Phenotypic analysis of 23andMe survey data: Treatment-resistant depression from participants' perspective

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A B S T R A C T

To improve understanding of treatment-resistant depression (TRD) in a large population of individuals with depression, a self-reported antidepressant efficacy survey was designed and administered to 23andMe research participants. Participants with a current depressive episode or with a depressive episode within the last 5 years were queried for the effect of pharmacotherapy during the episode. TRD was defined as non-response to at least two antidepressants taken for at least 5–6 weeks. Non-TRD (NTRD) was defined as responsive to either the first or second medication taken for at least 3–4 weeks. Participants who could not be classified as TRD or NTRD were excluded from the analysis. Approximately 56,000 participants completed the survey, among which approximately 33,000 took medication for a depressive episode. The 3409 participants with self-reported TRD tended to have younger age of onset, and a more persistent course prior to initiation of treatment (e.g., a longer prior average episode duration and residual symptoms between episodes) than the 18,511 participants classified as NTRD. This survey identified depression characteristics, comorbidities, trigger events, and early childhood trauma that distinguish TRD from NTRD.

1. Introduction

Notwithstanding the availability of numerous antidepressants, approximately 30% of individuals with major depressive disorder (MDD) do not achieve full remission after treatment with multiple agents at an adequate dose and duration. Such patients are characterized as having treatment-resistant depression (TRD) (Fava, 2003). TRD has a substantial, detrimental effect on the quality of life of affected individuals and contributes substantially to societal costs, with estimates of up to $64 billion annually in the United States (Mrazek et al., 2014).

Diagnosis of MDD relies heavily on signs and symptoms without the advantage of a biological means of characterizing the disorder. Large-scale mega-analyses of genomic data have been undertaken to examine genetic predispositions for MDD, but due to the heterogeneous nature of the disorder true genetic markers have yet to be identified (Sullivan, 2010). To date, 44 independent and significant loci have been identified by a meta-analysis combining 135,458 cases and 344,901 controls from research communities around the world (Wray et al., 2018). The responses to antidepressants are variable and genetic variability may contribute to differences in treatment response/

resistance, although this possibility currently remains unclear. However, phenotypic analysis has the potential to characterize specific traits that can be associated with antidepressant response/resistance.

Prospective identification of individuals who are likely to respond to a specific antidepressant would be of significant value to optimize clinical outcomes in TRD. Statistical models built by mining participant-reported data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study predicted citalopram treatment outcome via internal cross validation with accuracy significantly above chance (accuracy 64.6%; $p < 0.0001$; area under the receiver operating characteristic curve (AUC ROC) 0.7), although the accuracy of predictions varied by the type of antidepressant (Chekroud et al., 2016). Participant reported data has been shown to have predictive value in medical areas such as breast cancer (El Khouli et al., 2009) and gliomas (Ludemann et al., 2006). Using participant-reported data in STAR*D, treatment response was predicted with an AUC ROC of 0.71 (Perlis, 2013). Including clinician-rated scales could increase the upper bound of the AUC to 0.78, at the expense of model complexity (Nie et al., 2018). Identification of biobehavioral factors associated with TRD in a predictive capacity has not been entirely successful,

likely due to the complexity of the disorder (Bennabi et al., 2015).

Treatment non-response/resistance and fragile disease course (e.g. relapse/recurrence) may share common risk indications. In a psychiatric epidemiological cohort, the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), where the cumulative recurrence rate among remitted MDD cases was 4.3% at 5 years, 13.4% at 10 years and 27.1% at 20 years, and time to recurrence was predicted significantly by baseline vulnerability characteristics (childhood abuse, negative life events, parental psychopathology), physical health, functioning, clinical characteristics of depression (previous episodes, severity, medication use), psychiatric comorbidity and mental health use (Ten Have et al., 2018). In the same study, 12% of current MDD cases developed a chronic depressive episode over 6 years and the chronic course was predicted by many of the same risk indicators as recurrence.

