Title:
Psychiatric genetic counseling for serious mental illness: impact on psychopathology and psychotropic medication adherence

Authors: Emily Morris MSc*[1,2] & Rolan Batallones MA*[2], Jane Ryan MSc, MD, FRCPC^[2], Caitlin Slomp MSc^[2], Prescilla Carrion MSc[2], Arianne Albert, PhD[3], Jehannine Austin, PhD [1,2]

[1]Department of Medical Genetics, University of British Columbia, Vancouver, Canada
[2]Department of Psychiatry, University of British Columbia, Vancouver, Canada

[3]Women's Health Research Institute, BC Women's Hospital, Vancouver, BC

* ^ These authors contributed equally

Corresponding author:

Jehannine Austin,
UBC Departments of Psychiatry and Medical Genetics
Rm A3-112, 3rd Floor, Translational Lab Building,
938 W28th Ave, Vancouver, BC V5Z 4H4, Canada
Tel.: +1 604 875 2000x5943
fax: +1 604 875 3871
e-mail: jehannine.austin@ubc.ca

Running Title: Genetic counseling and psychiatric symptoms

ABSTRACT

For people with serious mental illness (SMI) (schizophrenia, bipolar disorder, schizoaffective disorder), psychiatric genetic counseling (PGC) has been shown to significantly increase empowerment and illness management self-efficacy. While these outcomes are important, they are also theoretical precursors for behaviour changes (e.g. improved medication adherence), and improved mental health. Therefore, we conducted the first study (repeated-measures/within-subjects design) to test the hypothesis that PGC would reduce psychiatric symptoms due to increased medication adherence. Between 2013-2018, we recruited N=109 individuals (age 19-72) with SMI and administered the short Positive and Negative Syndrome Scale (short-PANSS) and Brief Adherence Rating Scale (BARS) at four timepoints; twice Pre-PGC (T1: 1-month Pre-PGC and T2: immediately Pre-PGC), to assess change in adherence/symptoms without any intervention (internal control condition), and twice Post-PGC (T3: 1-month and T4: 2-months Post-PGC), to assess impact of PGC. A quantile regression model investigated the relationships between short-PANSS, timepoints, and BARS. There was a significant relationship between short-PANSS and timepoints at the 75th (T4 short-PANSS scores < T1 and T2) and 90th quantiles (T4 short-PANSS scores < T2), but these results were not explained by improved medication adherence. PGC for SMI may reduce psychiatric symptoms, but confirmatory work and studies to examine mechanism are needed.

Key Words: genetic counseling, medication adherence, serious mental illness

1. INTRODUCTION

Psychiatric disorders are common, and constitute the leading cause of disability in North America (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). The etiology of psychiatric disorders is complex and heterogeneous, typically resulting from the combined effects of genetic variants and environmental contributors; however, individuals with psychiatric illness often have misconceptions about the cause (Austin, Hippman, & Honer, 2012; Chong et al., 2016) and experience feelings of fear, guilt, shame, and stigma associated with the diagnosis.

Genetic counseling is an established healthcare service that is delivered by specialist trained healthcare professionals (Ormond et al., 2018), and psychiatric genetic counseling has emerged as a subspecialty within genetic counseling practice (Moldovan et al., 2019). Psychiatric genetic counseling explains the multifactorial etiology of mental illness (i.e. genetic

and environmental contributors) and is aimed at addressing misconceptions about etiology that often exist around mental illness and the emotions associated with these misconceptions (e.g. guilt, shame and stigma) (Austin, 2019; Inglis, Koehn, McGillivray, Stewart, & Austin, 2015; Inglis, Morris, & Austin, 2017). In using a heavily counseling-focused approach (Austin, Semaka, & Hadjipavlou, 2014) to help people understand cause of illness and its relationship to treatments, from a theoretical perspective, genetic counseling is conceptually rooted in the health beliefs model (Rosenstock, 1974). The health beliefs model is focused on helping people understand their condition and their perceived benefits and barriers to management strategies, but genetic counseling can overcome some of its limitations to produce behavior change by meaningfully attending to emotional barriers to behavior change (Austin, 2015; Kelly & Barker, 2016). While genetic *information* has been shown to be ineffective at producing behaviour change, genetic *counseling* is ideally positioned to do so (e.g. potentially including medication adherence) (Austin et al., 2014; Austin, 2015; Deacon & Baird, 2009; Kemp, Lickel, & Deacon, 2014; Schofield, Abdul-Chani, & Gaudiano, 2019).

In the context of psychiatric disorders, genetic counseling produces significant improvement in patient empowerment and self-efficacy to manage symptoms (Inglis et al., 2015; Moldovan, Pintea, & Austin, 2017), both of which have been postulated to be precursors to behavior change (Bravo et al., 2015; Holloway & Watson, 2002). Indeed, qualitative studies have documented an increase in protective behaviors (e.g. participants reported adopting better strategies for sleep, nutrition, and exercise) and improved mental health after psychiatric genetic counseling (Semaka & Austin, 2019). In non-psychiatric settings (pediatrics and cancer) genetic counseling has been shown to increase adherence to medical management recommendations (Hadley et al., 2004; Rutherford, Zhang, Atzinger, Ruschman, & Myers, 2014). However,

despite the need for interventions to improve psychotropic medication adherence, no studies have quantitatively investigated the impact of genetic counseling on mental health or health behaviors (Burkhart & Sabate, 2003; Goff, Hill, & Freudenreich, 2010; Lingam & Scott, 2002).

The purpose of this study was to examine the effect of psychiatric genetic counseling for people with serious mental illness (SMI – schizophrenia, bipolar disorder, schizoaffective disorder) on psychiatric symptoms (specifically psychotic symptoms) and psychotropic medication adherence. We hypothesized that psychiatric genetic counseling would reduce psychotic symptoms, and that this would be mediated by improved psychotropic medication adherence. Because the patient-counselor relationship has been documented to be a key component of psychological interventions (Horvath & Symonds, 1991), we also explored relationships between any change in psychiatric symptoms after psychiatric genetic counseling and the bond between the patient and the counselor.

