

1     **Is there Progress? An Overview of Select Biomarker Candidates for**  
2                                   **Major Depressive Disorder**

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14    **Abstract**

15    Major Depressive Disorder (MDD) contributes to a significant worldwide disease burden, expected  
16    to be second only to heart disease by 2050. However, accurate diagnosis has been a historical  
17    weakness in clinical psychiatry. As a result, there is a demand for diagnostic modalities with greater  
18    objectivity that could improve on current psychiatric practice that relies mainly on self-reporting of  
19    symptoms and clinical interviews. Over the past two decades, literature on a growing number of  
20    putative biomarkers for MDD increasingly suggests that MDD patients have significantly different  
21    biological profiles compared to healthy controls. However, difficulty in elucidating their exact  
22    relationships within depression pathology renders individual markers inconsistent diagnostic tools.  
23    Consequently, further biomarker research could potentially improve our understanding of MDD  
24    pathophysiology as well as aid in interpreting response to treatment, narrow differential diagnoses,  
25    and help refine current MDD criteria. Representative of this, multiplex assays using multiple sources  
26    of biomarkers are reported to be more accurate options in comparison to individual markers that  
27    exhibit lower specificity and sensitivity, and are more prone to confounding factors. In the future,  
28    more sophisticated multiplex assays may hold promise for use in screening and diagnosing  
29    depression and determining clinical severity as an advance over relying solely on current subjective  
30    diagnostic criteria. A pervasive limitation in existing research is heterogeneity inherent in MDD  
31    studies, which impacts the validity of biomarker data. Additionally, small sample sizes of most

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32 studies limit statistical power. Yet, as the RDoC project evolves to decrease these limitations, and  
33 stronger studies with more generalizable data are developed, significant advances in the next decade  
34 are expected to yield important information in the development of MDD biomarkers for use in  
35 clinical settings.

## 36 **1 Introduction**

37 Major Depressive Disorder (MDD) is a highly prevalent illness in the United States that causes broad  
38 functional impairments (1) with significant public health costs (2, 3) and evidence of increasing rates  
39 over the past few decades (4). Together, this indicates that there is significant need to develop an  
40 objective characterization of the disorder for screening and diagnostics. The diagnosis of MDD  
41 currently relies on the clinical judgment of individual clinicians with high levels of subjectivity and  
42 potential variability. Following the publication of the 5<sup>th</sup> edition of the Diagnostic and Statistical  
43 Manual of Mental Disorders (DSM 5), concerns have been expressed with regards to the revised  
44 definition of MDD (5). Although based on opinion, the response to the changes of diagnostic criteria  
45 has highlighted how differing beliefs exist with regards to the MDD diagnosis, the subjectivity of  
46 diagnosing depressed patients, and the perception of a decrease in the reliability of MDD criteria  
47 under DSM 5 guidelines (5). Concerns about the validity of psychiatric diagnosis for depressive  
48 disorders is disconcerting and further emphasize the demand for more objective diagnostic modalities  
49 to assess MDD, such as blood-based and cerebrospinal fluid (CSF) biomarkers. Although there has  
50 been a significant amount of research in the development of fluid biomarkers for use in establishing  
51 MDD diagnosis (6-10), a consensus on which biomarkers are sensitive and specific enough to be  
52 used in a clinical setting has yet to be reached (11). In fact, studies of putative monoaminergic  
53 biomarkers such as peripheral and CSF levels of serotonin, dopamine, and noradrenaline often report  
54 conflicting results (12). Fortunately, there has also been an increased interest in other potential  
55 approaches by which MDD biomarkers may be discovered (13, 14). The objective of this article is to  
56 provide a broad overview of several types of biomarkers for MDD currently being investigated and  
57 to describe recent progress in identifying biomarkers that may potentially aid in the standardization  
58 of MDD diagnosis. Due to the sizeable literature investigating candidate MDD biomarkers and the  
59 limited space afforded to the authors, this overview will only focus on a select number of tissue-  
60 based biomarkers and recent multiplex studies published before December 1, 2015, while excluding  
61 current literature from the burgeoning neuroimaging biomarker data of structural imaging that has  
62 been previously reviewed (15-17).

## 63 **2 Biomarker Candidates**

### 64 **2.1 Hypothalamic-Pituitary-Adrenal Axis (DST, DEX/CRH, Cortisol Response, Hypocretin)**

65 HPA-axis hyperactivity has been associated with a spectrum of neuropsychiatric disorders due to its  
66 deleterious effects on the nervous system including dendritic process atrophy, decreased  
67 neurogenesis and neuroplasticity, and neuronal losses (18, 19); consequently, a wide range of  
68 biomarkers may be disrupted by HPA-axis dysfunction, such as disturbed adrenocorticotrophic  
69 hormone (ACTH) regulation, dysfunctional corticosteroid receptor signaling, and glucocorticoid  
70 excess (18).

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71 Furthermore, mutations in genetic regions involved in abnormal HPA-axis function (such as the  
72 FKBP5 allele) have also been associated with an increased risk for depression, and are similarly  
73 associated with abnormal plasma cortisol and ACTH concentrations (20-23).

74 However, beyond genetic factors, epidemiologic and clinical studies have determined that  
75 disturbances in HPA axis function have been consistently associated with biological changes in  
76 depression (24, 25). For example, one facet of depression history that is associated with HPA axis  
77 changes is early life stress. Early life stress (e.g. maltreatment or abuse) was found to result in HPA  
78 axis dysfunction during childhood and adolescence, and contributed to an increased risk of  
79 developing MDD later in life (26).

80

81 Moreover, diminished cortisol suppression following dexamethasone (DEX) administration was  
82 observed in MDD patients with metabolic abnormalities of prefrontal and hippocampal regions, areas  
83 often related to MDD pathology (27). Other studies found that antidepressant treatment often  
84 resulted in decreased cortisol levels and a return to normal HPA axis function (28, 29).