MDD symptom severity can be measured by several brief self-reported scales such as the Patient Health Questionnaire (PHQ-9) (Kocalevent et al., 2013; Kroenke et al., 2001; Lowe et al., 2004) and the brief, unidimensional melancholia subscales of Inventory of Depressive Symptomatology (IDS-C_6) (containing mood [sad], outlook [self], involvement, psychomotor slowing, mood [anxious], and energy/fatigue items) IDS-C_6 was previously reported to be highly sensitive to the effect of citalopram and may have biological validity (Ostergaard et al., 2014). Additionally, the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) introduced two new specifiers for depression (American Psychiatric Association, 2013). The specifier "with mixed symptoms" allows for the presence of manic symptoms as part of the depression diagnosis in participants who do not meet the criteria for a manic episode, while the specifier "with anxious distress" has also been added since the presence of anxiety may capture a clinically valid construct and predicts a worse clinical course. The specifier "with anxious distress" significantly predicted poorer treatment outcomes such as chronicity, longer time to remission, lower functional disability, higher depression severity and lower remission rates in the Netherlands Study of Depression and Anxiety (NESDA) study, while the presence of DSM-IV-based comorbid anxiety disorders did not predict these treatment outcomes (Gaspersz et al., 2017a, 2017b). In the same study, the anxious distress specifier was also shown to be associated with increased innate cytokine production capacity but not with basal inflammation (Gaspersz et al., 2017c). Comorbidity of generalized anxiety disorder (GAD) and posttraumatic stress disorder (PTSD), however, was previously implicated to be a prognostic clinical feature of antidepressant treatment response in the STAR*D study (Jakubovski and Bloch, 2014). Likewise, anxiety comorbidity, co-morbid panic disorder, social phobia, and personality disorder were found to be associated with TRD in a European multicenter study (Souery et al., 2007).

A recent review of approaches using self-reported predictors of MDD treatment response documented significant associations of a number of self-reported measures and MDD outcomes (Kessler et al., 2017). Based on results such as these, it is plausible that a self-reported questionnaire based on constructs associated with poor overall depression might be useful in providing clinical decision support to select effective MDD treatments.

This approach would require a better understanding than currently exists of the phenotypic underpinnings of TRD. We report here the results of an antidepressant efficacy survey of a large cohort of 23andMe research participants with depression, to determine baseline characteristics, depression history, clinical symptoms, comorbidities, and stressful life events (SLEs) that distinguish participants with TRD from those who are treatment-responsive (non-TRD [NTRD]).

2. Methods

2.1. Study cohort

Approximately 56,000 participants, drawn from the customer base

of 23andMe, Inc. (Mountain View, CA), provided informed consent under a protocol approved by the Association for the Accreditation of Human Research Protection Programs accredited Institutional Review Board (Ethical and Independent Review Services, 2015). Participants completed and took the survey 'Antidepressant Efficacy' online between June 2015 and Jan 2017.

2.2. Outcomes

The Antidepressant Efficacy Questionnaire (AEQ) was designed by Janssen Research & Development and 23andMe Research in consultation with Dr. Ronald Kessler (Harvard Medical School) and deployed on the 23andMe survey platform. Portion of the AEQ were based on the World Health Organization World Mental Health Composite International Diagnostic Interview (WHO WMH-CIDI) (Kessler and Üstün, 2004) and the Army Study to Assess Risk and Resilience in Service members (Army STARRS) (Kessler et al., 2013) instruments. Answering each question was optional.

Respondents were asked about their use of antidepressants in the last 5 years and the qualitative effect on a 5-point Likert scale: very helpful, helpful, not very helpful, no change, worsened. Respondents were able to select from multiple choices. Sample questions included "How helpful would you say the treatment of your current episode has been overall?" or "How helpful would you say the treatment of that episode was overall?" If a study participant also used non-pharmacotherapy options, the AEQ asked "You had multiple components to your treatment. What part do you think medication played in your treatment being helpful?" or "You had multiple components to your treatment. What part do you think medication played in your treatment being very helpful?" followed by "How important would you say medication was in making your treatment helpful?" Medications listed in the AEQ were selective serotonin reuptake inhibitors (SSRIs) citalopram, escitalopram, fluoxetine, paroxetine, and sertraline; serotonin and norepinephrine reuptake inhibitors (SNRIs) duloxetine, venlafaxine, desvenlafaxine, and levomilnacipran; norepinephrine-dopamine reuptake inhibitor bupropion; serotonin antagonist and reuptake inhibitor trazodone; serotonin modulator vortioxetine; atypical antipsychotics (quetiapine, olanzapine, and aripiprazole); vilazodone; and Symbyax® (a combination of olanzapine and fluoxetine).