2. METHODS

2.1 Design

We conducted a study to explore the effect of genetic counseling on psychiatric symptoms and medication adherence using a repeated measures/within subjects design. First, all participants completed assessments at two timepoints separated by a month during which there was no intervention, and then completed the assessments again after receiving the intervention. This allowed us to compare change in outcomes between the two timepoints during which there was no intervention (an internal control condition), with change between pre and post intervention.

2.2 Recruitment and procedures

Between 2013 and 2018, we recruited 110 individuals with SMI (i.e. bipolar disorder, schizoaffective disorder, or schizophrenia) who were >18 years old and fluent in English from community-based mental health agencies, and by placing advertisements (e.g. Craigslist) in metro Vancouver and Victoria, Canada. To determine eligibility for the study, psychiatric diagnosis (bipolar disorder, schizophrenia, or schizoaffective disorder) was confirmed by structured clinical interview for DSM-IV (SCID) (First, Spitzer, Gibbon, Williams, 1997) administered by a trained team member by phone or in person (at the research institute), according to the needs of the participant. We chose to include individuals with bipolar disorder type II (in addition to individuals with bipolar disorder type I) because while the presence of psychosis during a manic episode precludes a diagnosis of bipolar disorder type II, individuals with bipolar disorder type II can (and do) experience psychosis in the context of depressive episodes (Mazzarini et al., 2010). Eligible participants completed four study visits: Timepoint 1 (T1), Timepoint 2 (T2), Timepoint 3 (T3) and Timepoint 4 (T4), each ~1 month apart) (See Figure 1).

<< Insert Figure 1 >>

At T1 we collected demographic information, administered the Brief Adherence Rating Scale (BARS) (Byerly, Nakonezny, & Rush, 2008) for each prescribed psychotropic medication (i.e. mood stabilizers, anti-depressants, and anti-psychotic medications) for their psychiatric diagnosis. We did not collect data on medications prescribed for unrelated reasons. We also conducted the short Positive and Negative Syndrome Scale (short-PANSS) (Kay, Fiszbein, & Opler, 1987). These same measures were completed again at T2 (one month after T1). As there was no intervention between T1 and T2, this design allowed participants to be their own internal control. Participants then received psychiatric genetic counseling (as described below)

immediately following the completion of measures at T2 (See Figure 1). At T3 (one month after T2), and at T4 (one month after T3) BARS and PANSS were repeated again to assess any impact of the intervention. Additionally, immediately after receiving genetic counseling, each participant and the genetic counselor completed four items from the Working Alliance Inventory – Short proposed bond subscale (Tracey & Kokotovic, 1989), with the genetic counselor and participant each completing independent ratings, Bond-GC and Bond-PT respectively.

All procedures involving human subjects/patients were approved by UBC Research Ethics Board (study ID: H12-01087). Written informed consent was obtained from all participants.

2.3 Intervention: Psychiatric Genetic Counseling

We report the details of the intervention provided according to the reporting standards for genetic counseling research (Hooker, Babu, Myers, Zierhut, & McAllister, 2017). Four board-certified genetic counselors and a psychiatrist (who was not involved in the clinical care of the participants) provided in-person genetic counseling to participants in this study. To ensure standardization of the intervention delivered between participants, all providers: completed training with and were approved as competent to provide psychiatric genetic counseling by the senior/corresponding author, and used a manual in delivering the psychiatric genetic counseling, completing a checklist for each participant (see Supplementary Material). All genetic counseling sessions included in this study adhered to the checklist protocol. Further, all providers participated in peer supervision sessions every two weeks, in which practice was reflected upon and discussed with peers with a view to ensuring quality and consistency of sessions.

The genetic counseling provided used a patient-centered, counseling oriented approach, with attention paid to issues around guilt, fear, blame, and stigma that patients attach to

explanations for cause of illness. This process is outlined in the Reciprocal Engagement Model (Veach, Bartels, & Leroy, 2007), and described in detail as it applies to psychiatric disorders specifically elsewhere (Austin, 2019; Peay & Austin, 2011). In brief, after establishing a mutually agreeable agenda for the session that addressed the participant's questions and concerns, and eliciting the participant's current existing explanation for the cause of their mental illness, the counselor documented a detailed three-generation psychiatric family history. This family history was then used together with visual counseling aids to help participants understand what research reveals about the etiology of mental illness. Discussion focused on helping participants understand that genes and environment work together to precipitate mental illness, and how mental health can be protected. Strategies for managing and protecting mental health (sleep, nutrition, exercise, social support, finding effective ways for managing stress, and medication) were discussed in the context of what is known about the etiology of mental illness. Throughout the session, this discussion was personalized as far as possible – e.g. by discussing specific strategies the participant uses, or has used and found helpful in maintaining better mental health. No genetic testing was provided. At the end of the genetic counseling appointment, all participants were provided an educational booklet that contained generalized information about the causes of SMI (Hippman et al., 2016), as a take-home resource.

2.4 Measures

2.4.1 Positive and Negative Syndrome Scale (PANSS) (Psychosis)

The PANSS is a well-validated instrument (completed by a clinically trained rater, on the basis of a semi-structured interview) that measures the presence and severity of psychiatric symptoms(Kay et al., 1987). Five of the PANSS items (delusions, conceptual disorganization, hallucinatory behaviour, suspiciousness, and unusual thought content) can be used to assess the

severity of symptoms of psychosis (short-PANSS). Each symptom is rated on a 7-point scale; a score of 1 means the symptom is not present, and a score of 3 indicates that a symptom of psychosis is present to a mild degree. Increasing scores indicate increasing severity with a score of 7 indicating that symptoms are present to an extreme degree. Thus total scores on the short-PANSS range from 5 (absent symptoms) to 35 (extreme symptoms). A score of 15, for example, would indicate that, on average, symptoms of psychosis are present, but to a mild degree. The PANSS was administered by a clinically trained member of the research and who participated in regular PANSS training sessions to ensure ratings aligned with the instrument's standards.