85

86 Originally, as corticotropin releasing hormone (CRH) has been reported to be associated with  
87 increased depressive symptoms such as anhedonia and reduced appetite (30), a combined DEX/CRH  
88 test was thought to be capable of increasing diagnostic power over the Dexamethasone Suppression  
89 Test (DST) (12, 31). However, abnormal DEX/CRH results also occur in other psychiatric disorders  
90 resulting in lack of specificity as a diagnostic biomarker for major depression (12). Measuring  
91 cortisol levels is a more direct and accurate method of assessing HPA axis activity in depressed  
92 patients (32). Additionally, more recent studies focusing on cortisol measurements have  
93 demonstrated a link between cortisol levels and depression severity or depressive subtypes.

94

95 A recent meta-analysis (33) reports a significant association between HPA-axis hyperactivity as  
96 measured by elevated cortisol levels and the presence of melancholic or psychotic depression while  
97 lower cortisol levels were characteristic of depression with atypical features. For example, a  
98 longitudinal study of adolescents with depressive symptoms found that male adolescents with high  
99 morning salivary cortisol levels and increased depressive symptoms were more susceptible to the  
100 development of MDD demonstrating a sex-linked differentiation (34).

101 Another study also reported that persistent increases in cortisol awakening response (CAR) in  
102 adolescents more strongly correlated with higher levels of depressive symptoms than with anxiety  
103 symptoms (35). Lastly, a large cohort study confirmed increased CAR and dynamic cortisol  
104 secretion in depressed patients compared to controls in both current MDD and remitted MDD  
105 subjects, indicating that both measurements reflect an inherent risk in the development of depression  
106 (29). These studies suggest the use of morning salivary cortisol as a trait-like biomarker for  
107 developing preventative measures for high-risk populations, especially in asymptomatic individuals  
108 with possible genetic risks (36). However, a recent study revealed that increased CAR in healthy  
109 female adolescents significantly correlated with higher magnitudes of Profile of Mood States  
110 (POMS) subscale scores for “Tension-Anxiety,” “Depression-Dejection,” “Fatigue,” and  
111 “Confusion” (37) suggesting that morning salivary cortisol levels may also be descriptive of mood  
112 states and episodic depressive symptoms rather than characteristic of a purely trait marker for MDD.  
113 Such findings suggest variability in the use of salivary cortisol as a depression biomarker. However,

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114 it is important to consider how these contrasting conclusions may be affected by methodological  
115 heterogeneity and differences in subject populations among these studies.

116 Another possible biomarker source includes hypocretin, a neuropeptide that plays a role in sleep and  
117 arousal. Recently, it has been suggested that decreased numbers and size of hypocretin-containing  
118 neurons may be associated with the development of depressive symptoms including eating/drinking  
119 behaviors and disrupted sleep (38, 39). One study found that hypocretin levels in the CSF of MDD-  
120 diagnosed patients with high suicidal ideation were significantly lower than those of patients with  
121 dysthymia and adjustment disorder (40). Additionally, hypocretin levels correlated significantly with  
122 CSF levels of other peptides that affect sleep and appetite including delta sleep-inducing-peptide-like  
123 immunoreactivity (DSIP-IL), corticotrophin releasing factor (CRF), and somatostatin. Not only are  
124 these results indicative of the diagnostic utility of measuring hypocretin concentrations, but these  
125 peptides may also be useful in discriminating affective disorders by associating differing biological  
126 characteristics with signs and symptoms of depression. However, one study reported results that  
127 counter the more common conception of lower hypocretin levels in depression (41). Bearing in mind  
128 the relatively few studies and the dynamic character of HPA axis components in general concerning  
129 hypocretin-based biomarkers for depression, future studies would be instrumental in further  
130 elucidating hypocretin effects in depressed patients.

### 131 **2.2 Thyroid Function and Thyroid Autoimmunity**

132 A number of studies have related thyroid dysfunction with depressive symptoms and depressive  
133 disorders (42-50). However, a direct correlation is indeterminate as evidenced by a number of  
134 conflicting studies (51-56). More recent studies have shown a relationship between levels of anti-  
135 thyroid antibodies with depression (57-59) and poorer “psychosocial well-being” (60). However,  
136 there also exists literature demonstrating equivocal data concerning this association (61). In fact, one  
137 group found that thyroid function and thyroid autoantibody levels were not associated with  
138 depression severity despite an association with the presence of depressive symptoms (58). Supporting  
139 these results, a general population study showed no significant difference in depressive symptoms  
140 between euthyroid individuals and those characterized to have subclinical hypothyroidism (62).  
141 Conversely, another general population study found an increase in prevalence of lifetime depression  
142 diagnosis in subjects positive for thyroid peroxidase antibodies, suggesting its use as a trait marker  
143 for depression despite finding no association between depression disorder diagnosis and TSH or free  
144 T4 levels (63). Interestingly, one study (64) found T3 and T4 levels derived from hair were  
145 significantly lower in patients concurrently having a depressed episode ( $P < 0.001$ ), which may  
146 indicate the use of thyroid hormones as a state-like biomarker. In this sense, future studies should  
147 focus on readily accessible markers of thyroid function that have some state-like diagnostic utility in  
148 major depression diagnosis as studies researching their use as trait-like markers have demonstrated  
149 mostly equivocal results.