All participants included in the analyses self-reported taking antidepressants for depression indication. TRD is typically diagnosed in patients who are non-responsive to two or more antidepressants used at an adequate dose and duration (Al-Harbi, 2012). In this study, participants were classified as having TRD if they had taken at least two medications for 5–6 weeks or more and reported that the overall treatment effect was: not very helpful, no change, worsened, or medication did not help despite that overall treatment effect was helpful or very helpful in the current or most recent episode. Participants were classified as having NTRD if they only received pharmacotherapy and the treatment effect was helpful or very helpful, or they also received non-pharmacotherapy but stated that the overall treatment effect was helpful or very helpful, and medication helped, and medication was the main reason the treatment was helpful, or medication was important but not the main reason the treatment was helpful. In both cases, participants took two or fewer medications for more than 3–4 weeks. Participants who could not be classified were excluded from the analyses.

Assessments included commonly-used antidepressant, depression clinical characteristics including symptoms during the two weeks in the episode when depressive symptoms were most severe and persistent, psychiatric comorbidity, vulnerability characteristics SLEs, childhood/lifetime traumatic experience, parental psychopathology, trigger, and social support.

2.3. MDD clinical characteristics descriptors

For the specifier "with anxious distress," participants were asked "How much of the time since the episode began have you had each of the following feelings?" The anxious distress symptoms questioned were: (1) Feeling keyed up or tense; (2) Feeling unusually restless; (3) Feeling so worried that you had difficulty concentrating; (4) Feeling fearful that something awful might happen; (5) Feeling like you might lose control. Each item was scored by None (0), Less than half (1), Most (2), and Nearly all (3) and the total score was the sum of each item scores. For the specifier "with mixed symptoms" and PHQ-9 (Kroenke and Spitzer, 2002) symptoms, participants were asked "Please think about the two weeks during the episode when your depressive symptoms were most severe and persistent. How much were you bothered by each of the following problems during those two weeks?" The mixed symptoms interrogated were (1) Feeling happy or excited; (2) A lot more interest than usual in pleasurable things (e.g., sex, gambling); (3) Decreased need for sleep without feeling tired; (4) Having an increase in energy; (5) Feeling especially good about yourself or optimistic about your abilities. The scoring of mixed symptom items was similar to PHQ-9 items using a scheme of Not at all (0); Several days (1), More than half the days (2) and Nearly every day (3). To operationalize the melancholia subscale, the six melancholia items were mapped to "Feeling down, depressed, or hopeless; "Feeling bad about yourself - or that you are a failure or have let yourself or your family down;" "Little interest or pleasure in doing things;" "Moving or speaking so slowly that other people could have noticed;" "Being so fidgety or restless that you were moving around a lot more than usual;" and "Feeling tired or having little energy," while leveraging as many PHQ-9 questions as possible.

2.4. Psychiatric comorbidity

Lifetime and concurrent psychiatric comorbidity prevalence rate difference was compared between TRD and NTRD. Frequency was tabulated and a Chi-Square test (2 × 2 table) was performed.

2.5. Vulnerability characteristics descriptors

Eight childhood traumatic experience questions were asked of the survey participants including: (1) People in your family said hurtful or insulting things to you; (2) Someone in your family hit you hard enough to leave a bruise; (3) Someone touched you or made you touch them in a sexual way against your will; (4) Nobody worried about making sure you had adequate food, clothing, or medical care; (5) You didn't have anyone to take care of you or protect you; (6) You were emotionally abused at home; (7) You were physically abused at home; (8) You were sexually abused at home. Each item was scored as Never (0), Rarely (1), Sometimes (2), Often (3), or Very (4) and the total childhood traumatic experience score was calculated. The stress in the weeks and months before the start of the most recent depressive episode in which medication was used to treat the symptoms was assessed in 5 domains (career, financial situation, health, love life, relationship with friends and family) and life overall, and rated as None (0), Mild (1), Moderate (2), Severe (3) and Very severe (4). The total childhood traumatic experience score and SLE score difference between TRD and NTRD was tested using Wilcoxon rank sum test.

Lifetime (up until the time of the most recent depressive episode in which medication was used) traumatic experience questions was asked and the answers ranged from Never, 1–2 times, 3–5 times, 6–10 times to more than 10 times. Parental psychopathology during the participant's childhood was also assessed by a question "How often did either of your parents have each of the following problems during your childhood" and rated as Never, Rarely, Sometimes, Often, and Very. Frequency was tabulated and a chi-square test (2 × 5 table) was performed for both parental psychopathology and lifetime traumatic experience.