2.4.2 Adherence measure: Brief Adherence Rating Scale (BARS)

The BARS is a validated, clinician-administered instrument for measuring medication adherence. It has excellent internal reliability (α=0.9), and good test-retest reliability *(r* =0.74-0.86, *p*< .01) (Byerly et al., 2008). The BARS contains three questions for each prescribed medication relating to: 1) how many pills the individual was instructed to take per day, 2) how many days the individual did not take their pills, and 3) how many days they took less than the prescribed number. These three questions are used to guide responses to the final outcome measure of the scale, which is an overall visual analog rating scale which asks the rater to indicate the proportion of doses taken in the past month (0-100%) for each medication that an individual is prescribed. A BARS score cut-off of ≤70% has been shown to maximize both sensitivity (73%) and specificity (71%) in detecting psychotropic medication non-adherence (as determined by comparison to the electronic medical record) (Byerly et al., 2008).

2.4.3 Bond – a subscale of Working Alliance Inventory-Short

Working Alliance Inventory – Short proposed bond subscale consists of four items rated on a Likert-scale, ranging from 1=never to 7=always endorsing aspects of a bond between

patient and counselor (Tracey & Kokotovic, 1989). Mean scores are calculated separately for client and counselor.

2.5 Analyses

2.5.1 Impact of psychiatric genetic counseling on psychiatric symptoms

Given that psychotic symptoms exist within the general population along a continuum (DeRosse and Karlsgodt, 2015), we calculated total PANSS scores as a continuous variable rather than categorizing individuals as meeting criteria for psychosis or not based on a threshold score. Due to the skewed distribution of the short-PANSS total scores (See Supplemental Data), to test our hypothesis that psychiatric genetic counseling reduces psychiatric symptoms, we used a quantile regression (Koenker, 2004), with Holm-corrected p-values, to evaluate how the distribution of PANSS scores changed over time. Quantile regression is useful when evaluation of the mean is not informative (Koenker, 2004); for example, in the context of our data, where the mean (and median) at all timepoints was the lowest possible PANSS score (i.e. absent symptoms). Given that the most informative analysis involves exploring the effect of the intervention among those who had clinically significant symptoms, quantile regression allowed us to investigate how scores of individuals with PANSS scores in the 75th and 90th quantiles (i.e. the 25% and 10% of individuals with most symptoms, respectively) changed, with differences between T1 and T2 representing changes after no intervention, and differences between T2 and T3 or T4 representing changes after receiving psychiatric genetic counseling. We also calculated mean BARS scores for all psychotropic medications at each timepoint, and added mean BARS scores at each timepoint to our model as a covariate to investigate the impact of adherence on the PANSS score quantiles.

To explore the relationship between any change in PANSS scores observed 2-months after psychiatric genetic counseling (by subtracting T4 scores from T2) and bond scores, we used Mann-Whitney U-Test to compare bond scores (for both Bond-PT and Bond-GC) between the participants who did and did not have any decrease in total PANSS scores.

2.5.2 Exploratory analysis: Impact of psychiatric genetic counseling on treatment adherence

Due to the mean BARS scores being very skewed, and the majority of participants reaching "adherent" thresholds (see above) on the BARS at all timepoints, we excluded participants who were "adherent" at all timepoints to further explore the impact of psychiatric genetic counseling on adherence. We categorized participants as "adherent" at a given timepoint if they scored >70% on the BARS for *all* their psychotropic medications; thus, participants were categorized as "non-adherent" if they scored ≤70% on the BARS for one or more of their prescribed psychotropic medications (Byerly et al., 2008). Participants who were not engaged with psychiatric care (i.e. not prescribed any psychotropic medications) at a given timepoint were also categorized as "non-adherent" for that timepoint. We then used a mixed effect logistic regression to compare the proportion of "adherent" participants across all four timepoints, with any changes in the proportion of those who were adherent between T1 and T2 serving as our internal control to contextualize any changes observed from T2 to after psychiatric genetic counseling (T3 or T4).

A significance threshold (α) of $p < .05$ was applied, with all analyses performed using IBM SPSS Statistics version 24 (IBM Corp. Armonk, N. Y) and R Statistical Software v3.5.3 (R Core Team (2019)). Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at BC Children's Hospital Research Institute (Harris et al., 2008). REDCap is a secure, web-based software platform designed to support data capture for research

studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

3. RESULTS

There were 109 participants who met diagnostic criteria on the SCID and enrolled in the study (Figure 1). At enrollment, n=7 individuals were not engaged with any psychiatric care (and therefore were not prescribed any psychotropic medications). Of the 102 individuals taking psychotropic medications at enrollment, 5 were only receiving medication via injection. See Table 1 for demographics. Both genetic counselors and participants rated e their bond as high (Bond-GC mean=5.96, Bond-PT mean=5.88 (i.e. both "very often" endorsing a strong bond)), with the majority (89% and 90% respectively) indicating at least a mean WAI score of 5 (i.e. "often" endorsing a strong bond). The PANSS and Bond scores demonstrated strong internal consistency - PANSS T1 $\alpha = 0.77$; T2 $\alpha = 0.80$; T3 $\alpha = 0.82$, T4 $\alpha=0.82$; Bond- GC $\alpha=0.90$ and Bond-PT $\alpha=0.84$.

<<Insert Table 1>>

3.1 Impact of psychiatric genetic counseling on psychiatric symptoms

The majority of participants (56/100) had completely absent symptoms (i.e. score of 5 on the short-PANSS) immediately prior to genetic counseling (T2). There was a significant relationship between short-PANSS and timepoints at the 75^{th} quantile and 90^{th} quantile; 75^{th} quantile having lower T4 short-PANSS scores than T1 ($p=0.002$) and T2 ($p=0.02$), and the 90^{th} quantile having lower T4 short-PANSS scores than T2 ($p=0.05$) (see Table 2). There was no relationship between the short-PANSS quantile scores and mean BARS scores at any timepoint.

<<Insert Table 2 here>>

3.2 Relationship between decrease in psychiatric symptoms and patient and counselor bond

There was no significant difference in the Bond-PT scores between those who had decreases (2 months after genetic counseling) in short-PANSS scores and those who did not (U=886, p=0.910, d=0.03); however, there was a significant difference in Bond-GC scores (U=551, p=0.003, d=0.64) - Bond-GC scores were lower for participants who had decreases in short-PANSS scores (2 months after genetic counseling) (See Table 3).