### 150 **2.3 Cytokines and Inflammatory Markers**

151 There also exists an abundance of evidence that elevated proinflammatory cytokine concentrations  
152 and an increased immune response are associated with depression diagnosis, symptomatology, and  
153 severity (65-69). Reflective of this significant proinflammatory response in depressive disorders, a  
154 recent proteomic study found elevated levels of acute phase reactants (e.g. ferritin, serotransferrin,  
155 Haptoglobin-related protein, ceruloplasmin) and proinflammatory markers (e.g. IL-16, MIF,

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156 Tenascin-C, EN-RAGE) in drug-naïve MDD patients, indicating a disorder-related increase in  
157 immune processes (70). These findings are supported by neuroimaging and animal studies, which  
158 have demonstrated that alterations in neuroplasticity promote manifestations of depressive  
159 phenotypes as a result of cytokine-induced neural apoptosis and metabolic dysregulation (71).  
160 Further, inflammatory cytokines have been described to alter basal ganglia processes leading to  
161 common depressive phenotypical characteristics including anhedonia, fatigue, and psychomotor  
162 retardation (72-75). A recent review also reported increased neopterin levels in a number of studies  
163 of depressed patients, specifically in melancholic subtypes of depression (76). Additionally,  
164 inflammatory markers IL-6 and soluble intercellular adhesion molecule (sICAM) have been  
165 associated with sleep disturbances in depressed patients (77). IL-8 and TNF- $\alpha$  have also been  
166 reported to remain elevated in certain subsets of depressed patients after antidepressant therapy,  
167 indicating possible trait characteristics (78).

168 C-reactive protein (CRP) and interleukin (IL)-6, specifically, have been found to exhibit trait  
169 characteristics (i.e. gender effects, impact of early life adverse events) as an inflammatory biomarker  
170 for depressive pathology (79-82). In their meta-analysis, Valkanova and colleagues (83) found that  
171 these two putative analytes had a small but significant association with the development of  
172 depressive symptoms, indicating the presence of raised inflammatory markers preceding the  
173 development of MDD. However, the authors cautioned that their results might have limited  
174 significance due to heterogeneity (i.e. of depression, methodologies, populations, etc.) across studies.

175 For instance, one study (84) found both higher and lower levels of different inflammatory markers in  
176 major depressed patients depending on the presence or absence of melancholic features, indicating  
177 that that the overall characteristics of depressive symptoms were more associated with the  
178 composition of inflammatory profiles and less so on concentrations of individual markers.  
179 Moreover, a study of an elderly population found that when controlling for age-related chronic  
180 diseases, CRP was not a statistically significant marker associated with the presence of MDD or sub-  
181 threshold depression (85). Lastly, one group reported significantly lower levels of IL-6 in subjects  
182 with high self-reported depressive symptoms while showing no significant differences of IL-8, IL-10,  
183 and TNF- $\alpha$  levels when compared to controls (86). As a whole, these studies demonstrate the  
184 complexities of relying on individual inflammatory marker concentrations to characterize generalized  
185 depression.

186 Yet, there is reasonable evidence that suggests inflammatory responses are more prominent in certain  
187 subsets of MDD than others. A study evaluating biomarker associations with depressive subtypes  
188 found that increased inflammatory markers (i.e. CRP, IL-6, TNF- $\alpha$ ) were significantly associated  
189 with atypical depression as compared to typical or melancholic depression (87). Consistent with  
190 these results, a more recent study (88) reported that elevated IL-6 levels were consistently higher in  
191 patients with atypical depression. Similarly, a recent study has detected consistently increased CRP  
192 levels in depressed patients with comorbid diabetes mellitus (89). Moreover, these studies reinforce  
193 clinical evidence that both inflammatory diseases and depression are often associated with comorbid  
194 illnesses like metabolic disorders (87, 90), especially in more elderly subjects (91-93). It is possible  
195 that in many cases, the predisposition to depression in patients with elevated inflammatory biomarker  
196 concentrations is affected by a number of outlying factors often present before the emergence of the  
197 first depressive symptoms. Therefore, in addition to their lack of specificity to MDD, the diagnostic  
198 value of individual inflammatory biomarkers could be hindered by some inherent heterogeneity of  
199 depression. Although they may be useful as MDD biomarkers in a research environment, their low  
200 sensitivity and specificity (6) prevent them from being utilized in the majority of clinical settings.

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201 In contrast to the relatively limiting findings of individual inflammatory analyte concentrations as  
202 biomarkers for depression, inflammatory markers have potential use as state markers by  
203 characterizing treatment response to antidepressants (94, 95). Significantly, antidepressant effects  
204 are associated with a decrease in proinflammatory/anti-inflammatory protein ratios, especially in  
205 patients that respond to treatment when compared to non-responders or healthy controls (96).  
206 Specified inflammatory markers tend to correlate well with treatment efficacy in depressed patients.  
207 For instance, TNF- $\alpha$  levels have been reported as a marker of treatment response and  
208 psychopathological improvement (94, 97). However, a recent meta-analysis (98) failed to detect  
209 pharmacological effects on serum levels of TNF- $\alpha$ , although they reported that IL-1 $\beta$  levels  
210 decreased after antidepressant treatment. Another analyte, high sensitivity C-reactive protein (hs-  
211 CRP), was found to be a highly specific baseline biomarker when evaluating patient response to  
212 Infliximab in treatment-resistant depression (TRD) (99). Similarly, CRP levels have been used to  
213 differentially evaluate treatment efficacy between escitalopram and nortriptyline (100). Considering  
214 the high incidence of treatment resistance in MDD diagnosed patients, inflammatory markers capable  
215 of determining antidepressant treatment response will have a significant impact in depression  
216 management and allow practitioners the ability to modify treatment plans according to personalized  
217 histories and peripheral biomarker results. For further review, please read the following articles:  
218 Dantzer et al. (101), Leonard & Maes (102), Miller et al. (9, 75), Müller & Schwarz (103) Raison &  
219 Miller (104), and Young et al. (105).