Evaluations were performed on the following MDD characteristics descriptors for TRD and NTRD: total score of "with anxious distress" specifier items, total score of "with mixed symptoms" specifier items, total score of PHQ-9 symptoms, total score of melancholic subscale items, and total score of five SLE domains. The survey question flow for phenotype definition is shown in Supplementary Fig. S1.

2.6. Statistical methods

Scoring functions, plot distributions comparing TRD and NTRD, Chi-Square test for categorical responses, and Wilcoxon rank sum evaluations were performed for the total scores derived from groups of variables such as PHQ-9, anxious distress specifier, with mixed symptom specifier, melancholia subscale, SLE score, and childhood traumatic experience total score.

3. Survey results

3.1. Participants

A total of 55,686 research participants completed the survey, among which approximately 33,000 took medication for a depressive episode in the past five years. 71.8% of them were currently taking medication, while 13.2% took medication in the past 2 years and 15.0% took medication between 2 and 5 years ago Mean (SD) age of TRD and NTRD participants were 48.0 (15.0) and 51.7 (15.0) years, respectively. More than two-thirds of the participants were female.

3.2. Clinical characteristics of depression

Frequencies of depression clinical characteristics comparing TRD and NTRD groups are shown in Table 1. TRD participants tended to have earlier age of onset of the depressive episode lasting two weeks or longer: 14.4% of TRD vs. 8.3% of NTRD participants had age of onset before 12 years, and 30.6% of TRD vs. 23.8% of NTRD participants had age of onset between 13 and 17 years (Supplementary Table S1). For conciseness, collapsed responses are reported in Table 1. TRD participants also tended to spend more time being depressed throughout their lives (93.2% of TRD vs 69.0% of NTRD spending three years or more in depressive episode lasting two weeks or longer); have a longer average episode duration (48.6% of TRD vs. 28.4% of NTRD endorsed having average duration of depressive episode longer than six months); have a greater degree of residual symptoms between episodes (82.8% of TRD vs. 60.6% of NTRD endorsed usually and almost always had at least some symptoms of residual depressive symptom between episodes); and have a shorter interval between depressive episodes (41.1% of TRD vs. 56.7% of NTRD participants endorsed having average interval of >7 months between depressive episodes).

TRD participants were inclined to endorse anxious and melancholic features more than mixture features. TRD participants tended to show more severe anxious distress specifier symptoms, and more melancholic subscale symptoms than NTRD participants. Overall depressive symptoms (measured by PHQ-9) were higher for TRD than NTRD participants, but the difference was not as great with respect to the mixed symptom specifier features (Table 1). Detailed frequency differences are listed in Supplementary Tables S1–S4. To avoid concern due to 5 year of recall period, a sub-analysis was also performed limiting to subjects currently taking medication for a depressive episode and the results were comparable to that for the full study cohort (Supplementary Tables S1).

3.3. Psychiatric comorbidity

Overall, TRD participants reported a higher prevalence of both lifetime and concurrent comorbidity than NTRD participants (Table 2). The comorbidities with the greatest difference in lifetime prevalence

Table 1
Depression clinical characteristics difference between TRD and NTRD.

	TRD *n* = 3409	NTRD *n* = 18,511	*p*-value
Demographic			
Age, mean (SD)	48.04 (15.00)	51.74 (14.99)	7.40×10^{-39}
Gender/male, *n* (%)	980 (28.75)	4611 (24.91)	2.57×10^{-6}
Clinical characteristics, n (%)			
Age of onset			
0–17 years old	1517 (44.9)	5785 (32.2)	$1.493.88 \times 10^{-46}$
18+ years old	1860 (55.1)	12,203 (67.8)	
Lifetime duration of depressive episode lasting two weeks or longer, years			
≤ 2	376 (11.2)	5544 (31.0)	1.53×10^{-285}
3 or more	2970 (88.8)	12,348 (69.0)	
Average duration of depressive episode			
1–6 months	1596 (51.4)	10,258 (71.6)	5.61×10^{-106}
More than 6 months	1512 (48.6)	4077 (28.4)	
Average interval between depressive episodes			
1–6 months	1790 (58.9)	5995 (43.3)	1.95×10^{-55}
>7 months	1246 (41.1)	7859 (56.7)	
Residual depressive symptoms			
No symptoms between episodes or Sometimes had symptoms, but with ≥ 3 months of no symptoms	531 (17.2)	5582 (39.4)	2.20×10^{-121}
Usually and Almost always had at least some symptoms	2561 (82.8)	8571 (60.6)	
Anxious distress specifier total score[a], mean (SD)	7.6 (3.5)	5.8 (3.3)	4.36×10^{-150}
Mixed symptom specifier total score[b], mean (SD)	1.8 (2.0)	1.7 (2.0)	1.05×10^{-06}
PHQ-9 total score[b], mean (SD)	17.4 (4.9)	14.1 (5.7)	4.74×10^{-215}
Melancholia subscale score[b], mean (SD)	10.7 (3.0)	8.7 (3.4)	7.90×10^{-204}