<<Insert Table 3 Here>>

3.3 Exploratory analysis: Impact of psychiatric genetic counseling on adherence

The majority (n=77, 71%) of participants were adherent (as defined by validated BARS criteria described above) at T1 and remained adherent for all completed study timepoints. After excluding these (n=77) participants who were "adherent" at all completed timepoints, there were 31 participants remaining with medication data for at least one timepoint (See Supplemental Table 1). These 31 participants included in our mixed effects logistic regression analysis, had118 observations (adherent = yes/no) across all four timepoints (6 observations were missing due to some participants missing adherence data for a given timepoint). There were no significant relationships between the proportion of adherent individuals and timepoint (p=0.40); however, the proportion of adherent individuals was greatest (48%) (average percent adherent = 48.1, 95%CI (27.6-69.3) at T4 (2 months after psychiatric genetic counseling) and lowest (29%) (average percent adherent = 24.9, 95%CI (11.4-46.2) at T2 (after no intervention, immediately prior to psychiatric genetic counseling) (See Supplemental Data).

For the participants who did not remain adherent throughout the entire study, change (or lack thereof) in adherence status (e.g. "Non-adherent" to "Adherent") from T1 to T2 (after no

intervention) and from T2 to T4 (two months after receiving psychiatric genetic counseling) is depicted in Figure 2.

<<Insert Figure 2 >>

Descriptive demographics of the participants depicted in Figure 2 who became adherent after psychiatric genetic counseling (i.e. were "non-adherent" at T2 but "adherent" by T4 (green line in Fig1A &B)) is displayed in Supplementary Table 1.

4. DISCUSSION

Our data show that the majority of participants in our study had no symptoms of psychosis upon enrollment and remained asymptomatic over the course of the study. In our analysis of participants who had the most symptoms (75^{th} and 90^{th} quantiles) prior to genetic counseling, however, we found a significant decrease in symptoms of psychosis after genetic counseling, which is not explained by increased adherence to psychiatric medications. To our knowledge, no studies have investigated the impact of genetic counseling on psychopathology to which we can compare our findings. Our results, however, are broadly in line with a recent qualitative study exploring the process and outcomes of psychiatric genetic counseling, which found that participants felt less stigmatized and more supported and empowered about their mental illness and medication, but reported that their medication adherence remained the same (Semaka & Austin, 2019), suggesting that the decrease in psychopathology observed in our study may be due to factors other than medication adherence. Interestingly, our exploratory analysis of counselor-participant bond found that there was no difference in how the participants rated the degree of their bond with the counselor when their mental health improved (i.e. fewer psychiatric symptoms) compared to when there was no improvement. Previous research has documented a relationship between the therapeutic alliance and psychotherapy outcomes (Horvath, Del Re,

Fluckiger, & Symonds, 2011); however, in our data Bond-PT scores were high regardless of outcome. Further studies exploring how the process of genetic counseling facilitates these improvements to mental health are warranted.

However, we did find that counselors rated their bond with the participant as lower in the group that had improved mental health (i.e. fewer psychotic symptoms) after genetic counseling. Differences in how clients and counselors rate working alliance has been found in other studies in populations of people with SMI (Ruchlewska et al., 2016). Since the participants that had fewer psychotic symptoms (i.e. decrease in short-PANSS scores) after psychiatric genetic counseling are also the participants who would have at least some symptoms (i.e. short-PANSS scores >5) immediately prior to genetic counseling, these results are likely a reflection of the genetic counselor feeling less certain about their rapport (and reporting lower WAI scores) with participants who were exhibiting active symptoms. While the participants in our study tended to have symptoms that were mild in severity, these results provide reassurance that even patients with active symptoms can potentially benefit from psychiatric genetic counseling, and that the bond with the counselor from the patients' perspective is not negatively impacted.

When we examined those who were not fully adherent throughout the entire study, the proportion of people who were adherent to their medications was lowest at T2 (29%) and greatest at T4 (48%), however, this increase was not significant; perhaps due to the smaller sample size for this test (which limited power), arising from the fact that participants were predominantly adherent and remained adherent throughout the study. Since studies have suggested that providing patients with a "biogenetic" or biological explanation of illness may improve perceptions of medication benefits and potentially adherence (Deacon & Baird, 2009; Kemp et al., 2014; Schofield et al., 2019), and genetic counseling has been shown to improve

understanding of cause of illness (and thus genetic contributors) for a variety of complex disorders, including psychiatric disorders (Hippman et al., 2016; Scherr, Christie, & Vadaparampil, 2016), larger studies with individuals who are struggling to take their medications are needed to fully assess the impact of psychiatric genetic counseling on treatment adherence.

4.1 Limitations

While the rate of non-adherence in populations of people with SMI is reported to be high (Burkhart & Sabate, 2003), only 20% of our total study population (See Figure 2) were classified as non-adherent immediately prior to psychiatric genetic counseling (i.e. at T2). Additionally, the majority (56%) of participants had completely absent psychotic symptoms immediately prior to genetic counseling. This limited the participants in our study for whom we could assess improvements to adherence and psychotic symptoms. With only 31 participants for whom we could assess improvements to adherence, we were underpowered to detect anything but very large effects. Our highly adherent participant population also suggests ascertainment bias; individuals who were struggling to take their psychotropic medications as prescribed and/or who were experiencing active symptoms of psychosis, were less likely to participate in the study. Relatedly, our study population primarily consisted of an outpatient population and may not be generalizable to patients primarily in inpatient settings. Additionally, while our categorization of the 7 individuals not engaged with pharmaceutical psychiatric care at enrollment as "non-adherent", was in-part based on the nature of their diagnoses (bipolar disorder type 1 and schizophrenia), and the fact that some of these individuals resumed adherence to pharmaceutical treatment over the course of the study, there may be medical reasons for why they were not taking medications that were not obtained in this study. Further studies are needed to assess impacts of psychiatric genetic counseling on broader psychopathology and medication adherence

over a timeframe longer than was followed in the context of this study; we only looked at psychosis symptoms, and it is possible that other psychiatric symptoms that we did not measure were influenced by the genetic counseling. This should be explored in future research.

