of incident prediabetes and type 2 diabetes in a 7-year cohort in a developing country: The Isfahan Cohort Study: *Journal of diabetes*, *7*(5), 633-641.

Sanderson, S. C., O'Neill, S. C., Bastian, L. A., Bepler, G., & McBride, C. M. (2010). What can interest tell us about uptake of genetic testing? Intention and behavior amongst smokers related to patients with lung cancer. *Public Health Genomics*, *13*(2), 116-124.

Santoro, M. L., Gadelha, A., Ota, V. K., Cunha, G. R., Asevedo, E., Noto, C. S., ... & Silva, P. N. (2015). Gene expression analysis in blood of ultra-high risk subjects compared to first-episode of psychosis patients and controls. *The World Journal of Biological Psychiatry*, *16*(6), 441-446.

Schellenberg, E. S., Dryden, D. M., Vandermeer, B., Ha, C., & Korownyk, C. (2013). Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. *Annals of internal medicine*, *159*(8), 543-551.

Schnittker, J. (2008). An uncertain revolution: Why the rise of a genetic model of mental illness has not increased tolerance. *Social science & medicine*, *67*(9), 1370-1381.

Senior, V., Marteau, T. M., & Peters, T. J. (1999). Will genetic testing for predisposition for disease result in fatalism? A qualitative study of parents responses to neonatal

screening for familial hypercholesterolaemia. *Social science & medicine*, *48*(12), 1857-1860.

Smit, F., Bolier, L., & Cuijpers, P. (2004). Cannabis use and the risk of later schizophrenia: a review. *Addiction*, *99*(4), 425-430.

Stevens, J. W., Khunti, K., Harvey, R., Johnson, M., Preston, L., Woods, H. B., ... & Goyder, E. (2015). Preventing the progression to type 2 diabetes mellitus in adults at high risk: a systematic review and network meta-analysis of lifestyle, pharmacological and surgical interventions. *Diabetes research and clinical practice*, *107*(3), 320-331.

Strauss, A., & Corbin, J. M. (1997). *Grounded theory in practice*. Sage.

Swami, M. (2011). New from NPG: Genome-wide association study identifies five new schizophrenia loci. *Nature Medicine*, *17*(10), 1199.

Tabák, A. G., Herder, C., Rathmann, W., Brunner, E. J., & Kivimäki, M. (2012). Prediabetes: a high-risk state for diabetes development. *The Lancet*, *379*(9833), 2279-2290.

Vähäsarja, K., Kasila, K., Kettunen, T., Rintala, P., Salmela, S., & Poskiparta, M. (2015). 'I saw what the future direction would be…': Experiences of diabetes risk and physical activity after diabetes screening. *British journal of health psychology*, *20*(1), 172-193.

Van Os, J., Rutten, B. P., & Poulton, R. (2008). Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophrenia bulletin*, *34*(6), 1066-1082.

van Rijn, S., Schothorst, P., van't Wout, M., Sprong, M., Ziermans, T., van Engeland, H., ... & Swaab, H. (2011). Affective dysfunctions in adolescents at risk for psychosis: emotion awareness and social functioning. *Psychiatry Research*, *187*(1-2), 100-105.

Vassy, J. L., O'Brien, K. E., Waxler, J. L., Park, E. R., Delahanty, L. M., Florez, J. C., ... & Grant, R. W. (2012). Impact of literacy and numeracy on motivation for behavior change after diabetes genetic risk testing. *Medical Decision Making*, *32*(4), 606-615.

Volkow, N. D., Swanson, J. M., Evins, A. E., DeLisi, L. E., Meier, M. H., Gonzalez, R., ... & Baler, R. (2016). Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. *JAMA psychiatry*, *73*(3), 292-297.

Wang, J., Zuo, X., Dai, Z., Xia, M., Zhao, Z., Zhao, X., ... & He, Y. (2013). Disrupted functional brain connectome in individuals at risk for Alzheimer's disease. *Biological psychiatry*, *73*(5), 472-481.

Widmer, C. L., Wolfe, C. R., Reyna, V. F., Cedillos-Whynott, E. M., Brust-Renck, P. G., & Weil, A. M. (2015). Tutorial dialogues and gist explanations of genetic breast cancer risk. *Behavior research methods*, *47*(3), 632-648.

Wilde, A., Meiser, B., Mitchell, P. B., & Schofield, P. R. (2010). Public interest in predictive genetic testing, including direct-to-consumer testing, for susceptibility to major depression: preliminary findings. *European Journal of Human Genetics*, *18*(1), 47.

Wolfe, C. R., Reyna, V. F., Widmer, C. L., Cedillos, E. M., Fisher, C. R., Brust-Renck, P. G., & Weil, A. M. (2015). Efficacy of a web-based intelligent tutoring system for communicating genetic risk of breast cancer: A fuzzy-trace theory approach. *Medical Decision Making*, *35*(1), 46-59.

Wolfe, C. R., Reyna, V. F., Widmer, C. L., Cedillos-Whynott, E. M., Brust-Renck, P. G., Weil, A. M., & Hu, X. (2016). Understanding genetic breast cancer risk: Processing loci of the BRCA Gist intelligent tutoring system. *Learning and individual differences*, *49*, 178-189