N = 55,686 participants; *n* = participants who answered the question.
NTRD = non-treatment-resistant depression; SD = standard deviation; TRD = treatment-resistant depression.
  [a] Prompted by recall period: "How much of the time during the episode did you have each of the following feelings?"
  [b] Prompted by recall period: "Please think about the two weeks during the episode when your depressive symptoms were most severe and persistent. How much were you bothered by each of the following problems during those two weeks?"

were anxiety disorders, such as social anxiety disorder ($p = 2.74 \times 10^{-121}$), PTSD ($p = 4.29 \times 10^{-103}$), and GAD ($p = 6.94 \times 10^{-79}$). Other comorbidities such as panic disorder and personality disorder also showed a greater prevalence rate in TRD than NTRD. The difference in lifetime prevalence rate was more dramatic than concurrent prevalence rate. Furthermore, the presence of having more than one lifetime and concurrent comorbidity was substantially more prevalent in TRD participants than NTRD participants. For example, 35.6% of TRD participants reported having three or more lifetime comorbid conditions as compared to 16% of NTRD participants. Likewise, 27.1% of TRD participants reported having three or more concurrent comorbid conditions as compared to 9.6% of NTRD participants (Table 2).

3.4. Vulnerability characteristics

Vulnerability characteristics such as childhood abuse or traumatic experience, life time traumatic experience, negative/stressful life events, and parental psychopathology were compared between TRD and NTRD and are summarized Table 3. TRD participants in general suffered greater SLE than NTRD participants and experienced more childhood traumatic experience, life time traumatic experience, and parental psychopathology. Furthermore, TRD participants tended to have fewer social supports (Supplementary Table S5), and the depressive episode tended to be occur "out of the blue," as opposed to triggered by a SLE (Supplementary Table S6).

4. Discussion

This AEQ is the first survey of its kind to distinguish treatment responsive participants from non-treatment responsive participants in a large population of individuals with depression. The AEQ survey was developed using an extensive array of predictors associated with poor response to depression treatment; some of the self-reportable predictors were previously reviewed (Kessler et al., 2017). We deployed the survey to a large population of 23andMe research participants with depression

for phenotypic analysis to identify characteristics that distinguish TRD from NTRD. Results of this large observational study of the AEQ identify depression history, trigger, and symptom predictors such as earlier age of onset, high melancholic features, longer episodes, greater number of episodes, and the comorbid disorder and symptom predictors such as personality disorder, psychotic disorder, anxiety disorder/ symptoms, substance use/abuse as potential predictors for antidepressant treatment response. Stress and adversity including childhood maltreatment/trauma, and poor social support/relationships were also found to be predictors.

Anxious distress specifier was recently introduced in DSM-V. In this study, anxious distress specifier total score was found to be higher in participants with TRD than with NTRD, which is consistent with previous reports from the NESDA-2 study that anxious distress specifier predicted greater depression severity and lower remission rate as well as chronicity, time to remission, and functional disability (Gaspersz et al., 2017a, 2017b). Similar to anxious distress specifier, both melancholic subscale and PHQ-9 total score were also found to be higher in participants with TRD than with NTRD. Even though the mixed symptom specifier total score was slightly higher in participants with TRD than with NTRD, the extent of difference was far less compared to anxious distress specifier total score, melancholia subscale score, or PHQ-9 total score.

Although it is associative, the relationships between prevalence and type of lifetime and concurrent comorbidities suggest these characteristics may play an important role in contributing to TRD (Fava, 2003). This is consistent with the review of Steinert et al., where 12 cohorts were included with outcome data from a follow up period of at least three years or more; an unfavorable disease course was predicted by variables within the course of depression itself such as history of depression, baseline severity, and comorbidity (Steinert et al., 2014). Analyses using data from the WHO World Mental Health surveys also used comorbidities in addition to incidence episode characteristics to predict MDD persistence, chronicity, and severity (hospitalization, suicide attempt, or disability) and replicated the finding using data from the US National Comorbidity Survey and National Comorbidity

Table 2
Lifetime and concurrent psychiatric comorbidity.