It is also difficult to comment on the clinical importance of the decrease in psychiatric symptoms observed in our study. Studies have suggested that minimum clinically important difference (MCID) can be approximated by using half a standard deviation (SD) of the change (Norman, Sloan, & Wyrwich, 2003). Using this estimation for MCID in our population (SD of change in short-PANSS scores from T2 to T4 = 3.0, thus MCID = 1.5) suggests that there appears to be meaningful *and* statistically significant decreases two months after genetic counseling for individuals with PANSS scores at the 75^{th} and 90^{th} quantile prior to genetic counseling (See Table 2); however, further studies investigating the MCID for the short-PANSS are needed, as current MCID estimates are based on the full-scale PANSS and are not directly applicable to the short-PANSS. Finally, our results may be influenced by participants with more psychopathology at baseline potentially being more likely to drop out of the study; however, there were no significant differences in T2 PANSS scores between those who dropped out of the study, and those who completed T4 assessments ($U=342$, $p= 0.07$). While randomized control trials (RCTs), are ideal for evaluating the impact of an intervention, our study design, using an internal control design (outcomes were measured at T1 and T2 with no intervention) provides preliminary data on which to base future studies.

We also chose to focus only on the bond aspect of the patient-counselor working alliance, and thus our results cannot be used to draw conclusions about the role of working alliance as a whole. Further it is also possible that other, non-pharmaceutical treatments that participants were

engaged with over the course of the study influenced symptoms and this could be explored in future research.

Finally, though it may have been ideal to look only at adherence to antipsychotic/mood stabilizing medications in our analyses, issues regarding off label drug use for example, precluded complete certainty regarding how each psychotropic drug was being used for each individual patient.

4.2 Conclusion

Our data suggest that psychiatric genetic counseling reduces some psychiatric symptoms in individuals with SMI, compared to when they receive no intervention, which appears to not be explained by improved medication adherence. Larger studies, purposively sampled for individuals for whom medication adherence is a problem, and investigation of other psychiatric outcomes would provide further insight into the impact of psychiatric genetic counseling on medication adherence and mental health.

ACKNOWLEDGMENTS

This work was supported financially by Pfizer Canada (# 53234767). Pfizer Canada had no role in the design, analysis, interpretation or publication of this study. Dr. Austin was supported by BC Mental Health and Substance Use Services, and the Canada Research Chairs program. The authors thank the BC Schizophrenia Society, Mood Disorders Association of BC, The Kettle Society, Coast Foundation, and the Vancouver Coastal Health and Vancouver Island Health Authority community mental health teams for their help with recruitment. The authors thank all members of the Translational Psychiatric Genetics Group for their support, and the

numerous volunteers over the years who helped with data entry. The authors would also like to thank the participants who generously participated in the study.

REFERENCES

Austin, J. C. (2019). Evidence-based genetic counseling for psychiatric disorders: A road map. *Cold Spring Harbor Perspectives in Medicine,* doi:a036608 [pii]

Austin, J., Semaka, A., & Hadjipavlou, G. (2014). Conceptualizing genetic counseling as psychotherapy in the era of genomic medicine. *Journal of Genetic Counseling, 23*(6), 903-909. doi:10.1007/s10897-014-9728-1 [doi]

Austin, J. (2015). The effect of genetic test-based risk information on behavioral outcomes: A critical examination of failed trials and a call to action. *American Journal of Medical Genetics.Part A, 167A*(12), 2913-2915. doi:10.1002/ajmg.a.37289

Austin, J. C., Hippman, C., & Honer, W. G. (2012). Descriptive and numeric estimation of risk for psychotic disorders among affected individuals and relatives: Implications for clinical practice. *Psychiatry Research, 196*(1), 52-56. doi:10.1016/j.psychres.2012.02.005

Bravo, P., Edwards, A., Barr, P. J., Scholl, I., Elwyn, G., McAllister, M., & Cochrane Healthcare Quality Research Group, Cardiff University. (2015). Conceptualising patient empowerment: A mixed methods study. *BMC Health Services Research, 15*, 252-z. doi:10.1186/s12913-015-0907-z [doi]

Burkhart, P. V., & Sabate, E. (2003). Adherence to long-term therapies: Evidence for action. *Journal of Nursing Scholarship : An Official Publication of Sigma Theta Tau International Honor Society of Nursing, 35*(3), 207.

Byerly, M. J., Nakonezny, P. A., & Rush, A. J. (2008). The brief adherence rating scale (BARS) validated against electronic monitoring in assessing the antipsychotic medication adherence of outpatients with schizophrenia and schizoaffective disorder. *Schizophrenia Research, 100*(1-3), 60-69. doi:10.1016/j.schres.2007.12.470 [doi]

Chong, H. Y., Teoh, S. L., Wu, D. B., Kotirum, S., Chiou, C. F., & Chaiyakunapruk, N. (2016). Global economic burden of schizophrenia: A systematic review. *Neuropsychiatric Disease and Treatment, 12*, 357-373. doi:10.2147/NDT.S96649 [doi]

Deacon, B. J., & Baird, G. L. (2009). The chemical imbalance explanation of depression: Reducing blame at what cost? *Journal of Social and Clinical Psychology, 28*(4), 415-435. doi:10.1521/jscp.2009.28.4.415

DeRosse, P., Karlsgodt, K.H., 2015. Examining the Psychosis Continuum. Current behavioral neuroscience reports 2, 80-89.

First, MB, Spitzer, RL, Gibbon ,M, Williams, JBW. (1997). Structured clinical interview for DSM-IV axis I disorders- clinician version (SCID-CV). *American Psychiatric Press,*

Goff, D. C., Hill, M., & Freudenreich, O. (2010). Strategies for improving treatment adherence in schizophrenia and schizoaffective disorder. *The Journal of Clinical Psychiatry, 71 Suppl 2*, 20-26. doi:10.4088/JCP.9096su1cc.04 [doi]

Hadley, D. W., Jenkins, J. F., Dimond, E., de Carvalho, M., Kirsch, I., & Palmer, C. G. (2004). Colon cancer screening practices after genetic counseling and testing for hereditary nonpolyposis colorectal cancer. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 22*(1), 39-44. doi:10.1200/JCO.2004.06.128 [doi]

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2008). Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics, 42*(2), 377-381. doi:10.1016/j.jbi.2008.08.010

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), 190. doi:10.4088/JCP.14m09710 [doi]

Holloway, A., & Watson, H. E. (2002). Role of self-efficacy and behaviour change. *International Journal of Nursing Practice, 8*(2), 106-115.