### 220 **2.4 Markers of Oxidative Stress**

221 Oxidative stress has also been proposed to have an important role in depression pathology (102, 106-  
222 108). Consistent with preclinical studies that display increased antioxidant capacity with  
223 antidepressant therapy (109-111), human studies have demonstrated that increased oxidative activity  
224 is reversible by SSRI action in severely depressed, medication-naïve patients (112) or melancholic  
225 patients (113), implying the involvement of oxidative processes in depressive disorders and  
226 monoamine metabolism. However, one study (114) found that treatment with antidepressants did not  
227 affect oxidative-antioxidative markers in MDD subjects while another found increased oxidative  
228 stress after treatment (115). An explanation for these inconsistent results may be the varying  
229 oxidative effects of different antidepressant formulations and duration of treatment that vary between  
230 studies. Whatever the case, the extensive literature associating oxidative processes and depression  
231 suggests markers of oxidative stress may be able to identify depressed patients and quantify severity.

232 Several studies have found significantly increased oxidative stress markers (e.g. 8-hydroxy-  
233 deoxyguanosine (8-OHdG), F2 isoprostane, peroxidase, malondialdehyde (MDA), superoxide  
234 dismutase (SOD)) and decreased antioxidative capacity in MDD patients (112-118). Some studies  
235 have also demonstrated specific correlations of depressive subtypes or features with oxidative stress,  
236 yet results remain conflicting. Decreased GSH has also been found to correlate with severity of  
237 anhedonia in depressed patients (119) while plasma GSH-R and erythrocyte glutathione peroxidase  
238 (GPX) levels were elevated in MDD patients with melancholic features (113). A study determining  
239 the relationship between psychological responses and 8-OHdG levels found a positive correlation  
240 with depression-rejection scores of the POMS scale in females compared to a negative correlation in  
241 men, suggesting gender differences in depression-associated oxidative damage markers (120).  
242 Additionally, increased expression and distribution of allele frequencies of enzymatic proteins  
243 involved in the production of oxidative free radicals (e.g. inducible nitric oxide synthase and  
244 myeloperoxidase) were characteristic of patients with recurrent depression (121). Recently, Smaga

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245 and colleagues (122) completed a review of a number of clinical studies that demonstrated higher  
246 oxidant status in depressed patients including higher plasma peroxide levels, higher nitric oxide  
247 levels in serum, and higher xanthine oxidase levels. The authors also found that oxidative DNA  
248 damage and higher levels of lipid peroxidation markers were also prevalent in a number of  
249 depression studies.

250 In elderly populations, free radicals have been implicated in the pathophysiology of other  
251 neurodegenerative disorders along with MDD (123, 124). A study by our group has shown increased  
252 CSF F2-isoprostanes in geriatric patients diagnosed with MDD; further, an inverse relationship was  
253 found between amyloid- $\beta$  42 and F2-isoprostane CSF levels, suggesting that increased oxidative  
254 stress pathology may be associated with increased brain amyloid burden (125). These findings are  
255 corroborated by other published findings that imply similar pathological mechanisms (e.g. increased  
256 levels of lipid peroxidation) between major depressive disorder and chronic, age-related diseases  
257 (126). Due to the complex neurobiological complications that are present in late-life depression,  
258 there is a need to identify specific markers in order to direct biology-based treatment.

### 259 **2.5 Neurotrophins**

260 Neurotrophins (i.e. nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF),  
261 neurotrophin (NT)-3, 4, and 5) are homodimeric proteins that interact with the tropomyosin receptor  
262 kinase (Trk) family of receptors through which they mediate the processes of neurogenesis and  
263 neural plasticity in both the peripheral and central nervous systems (127). Several connectomic  
264 studies have increasingly indicated the disruption of integral whole-brain structural networks in  
265 MDD, suggesting the presence of abnormal neuronal synapse formation within certain populations of  
266 depressed patients (128, 129). In fact, there is evidence that disrupted neurogenesis may be a  
267 characteristic of MDD pathophysiology; especially of the hippocampus (130, 131). Due to the role  
268 of neurotrophins in neuroplasticity, their use as potential biomarkers has often been reviewed. Of  
269 these, the most researched is BDNF, with studies finding its downregulation in the limbic structures  
270 of chronic-stress exposed rats and reports of decreased peripheral levels in MDD patients (132-136).  
271 Significantly, a recent study (137) has shown serum BDNF may also have significant potential as a  
272 discriminatory diagnostic tool for first major depressive episode (MDE) patients, prompting the need  
273 for more expansive studies concerning its use in clinical settings. While there have been conflicting  
274 results concerning correlations of depression severity with BDNF levels (138), BDNF concentrations  
275 have been reported to increase after antidepressant therapy with more prominent elevations in  
276 patients with higher baseline depression severity (139-145). Several studies have also reported  
277 elevated BDNF levels in responders to antidepressant treatment compared to non-responders that  
278 continued to demonstrate lower BDNF concentrations after pharmacologic management (146, 147).  
279 These findings suggest that BDNF may be utilized as a state marker to assess psychopharmacological  
280 therapy and prognosis of individual MDD patients (148), although the effect on BDNF levels may  
281 vary between different classes of antidepressants (149). Ultimately, due to its intrinsic function in  
282 influencing the development and maintenance of a patient's cognitive abilities, BDNF could have  
283 potential for evaluating other therapy effects involving learning, memory, and executive functions  
284 (134, 150).

285 Alternatively, de Azevedo Cardoso and colleagues (151) have suggested that BDNF may also have  
286 trait-like properties. For example, differences between male and female BDNF levels have been  
287 associated with contrasting antidepressant effects between the two genders (145). Additionally, there

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288 is evidence that BDNF levels are more negatively affected in patients with chronic depression who  
289 have experienced more adverse life events (152). Supporting this theory, several groups have  
290 illustrated how BDNF genotypic variations were associated with risk for depression (151, 153-157).  
291 BDNF DNA methylation patterns have also been associated with depression severity, and the  
292 presence of suicidal ideation in MDD subjects (158-160). Consequently, the potential for BDNF to  
293 be a trait and state-like marker makes it one of the more versatile biomarker candidates being  
294 researched today.