	Lifetime co-morbidity			Concurrent co-morbidity		
	TRD	NTRD	*p*-value	TRD	NTRD	*p*-value
Psychotic disorder or schizophrenia, n (%)						
Yes	84 (2.5)	152 (0.8)	2.97×10^{-17}	52 (1.5)	53 (0.3)	2.36×10^{-21}
No	3307 (97.5)	18,253 (99.2)		3342 (98.5)	18,361 (99.7)	
Panic disorder, n (%)						
Yes	1132 (33.4)	3667 (19.9)	2.49×10^{-67}	871 (25.7)	2370 (12.9)	2.82×10^{-82}
No	2259 (66.6)	14,726 (80.1)		2520 (74.3)	16,019 (87.1)	
Social anxiety disorder, n (%)						
Yes	1174 (34.6)	3149 (17.1)	2.74×10^{-121}	991 (29.3)	2373 (12.9)	8.73×10^{-129}
No	2218 (65.4)	15,229 (82.9)		2397 (70.7)	16,002 (87.1)	
Other phobias, n (%)						
Yes	695 (20.5)	2378 (12.9)	6.12×10^{-31}	493 (14.5)	1409 (7.7)	1.50×10^{-38}
No	2703 (79.6)	16,026 (87.1)		2901 (85.5)	16,983 (92.3)	
Obsessive compulsive disorder, n (%)						
Yes	535 (15.8)	1784 (9.7)	9.41×10^{-26}	402 (11.8)	1238 (6.7)	5.25×10^{-25}
No	2861 (84.3)	16,618 (90.3)		2994 (88.2)	17,155 (93.3)	
Post-traumatic stress disorder, n (%)						
Yes	1205 (35.6)	3490 (19.0)	4.29×10^{-103}	984 (29.1)	2356 (12.8)	1.61×10^{-128}
No	2182 (64.4)	14,903 (81.0)		2398 (70.9)	16,030 (87.2)	
Generalized anxiety disorder, n (%)						
Yes	1866 (55.2)	6956 (37.9)	6.94×10^{-79}	1686 (50.0)	5916 (32.3)	7.48×10^{-87}
No	1513 (44.8)	11,389 (62.1)		1689 (50.0)	12,408 (67.7)	
Personality disorder, n (%)						
Yes	215 (6.4)	315 (1.7)	6.70×10^{-58}	163 (4.8)	176 (1.0)	7.16×10^{-62}
No	3171 (93.7)	18,089 (98.3)		3222 (95.2)	18,229 (99.0)	
Alcohol or drug abuse, n (%)						
Nearly all of the time	N/A[a]	N/A[a]		176 (5.3)	534 (3.0)	4.31×10^{-28}
Most of the time	N/A[a]	N/A[a]		202 (6.1)	715 (4.0)	
Sometimes	N/A[a]	N/A[a]		424 (12.7)	1734 (9.7)	
Rarely	N/A[a]	N/A[a]		422 (12.6)	1986 (11.1)	
Never	N/A[a]	N/A[a]		2116 (63.4)	12,946 (72.3)	
With(out)……comorbid condition(s)						
Without any	694 (20.5)	7381 (40.1)		958 (28.3)	9461 (51.4)	
With one	795 (23.4)	4940 (26.8)	$1.04 \times 10^{-22*}$	861 (25.4)	4682 (25.4)	$4.97 \times 10^{-33*}$
With two	696 (20.5)	3136 (17.0)	$6.51 \times 10^{-52*}$	654 (19.3)	2498 (13.6)	$7.58 \times 10^{-69*}$
With three or more	1207 (35.6)	2944 (16.0)	$3.58 \times 10^{-192*}$	918 (27.1)	1759 (9.6)	$2.96 \times 10^{-239*}$

[a]Not surveyed; n (%) = participants who answered the question.
NTRD = nontreatment-resistant depression; TRD = treatment-resistant depression.
[b]Reference group is without any comorbid condition. Comorbid conditions considered here were psychotic disorder or schizophrenia, panic disorder, social anxiety disorder, other phobias, obsessive compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder, and personality disorder.