Hooker, G. W., Babu, D., Myers, M. F., Zierhut, H., & McAllister, M. (2017). Standards for the reporting of genetic counseling interventions in research and other studies (GCIRS): An NSGC task force report. *Journal of Genetic Counseling, 26*(3), 355-360. doi:10.1007/s10897-017-0076-9 [doi]

Horvath, A. O., Del Re, A. C., Fluckiger, C., & Symonds, D. (2011). Alliance in individual psychotherapy. *Psychotherapy (Chicago, Ill.), 48*(1), 9-16. doi:10.1037/a0022186 [doi]

Horvath, A. O., & Symonds, B. D. (1991). Relation between working alliance and outcome in psychotherapy: A meta-analysis. *Journal of Counseling Psychology, 38*(2), 139-149. doi:10.1037/0022-0167.38.2.139

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. doi:10.1111/cge.12415 [doi]

Inglis, A., Morris, E., & Austin, J. (2017). Prenatal genetic counselling for psychiatric disorders. *Prenatal Diagnosis, 37*(1), 6-13. doi:10.1002/pd.4878 [doi]

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*(2), 261-276.

Kelly, M. P., & Barker, M. (2016). Why is changing health-related behaviour so difficult? *Public Health, 136*, 109-116. doi:10.1016/j.puhe.2016.03.030 [doi]

Kemp, J. J., Lickel, J. J., & Deacon, B. J. (2014). Effects of a chemical imbalance causal explanation on individuals' perceptions of their depressive symptoms. *Behaviour Research and Therapy, 56*, 47-52. doi:10.1016/j.brat.2014.02.009 [doi]

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry, 62*(6), 617-627. doi:10.1001/archpsyc.62.6.617

Koenker, R. (2004). *Quantile regression for longitudinal data* doi://doi.org/10.1016/j.jmva.2004.05.006

Lingam, R., & Scott, J. (2002). Treatment non-adherence in affective disorders. *Acta Psychiatrica Scandinavica, 105*(3), 164-172. doi:1r084 [pii]

Mazzarini, L., Colom, F., Pacchiarotti, I., Nivoli, A.M.A., Murru, A., Bonnin, C.M., Cruz, N., Sanchez-Moreno, J., Kotzalidis, G.D., Girardi, P., Tatarelli, R., Vieta, E., 2010. Psychotic versus non-psychotic bipolar II disorder. J. Affect. Disord. 126, 55-60.

Moldovan, R., Pintea, S., & Austin, J. (2017). The efficacy of genetic counseling for psychiatric disorders: A meta-analysis. *Journal of Genetic Counseling, 26*(6), 1341-1347. doi:10.1007/s10897-017-0113-8 [doi]

Moldovan, R., McGhee, K. A., Coviello, D., Hamang, A., Inglis, A., Ingvoldstad Malmgren, C., . . . Austin, J. C. (2019). Psychiatric genetic counseling: A mapping exercise. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 0*(0) doi:10.1002/ajmg.b.32735

Norman, G. R., Sloan, J. A., & Wyrwich, K. W. (2003). Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. *Medical Care, 41*(5), 582-592. doi:10.1097/01.MLR.0000062554.74615.4C [doi]

Ormond, K. E., Laurino, M. Y., Barlow-Stewart, K., Wessels, T., Macaulay, S., Austin, J., & Middleton, A. (2018). Genetic counseling globally: Where are we now? *American Journal*

of Medical Genetics.Part C, Seminars in Medical Genetics, 178(1), 98-107. doi:10.1002/ajmg.c.31607

Peay, H., & Austin, J. (2011). *How to talk with families about: Genetics and psychiatric illness*. New York, NY, US: W W Norton & Co.

Rosenstock, I. M. (1974). Historical origins of the health belief model. *Health Education Monographs, 2*(4), 328-335. doi:10.1177/109019817400200403

Ruchlewska, A., Kamperman, A.M., van der Gaag, M., Wierdsma, A.I., Mulder, N.C.L., 2016. Working Alliance in Patients with Severe Mental Illness Who Need a Crisis Intervention Plan. Community Ment. Health J. 52, 102-108.

Rutherford, S., Zhang, X., Atzinger, C., Ruschman, J., & Myers, M. F. (2014). Medical management adherence as an outcome of genetic counseling in a pediatric setting. *Genetics in Medicine : Official Journal of the American College of Medical Genetics, 16*(2), 157-163. doi:10.1038/gim.2013.90 [doi] Scherr, C. L., Christie, J., & Vadaparampil, S. T. (2016). Breast cancer survivors' knowledge of hereditary breast and ovarian cancer following genetic counseling: An exploration of general and survivor-specific knowledge items. *Public Health Genomics, 19*(1), 1-10. doi:10.1159/000439162 [doi]

Schofield, C. A., Abdul-Chani, M., & Gaudiano, B. A. (2019). Impact of causal explanations for social anxiety disorder on stigma and treatment perceptions. *Journal of Mental Health,* , 1-8. doi:10.1080/09638237.2018.1487543

Semaka, A., & Austin, J. (2019). Patient perspectives on the process and outcomes of psychiatric genetic counseling: An “Empowering encounter”. *Journal of Genetic Counseling, 0*(0) doi:10.1002/jgc4.1128

Tracey, T. J., & Kokotovic, A. M. (1989). Factor structure of the working alliance inventory. *Psychological Assessment: A Journal of Consulting and Clinical Psychology, 1*(3), 207-210. doi:10.1037/1040-3590.1.3.207

Veach, P. M., Bartels, D. M., & Leroy, B. S. (2007). Coming full circle: A reciprocal-engagement model of genetic counseling practice. *Journal of Genetic Counseling, 16*(6), 713-728. doi:10.1007/s10897-007-9113-4 [doi]