295 In contrast, fewer studies have focused on other neurotrophins, with the notable exception of NGF,  
296 which has been found to be increased during circumstances that cause anxiety or anticipation of  
297 anxiety (161). Regarding NGF's relationship to depressive symptoms, reports of NGF  
298 concentrations have yielded conflicting results (151, 162, 163). Additionally, due to its association  
299 with other affective disorders such as bipolar disorder (BPD) (164), it is unlikely to be specific to  
300 MDD. These limitations, however, should not preclude it from further research.

### 301 2.6 Markers in Genetics and Genomics for MDD

302 Past studies have suggested that there is a complex genetic component to the development of MDD,  
303 with evidence that heritability is a key factor in a significant number of depression cases (165-167).  
304 Additionally, several studies have revealed various polymorphisms and overexpression of certain  
305 genes in patients presenting with depressive symptoms (168-170). One example is a blood-based  
306 study that found increased serotonin type 1A receptor (5-HT<sub>1A</sub>) expression within platelets of MDD  
307 patients compared to controls (171). The authors also reported decreased levels of serotonin (5-HT),  
308 platelet poor plasma (PPP) 5-HT, and a decrease of the 5-HT metabolite, 5-hydroxyindoleacetic acid  
309 (5-HIAA), suggesting that increased 5-HT<sub>1A</sub> expression inversely correlated with 5-HT activity via a  
310 negative feedback mechanism. Often, such genetic variants imply pathological mechanisms  
311 associated with the dysfunction of different biological systems implicated in depression. Another  
312 example is HPA axis hyperactivity, which is believed to influence the pathogenesis of MDD due to  
313 findings of glucocorticoid (GR) and mineralocorticoid (MR) receptor dysfunction in depressed  
314 patients (24). For instance, a longitudinal study focusing on neuropsychiatric disorders in an elderly  
315 community found that several single-nucleotide polymorphisms (SNPs) of angiotensin-converting  
316 enzyme (ACE) were significantly associated with the risk of late-life depression (172). Additionally,  
317 they reported that two SNPs (rs4291 and rs4295) were associated with the risk of incident depression  
318 over the study's 10-year follow-up. More recent studies have determined that polymorphisms of the  
319 FKBP5 gene (a gene that plays a role in immune regulation) also modulate GRs, and have been  
320 associated with the development of depression (20-23). A meta-analysis of HPA axis dysfunction  
321 associated with GR abnormalities found that glucocorticoid-induced leucine zipper (GILZ), a product  
322 of GR-initiated gene transcription, has been suggested to be associated with biological pathways  
323 relevant to depression (173). Though few studies have focused on GILZ concerning depressive  
324 disorders, there is clinical evidence that a reduction in its expression is associated with reduced  
325 hippocampal volumes found in MDD diagnosed subjects (174).

326 More comprehensive data concerning the heritability of depressive disorders will likely come from  
327 the increasingly complex genome-wide research being conducted today. For example, the GeneQol  
328 Consortium (175) gathered data from a substantial number of studies that undoubtedly demonstrate  
329 the involvement of genetic variables in quality of life (QOL) domains (e.g fatigue, pain, general  
330 functioning, social functioning, general health). Of the biomarker candidates they reviewed,  
331 candidate genes and molecular markers that had the most evidence of association with QOL domains



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332 were genes for inflammatory cytokines (e.g. IL-1 $\beta$ , IL-6, IL-8, TNF- $\alpha$ ). Additionally, inflammatory  
333 markers (e.g. CRP), and anti-inflammatory markers (e.g. IL-1RN, IL-1RA, IL-10) were also  
334 associated with a smaller number of QOL domains. Other QOL associated markers include genes for  
335 dopaminergic and serotonergic synapses (MAOA, 5-HTT (SLC6A4), TPH1), the glutathione  
336 metabolic pathway (DPYD), and pain receptor pathways (OPRM1). However, the specificity and  
337 accuracy of these markers for MDD may be limited by significant genetic heritability among  
338 psychiatric disorders (176), and the fact that current MDD genomic data is limited by heterogeneity  
339 and insufficient power (177). Yet, these findings still underlie the potential of genetic irregularities to  
340 play a role in more accurately characterizing and diagnosing depressive disorders. Currently, better  
341 powered studies are required to determine the etiologic and genetic variables involved in MDD  
342 pathology, especially when conducting genome-wide research.

343 MicroRNAs (miRNAs) are a popular genetic marker in researching MDD biomarkers due to their  
344 role as small RNA regulators involved in neural stem cell proliferation, neurogenesis, and neural  
345 plasticity (178). In addition, several miRNA alterations were associated with an increase in risk for  
346 major depression and negatively regulate the expression of either serotonin receptors (SERT) or 5-  
347 HT1B receptors (179). Significantly, one study (180) has indicated that miRNA profiles are capable  
348 of separating Major Depressive Episode (MDE) patients from controls while a second study (181)  
349 found 30 miRNAs to be differentially expressed in MDD patients after escitalopram treatment.  
350 These findings are further corroborated by results from a study demonstrating gene variations in  
351 Drosha RNase and Digeorge syndrome critical region 8 (DGCR8), a known cofactor in miRNA  
352 processing, and AGO1, a component protein involved in the production of mature miRNAs, as being  
353 capable of significantly differentiating MDD patients and healthy controls in relation to genotype and  
354 allele frequencies (182). Another study demonstrated that dysregulation of circadian rhythms in  
355 MDD patients was associated with the rs76481776 polymorphism of miR-182, suggesting that  
356 symptoms of MDD may be inherently linked to genetic variations that affect miRNA function (183).  
357 These distinctive miRNA profiles in depressive disorders predispose them to becoming a promising  
358 source of biomarkers for MDD research and diagnostics. With more studies confirming their  
359 involvement in depression and with advances in miRNA expression measurement techniques (184),  
360 miRNA data may prove to be useful additions to MDD biomarker panels.