Survey Follow-Up. (Kessler et al., 2016)

TRD participants experienced more negative/stressful life events (which include career, financial situation, health, love life, relationships with friends and family and life overall), childhood/lifetime traumatic experience, and parental psychopathology than NTRD participants. A greater burden of illness was found with clinical depression characteristics, co-morbidities and SLE in participants with TRD.

Despite the large number of predictors tested, most of the statistical tests were significant even after adjusting for multiple testing correction, which to some extent could be attributed to the large sample size and the hypotheses tested were based on prior knowledge. However, the direction of association between question and TRD status was consistent with what would be hypothesized.

Limitations of this study include that survey participants might not be representative of all patients with depression, as they volunteered to provide samples for genetic testing, and that outcome assessments were based entirely on retrospective self-reporting. The survey itself has not been evaluated for test-retest reliability. The symptom severity level of a study participant at the time of survey completion could have impacted his/her insight.

Overall, the results of this analysis substantiate the use of predictive characteristics for treatment response. Further refinement of the survey methods and application of the results may be used to guide clinical decision-making for optimal treatment outcomes.

Table 3

Comparison of vulnerability characteristics between TRD and NTRD.

Stressful life event[a]		TRD	NTRD	p-value
SLE total score[b], mean (SD)		11.8 (4.5)	9.3 (4.3)	6.75×10^{-181}
SLE total score[c], mean (SD)		9.4 (3.9)	7.4 (3.6)	2.05×10^{-158}
Childhood traumatic experience total score, mean (SD)		8.4 (7.1)	6.2 (7.1)	1.06×10^{-63}
Lifetime traumatic experience, n (%)				
Physical or sexual assault?	Never, 1–2 times	2388 (72.2)	14,288 (80.3)	6.24×10^{-26}
	3 times or more	921 (27.8)	3505 (19.7)	
A life-threatening accident or injury?	Never, 1–2 times	3028 (90.9)	16,987 (95.0)	7.33×10^{-21}
	3 times or more	921 (9.1)	890 (5.0)	
Witnessing a death or other traumatic event?	Never, 1–2 times	2594 (78.0)	15,100 (84.5)	2.77×10^{-20}
	3 times or more	731 (22.0)	2769 (15.5)	
Combat experience in the military?	Never, 1–2 times	3208 (96.3)	17,660 (98.6)	2.77×10^{-21}
	3 times or more	123 (3.7)	242 (1.4)	
Any other experience that put you at risk of death or serious injury?	Never, 1–2 times	2865 (86.2)	16,553 (92.6)	5.15×10^{-34}
	3 times or more	457 (13.8)	1318 (7.4)	
Parental psychopathology, n (%)				
Episodes of depression?	Never, Rarely, Sometimes	2183 (68.9)	12,764 (74.7)	1.15×10^{-11}
	Often, Very often	986 (31.1)	4328 (25.3)	
Bipolar disorder	Never, Rarely, Sometimes	2892 (91.7)	15,988 (93.4)	5.55×10^{-4}
	Often, Very often	263 (8.3)	1134 (6.6)	
Panic attacks?	Never, Rarely, Sometimes	2943 (93.6)	16,354 (96.0)	6.14×10^{-9}
	Often, Very often	200 (6.4)	687 (4.0)	
Problems with nerves or anxiety?	Never, Rarely, Sometimes	2302 (71.9)	13,314 (77.4)	3.13×10^{-11}
	Often, Very often	899 (28.1)	3898 (22.6)	
Problems with alcohol or drugs?	Never, Rarely, Sometimes	2359 (72.2)	13,568 (77.2)	6.70×10^{-10}
	Often, Very often	910 (27.8)	4013 (22.8)	
Any other serious behavioral or emotional problem?	Never, Rarely, Sometimes	2475 (76.9)	14,650 (84.5)	4.13×10^{-26}
	Often, Very often	742 (23.1)	2684 (15.5)	

n (%) = participants who answered the question.

SD = standard deviation; SLE = stressful life event; NTRD = nontreatment-resistant depression; TRD = treatment-resistant depression.

[a] The stressful life events were in reference to the weeks and months before the start of the most recent depressive episode in which the study participant used medication.

[b] Total score of 5 SLE domains including career, financial situation, health, love life, relationships with friends and family and life overall.

[c] Total score of 5 SLE domains including career, financial situation, health, love life, relationships with friends and family excluding life overall.

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Supplementary materials

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