Table 1. Demographics

DEMOGRAPHICS	**N=109**
Age	
Mean (SD), Median (Range)	41.73 (13.59), 42.0 (19-72)
Gender %(n)	
Male	43.1(47)
Female	55.0(60)
Transgender	1.8(2)
Diagnosis %(n)	
Bipolar Disorder 1	51.4(56)
Bipolar Disorder 2	14.7(16)
Schizoaffective Disorder	12.8(14)
Schizophrenia	21.1(23)
Ethnicity %(n)	
European	77.1(84)
Asian	13.8(15)
Aboriginal	2.8(3)
Mixed	6.4(7)
Marital Status %(n)	
Single	81.7(89)
Married/Common-law	18.3(20)
Housing %(n)	
Lives alone	43.5(47)
Lives with someone	50.9(55)
Lives in a group home	5.6(6)
Household Income %(n)	
Below 20,000	58.3(63)
20,001 - 40,000	21.3(23)
40,001 – 60,000	10.2(11)
60,001 – 100,000	8.3(9)
>100,000	1.9(2)
Education %(n)	
Completed highschool	93.6(102)
Attended college/university	83.5(91)
Employment %(n)	
Employed	36.7(40)
Not Employed	49.5(54)
Volunteer Work	13.8(15)

Followed by a psychiatrist upon enrollment %(n)	
Yes	78.9(86)
No	21.1(23)

Table 2 Short-PANSS (higher short-PANSS = greater severity of psychiatric symptoms) scores[1] which define the 50th, 75th, and 90th Quantile.

	PANSS Scores	**p-value for comparison to T1 score**	**p-value for comparison to T2 score**
50th Quantile			
T1	5		1.0
T2	5	1.0	
T3	5	1.0	1.0
T4	5	1.0	1.0
75th Quantile			
T1	9		1.0
T2	9	1.0	
T3	7	0.07	0.07
T4	6	.002*	.02*
90th Quantile			
T1	11		.43
T2	12	.43	
T3	10	.46	0.07
T4	8	.06	.05*

[1] Change (T2 to T4) in PANSS scores: Mean (-0.93), SD (3.0), Minimal Clinically Important Difference (MCID), using half a standard deviation (SD) of the change = 1.5 (Norman et al., 2003).

Table 3. Bond scores determined by the genetic counselor (Bond-GC) and the participant (Bond-PT) shown for those who had a decrease in short-PANSS scores (i.e. less psychiatric symptoms) and those whose short-PANSS scores remained the same/increased.

	No decrease in PANSS Score n=58*	**Decrease in PANSS Score** n=31	p	d
Bond-GC			0.003	0.64
Mean (SD)	6.1 (0.77)	5.6 (0.87)		
Median (SEM)	6.25 (0.10)	5.75 (0.16)		
95% CI Median	6.0 - 6.5	5.25-6.25		
Bond-PT			0.910	0.03
Mean (SD)	5.93 (0.88)	5.90 (0.79)		
Median (SEM)	5.88 (0.12)	6.0 (0.14)		
95% CI Median	5.75 - 6.38	5.75 – 6.25		

*n=43 had absent PANSS (score=5) symptoms at both timepoints (T2 and T4).

Figure 1. Participant recruitment, eligibility determined by the structured clinical interview for DSM-IV (SCID), study procedures, and participant drop-out (i.e. lost to follow-up)

Figure 2. Adherence status (adherent (>70% to all psychotropic medications) or non-adherent (≤70% to any psychotropic medication)) at T1 and T2 (after no intervention), and T4 (after psychiatric genetic counseling (PGC). Participants who were not prescribed any psychotropic medications at a given timepoint were categorized as "non-adherent" for that timepoint.
A) Adherence status over the course of the study for participants who were adherent at enrollment (T1).

[a] 2 participants who were adherent at enrollment are not depicted due to missing data at T4.

[b] While these 2 participants were adherent at T1, T2, and T4, they were non-adherent at T3 and thus were not excluded (i.e, we only excluded n=77 participants who were adherent at *all* timepoints).

B) Adherence status over the course of the study for participants who were non-adherent at enrollment (T1).