361 Several studies have demonstrated an association between telomere length and depressive disorders.  
362 Szebeni and colleagues' recent post-mortem study, previously described, found decreased expression  
363 of telomerase reverse transcriptase (TERT), an enzyme whose function is to prevent telomere  
364 shortening (TS), in oligodendrocytes derived from different parts of the brain (185). Another study  
365 found over expression of certain genes involved in propagating TS in the leukocytes of female MDD  
366 subjects (186). Specifically, these genes have been associated directly or indirectly with telomere  
367 dysfunction (STMN1, P16<sup>ink4a</sup>), oxidative stress (OGG1), and aging (OGG1) while others (FOS,  
368 DUSP1) were linked to the stress-related p38MAPK pathway, although they are not specific to  
369 depression and may be found in normal aging or anxiety disorders (186). In fact, at least one large-  
370 scale study has shown an association between symptoms of anxiety and TS in comparison to  
371 depression-associated telomere dysfunction over a 2-year period of time (187). Considering that  
372 telomere length is a biomarker of cellular aging, it is not surprising that it is more commonly  
373 associated with chronic periods of life-long depression rather than acute episodes (188).

374 Yet, shorter telomere lengths have also been observed in children of lower socioeconomic status with  
375 coexisting dopaminergic/serotonergic genetic sensitivity to harsher social environments (189). This  
376 study suggests that significant stress at an early age may be associated with genetic and biological

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377 changes that predispose children to depressive disorders. Therefore, TS may not be exclusively  
378 valuable as a biomarker in older populations, but may also be useful in identifying children who are  
379 more prone to TS as a result of immature protective mechanisms against inflammatory, oxidative,  
380 and HPA-axis effects on cellular genetic coding. Furthermore, a recent study reported a negative  
381 correlation between telomere length and cortisol reactivity in female adolescent subjects with familial  
382 risk for depression (190). This study implies how inherent HPA axis dysregulation, consistent with  
383 biological changes in depression pathology, is associated with telomere shortening that typifies the  
384 accelerated cellular aging in younger cohorts (190). Accordingly, such studies indicate TS could find  
385 more use as a predictive or screening marker in younger and geriatric populations, respectively, than  
386 a specific biomarker for MDD. However, a recent large-scale study found increased mitochondrial  
387 DNA and shortened telomere length in subjects with major depression status, but did not find either  
388 variable to correlate with increased risk of developing major depression, suggesting characteristics of  
389 a state biomarker (191). Further research will be required to elucidate the basis for these contrasting  
390 findings.

391 Lastly, significant consideration should be given to the difficulty of directly associating genetic  
392 phenotypes with psychiatric disorders. In response to this challenge, Gottesman and Gould (192)  
393 proposed criteria for developing endophenotypes, intermediary constructs that would act as tractable  
394 traits that could more effectively characterize the heritability of psychiatric disorders. Hasler et al.  
395 (193), and more recently Goldstein and Klein (194), have published detailed reviews about both  
396 psychopathological (e.g. neuroticism, anhedonia, depressed mood, increased stress sensitivity) and  
397 biological (e.g. morning cortisol, tryptophan depletion, DEX/CRH, CRH dysfunction, hippocampal  
398 volume, reduced 5HT1A receptor expression) endophenotypes for depression. However, there  
399 continues to be a relative lack of evidence for current putative endophenotypes, specifically due to a  
400 deficiency of family and twin studies (194). It is therefore possible that future endophenotype studies  
401 and analysis may contribute to the growing literature characterizing MDD as well as further the  
402 development and understanding of MDD etiology and pathophysiology that remain the most  
403 heterogeneous components of the disorder.

### 404 2.7 Epigenetics

405 Epigenetic mechanisms have been used to explain how early life exposures to toxic or stressful  
406 stimuli may contribute to the predisposition or development of mental illness (195). For depressive  
407 disorders, histone modification at the amino (N)-terminal tails and DNA methylation have been the  
408 most studied in determining how epigenetic factors affect the progression, severity, symptomatology,  
409 and treatment response of depression (196, 197). Significantly, these epigenetic modifications may  
410 affect expression of certain receptors (e.g. glucocorticoid receptors in the hippocampus), which leads  
411 to either an increased or decreased risk for depression in the future (196). This is supported by animal  
412 studies that show antidepressant-like effects of histone deacetylase inhibitors (195, 196, 198-200),  
413 which are thought to induce histone acetylation in certain regions of the brain. Overexpression of  
414 DNA methyltransferases also leads to an increase in DNA methylation and has been associated with  
415 abnormal dendritic spine plasticity and alterations in behavioral responses. Supporting this, one  
416 group found site-specific hypermethylation of TrkB-T1 to be increased in suicide completers (201),  
417 suggesting a pattern of methylation abnormalities in subjects with depressive phenotypes. Recently,  
418 epigenome-wide association studies have demonstrated several genes with methylation associations  
419 in depressed subjects compared to controls. As these studies are mostly array-based, they have had  
420 the advantage of investigating the entire genome, but replication studies are currently lacking (202).

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421 One recent genome-wide study (203) was able to separate medication naïve MDD subjects from  
422 controls by observing differences at 363 CpG sites that differed from the pattern they observed in  
423 their schizophrenia patients (204) indicating disease-specific patterns. Furthermore, several candidate  
424 gene studies involving DNA methylation have been investigated and include genes that have been  
425 previously implicated in depression. Among these genes, SLC6A4, BDNF, and NR3C1 have been  
426 the most studied, with BDNF methylation having the most consistent data concerning associations  
427 between DNA methylation and depressive symptoms/antidepressant response (202). This study  
428 demonstrated a significant association between depression and methylation levels of BDNF at  
429 specific CpG sites. Notably, the authors have shown that such robust biomarkers may come from  
430 easily obtainable specimens such as buccal samples. Although epigenetic research is still in its  
431 infancy, these epigenetic mechanisms and resulting patterns in chromatin remodeling are becoming  
432 established as a basis by which chronic social defeat, early life stress, variability of maternal care,  
433 and antidepressant therapy may influence the progression or resolution of depressive symptoms (197,  
434 202, 205, 206). Further studies and elaboration on these mechanisms will likely lead to significant  
435 advances in the development of an epigenetic model from which MDD biomarkers may be retrieved.  
436 Please see Nestler et al. (195), Tsankova et al. (197), and Januar et al (202) for further review.

### **3 Proteomics, Metabolomics, and the Utility of Multiplex Assays**

#### **3.1 Proteomic and Metabolomics Research**

439 There have been recent technological advances that have allowed more in-depth characterization of  
440 medical disorders on both the analytical and clinical level. Mass spectrometry (MS) proteomics has  
441 allowed researchers to quantify expression levels of proteins for detecting changes after translation or  
442 protein interactions (207). High performance liquid chromatography (HPLC) has been used to  
443 separate and assess proteomes/metabolites in both schizophrenia (208) and BPD (209). With  
444 depression, Martins-de-Souza's group was able to observe differing levels of various proteins  
445 involved in metabolic pathways and molecule transport between MDD subjects and control subjects  
446 ( $P < 0.05$ ) (210). Interestingly, they found that those with MDD who developed psychosis had  
447 differentially expressed proteins that were different from MDD subjects who did not develop  
448 psychosis. Thus, their report suggests that proteomes may aid in the characterization of MDD  
449 subtypes and the varied symptomology of psychiatric patients. There has also been an increase in use  
450 of high-resolution nuclear magnetic resonance (NMR) spectroscopy to evaluate biofluids to  
451 document not only baseline levels of metabolites, but produce complete time-lines of metabolite  
452 variability that may result from drug administration or medical disorders (211). Consequently, a  
453 number of recent studies have taken advantage of these more complex analytical tools to search for  
454 possible MDD biomarkers in different biological systems.

455 Using gas chromatography/mass spectrometry (GC/MS) coupled with multivariate statistical  
456 analysis, Ding and colleagues were able to produce distinct blood-based metabolic profiles that were  
457 able to separate MDD patients from healthy controls (212). Critically, their study found significant  
458 separation between a subgroup of MDD patients with "early life stress" (ELS) versus those that did  
459 not have ELS, indicating possible use for characterizing depressive subtypes. Their investigation  
460 further supports the theory of separate pathophysiologic mechanisms that cause differing metabolite  
461 concentrations between MDD subtypes. This is a significant finding given that ELS has been  
462 considered a preventable risk factor for a number of pathological psychiatric disorders (213).  
463 Similarly, Zheng and colleagues (214) used a GS/MS-based urinary metabolite signature to

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464 demonstrate significant separation of MDD from controls in both training samples and an  
465 independent test cohort that included medicated MDD subjects. Another group used HPLC to  
466 evaluate plasma levels of glutamic acid, aspartic acid, glycine, gamma-aminobutyric acid (GABA),  
467 and nitric oxide (NO) of medication-naïve melancholic MDD patients, and differentiate them from  
468 matched controls (215). The resulting data indicated that plasma GABA levels were associated with  
469 anhedonia and suicidal ideation in affected MDD subjects. The authors observed that the studied  
470 analytes could be used as trait-like biomarkers since metabolite plasma concentrations continued to  
471 be abnormal even after 2 months of fluoxetine treatment despite having no significant correlation  
472 with Hamilton Depression Rating Scale (HAM-D) scores or severity of depression. The results of  
473 this study may indicate how dysregulation of the metabolism of monoamine neurotransmitters may  
474 vary and predict the course of depression in certain individuals. Ditzen et al. (216) used 2D  
475 polyacrylamide gel electrophoresis and time-of-flight mass spectrometry peptide profiling to  
476 determine differences in CSF proteomes between depressed patients and controls finding 11  
477 significantly differentially expressed proteins and 16 phosphorylated proteins that separated the two  
478 groups. These proteins have been implicated in CNS diseases, nervous system development, and cell  
479 death. Additionally, Stelzhammer and colleagues (70) have demonstrated a number of proteomic  
480 changes in first onset, drug-naïve MDD patients including markers of inflammation (ferritin, EN-  
481 RAGE, ceruloplasmin, IL-16, serotransferrin, tenascin-C), oxidative stress (cortisol), RAS markers  
482 (ACE), and changes in growth factors (BDNF and GH). Lastly, Wang and colleagues (217) have also  
483 reported consistently high sensitivity, specificity, and accuracy in discriminating between MDD  
484 subjects and healthy controls by using matrix-assisted laser desorption ionization time-of-flight MS  
485 to determine peptide profiles in first episode, drug-naïve MDD. The potential for a laboratory-based  
486 analysis to aid in MDD patient identification validates future research using these developing  
487 technologies along with further evaluating any candidate biomarkers found to be capable of  
488 discriminating affective disorders.

### 489 3.2 Emerging Multiplex-Based Biomarkers

490 Though there have been a number of studies analyzing the various neurobiological features  
491 persistently found in depressed patients, no specific marker from a single biological system has been  
492 capable of significantly improving upon the current diagnostic criteria set for MDD patients. As  
493 several of the aforementioned biomarkers seem necessary but not individually sufficient, multiplex  
494 assays are currently the most promising to contribute consistent results to aid in further standardizing  
495 MDD diagnosis and research. As past studies have demonstrated, depression pathology is influenced  
496 by disruption from multiple systems including the HPA axis, oxidative pathways, inflammatory  
497 processes, and neurotrophic homeostasis. Collectively measuring the putative analytes of each  
498 system will likely increase the power of any diagnostic panel developed for MDD. This concept is  
499 supported by studies that used multiple analytes of different origins and considered to be potential  
500 biological markers of depressive disorders to increase specificity and sensitivity in diagnosing MDD.  
501 One study worth noting achieved high sensitivity (above 90%) and specificity (above 80%) in  
502 distinguishing MDD patients from healthy controls (218). The authors used nine biomarkers from  
503 different biological sources such as inflammatory and oxidative indices ( $\alpha 1$  antitrypsin,  
504 apolipoprotein CIII, myeloperoxidase, soluble TNF $\alpha$  receptor type II); the HPA axis (epidermal GF,  
505 cortisol); neurogenesis (BDNF); and metabolism (prolactin, resistin) to develop an algorithm that  
506 produces a score that could potentially be used for an objective diagnosis of MDD. In addition to  
507 achieving high sensitivity and specificity in their pilot study, Papakostas et al. also produced a similar  
508 performance in their replication study. This group further refined their model algorithm by factoring