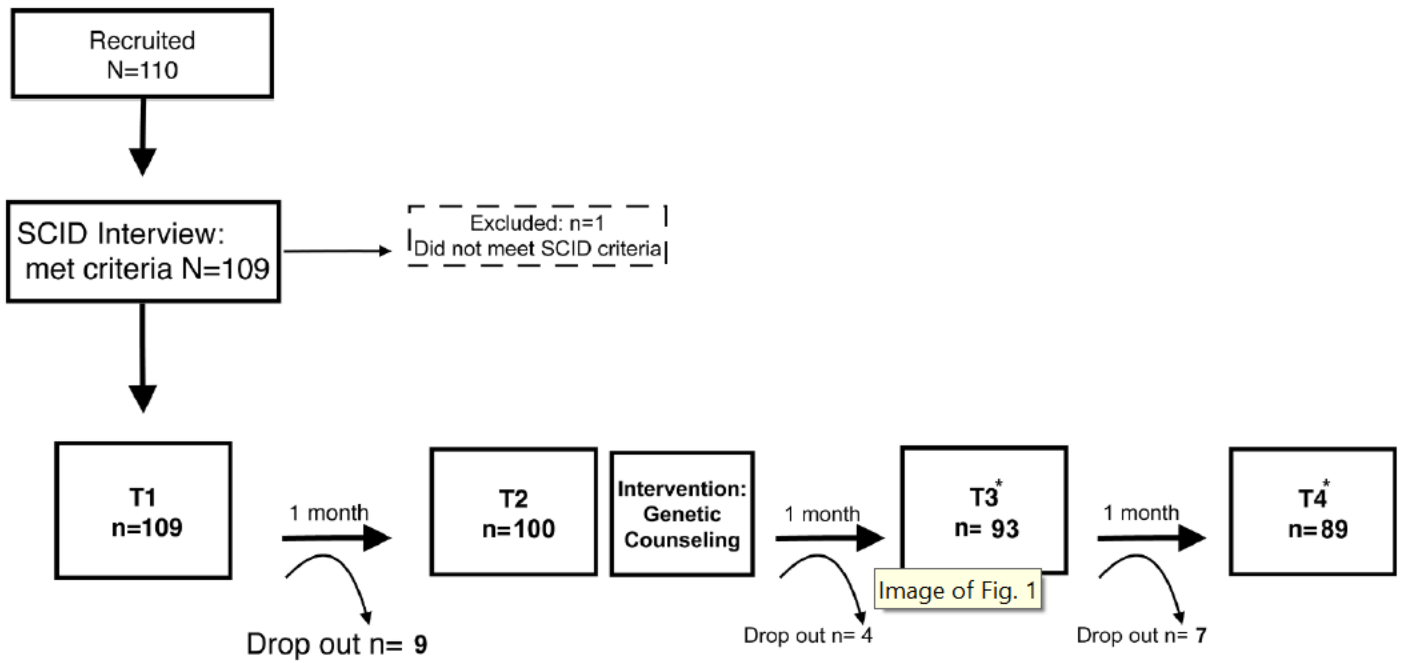
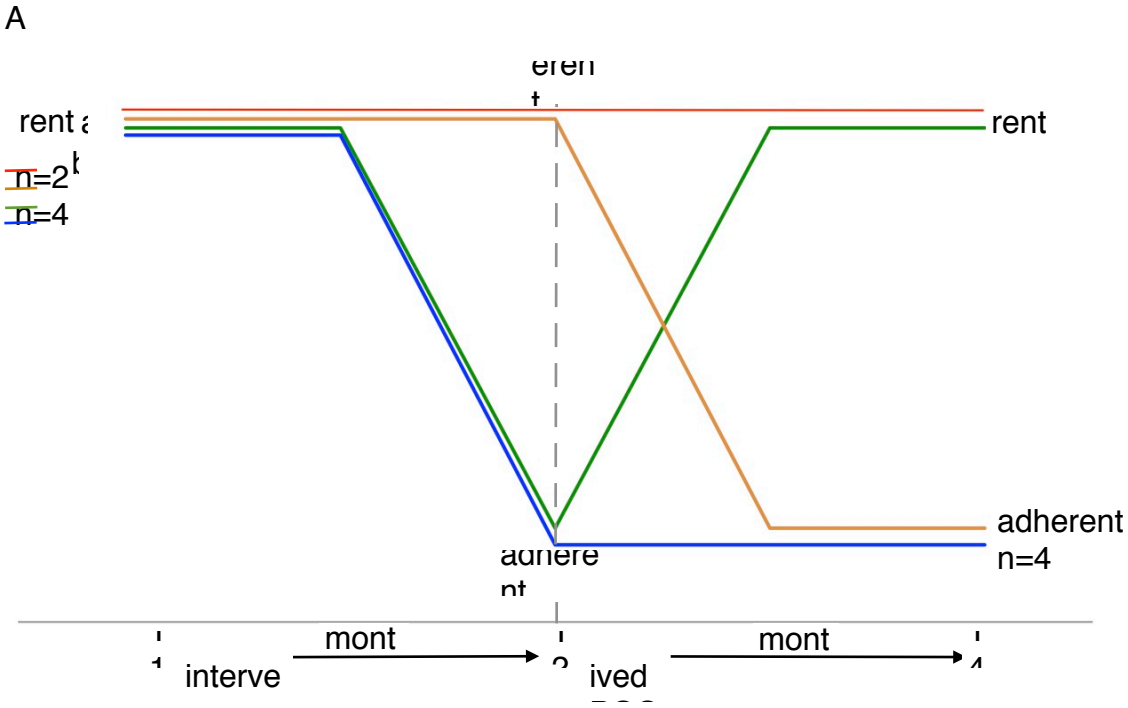
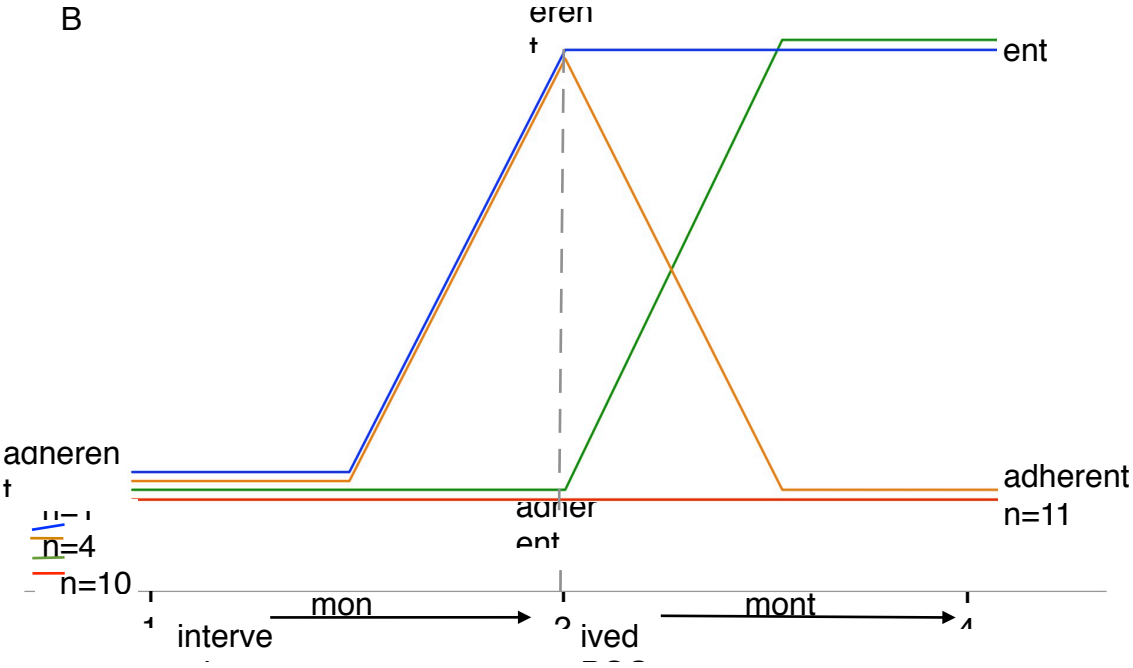


Image of Fig. 1

*n=3 missed T3, but completed t4


A
rent
n=2
n=4
adherent
n=4
mont
mont
interve
ived


B
ent
adherent
n=11
n=4
n=10
mon
mont
interve
ived