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509 in gender, BMI, and normalized cortisol levels (219). Another group used CSF concentrations of  
510 multiple analytes including inflammatory biomarkers (IL-6), serotonin metabolites (5-  
511 hydroxyindoleacetic acid), dopamine metabolites (homovanillic acid), and HPA axis biomarkers  
512 (hypocretin) to detect severe suicidal behavior and increased risk of completing suicidal attempts in  
513 MDD patients (220). Likewise, CSF protein biosignatures were found to be capable of  
514 discriminating depressed, bipolar, and schizophrenic patients from healthy controls (221). These  
515 markers included proteins involved in neurogenesis (e.g. neuronal growth regulator 1, neural  
516 proliferation differentiation and control protein); neurotransmission (seizure related 6 homolog  
517 protein); and oxidative damage (glutathione peroxidase 3). However, Maccarrone and colleagues  
518 have indicated difficulties differentiating between individual psychiatric disorders and controls, as  
519 only a few proteins of their CSF biosignatures were found competent enough to distinguish between  
520 disease groups. They have reported high accuracy rates of distinguishing bipolar, depressed, and  
521 schizophrenic patients (i.e. 83.3% for MDD). Other multiplex studies that have been discussed in  
522 previous sections have also shown significant inflammatory/oxidative features (70) and epigenetic  
523 variations (203) in MDD subjects. Due to their inherent sophistication and more comprehensive  
524 analysis relative to individual markers, these multiplex assays have the potential to reduce  
525 inconsistent data that develop due to differences in study populations and methods seen in past,  
526 single biomarker studies (219). However, it is currently imperative to conduct future studies that  
527 focus on replicating and confirming such findings that yield increased MDD diagnostic accuracy  
528 using these methods.

### 529 4 Limitations of Current Research

530 The main variables that are consistently problematic in the development of a reliably viable MDD  
531 biomarker involves the heterogeneity of depressive disorder pathophysiology, etiology, and study  
532 designs, which in turn may contribute to conflicting data. As a result, variations between studies  
533 reviewed here limit the precision and generalizability of the findings. Additionally, although with  
534 notable exceptions mentioned (e.g., the ADNI study and Vreeburg *et al.* study (29)), most studies we  
535 reviewed collected data from small samples sizes often consisting of fewer than 100 subjects.  
536 Another difficulty is how to consistently associate biomarkers with DSM criteria for MDD (e.g. low  
537 mood, poor concentration, suicidal ideation), which are not always necessary in diagnosing  
538 depression and could be present in other psychiatric disorders including schizophrenia.  
539 Consequently, any biomarkers that are heavily associated with non-specific clinical symptoms of  
540 depression may produce a high rate of false positives. This is significant as the majority of studies  
541 focus on exploring biological differences between depressive disorders and control groups, but do not  
542 extensively evaluate putative biomarkers' diagnostic specificity against other psychiatric disorders.  
543 Although current research has an increasing neuroscience focus advocated by the National Institute  
544 of Mental Health through the novel Research Domain Criteria (RDoC) project (222), we are likely  
545 decades away from discovering the basic underpinnings of neurobiological changes present in  
546 psychiatric disorders and how they relate to behavioral shifts; discoveries that are necessary to  
547 determine the adequacy of developing biomarkers (223). Consequently, the only standards available  
548 to compare the validity and specificity of diagnostic biomarkers are syndromic and descriptive  
549 categories developed by expert consensus (224). Although the most recent research on MDD  
550 biomarkers has suggested the possibility of finding more objective forms of diagnostics compared to  
551 the aforementioned diagnostic criteria in clinical use today, it is still unclear how these discrete

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552 markers would relate to the diverse clinical presentations and differing populations that continuously  
553 confound research on MDD.

### 554 **5 Conclusions**

555 Multiple biological pathways are robust sources of tissue-based MDD biomarkers with trait and state  
556 characteristics. However, individual biomarkers currently impart limited clinical utility. In the  
557 future, multiplex assays comprised of putative depression biomarkers may improve upon the clinical  
558 evaluation of MDD, assess treatment efficacy, and serve to standardize discharge criteria. However,  
559 independent replication studies with large sample sizes are needed to fully substantiate the validity of  
560 such panels. Furthermore, the use of these markers are limited by high costs and confounding factors  
561 associated with each component of prospective diagnostic constituents (225). If these markers  
562 become reproducible and translate into readily available diagnostic tools with ease of access, low  
563 cost, rapid formulation, and high sensitivity/specificity, the implications for clinical use would be  
564 tremendous. After decades of investigations and several promising markers falling into obscurity, it  
565 is difficult to say whether we are getting closer or farther away from one of the holy grails of  
566 diagnostic biomarkers for depression. Suffice it to say, every study that contributes to the  
567 development of such biomarkers will assuredly be needed if such a goal is to be achieved. As the  
568 RDoC project and current technology evolve to lessen the limitations of past studies, future large  
569 scale MDD biomarker studies will be necessary to yield advances that will hopefully have utility in  
570 the clinical setting.

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