Supporting Information

1. Supplemental Note S1.
2. Supplemental Note S2. Experimental
3. Supplemental Tables T1-T6.
4. Supplemental Figures S1-S4.

Supplemental Note S1

S1.1. Definition of dementia used

As previously detailed [11], we identified significant cognitive decline/dementia by caregiver and patient report of cognitive impairment in more than one cognitive domain that interfered with function. This was rated using the Clinical Dementia Rating (CDR), which was administered as a semi-structured interview. The investigators also used the MMSE, the Dementia Rating Scale (DRS), the Frontal Assessment Battery and the Short Orientation, Memory Concentration Test, which allowed assessment of a broad range of cognitive function. This classification was highly correlated with cortical atrophy, suggesting validity.[11] We did not use the Movement Disorder Society (MDS)-criteria, which were not available at the time of classification of subjects; however, we recently retrospectively examined all subjects using our CDR-based or DRS based classification and showed considerable overlap (57-78%) with classification using an independent neuropsychological battery (using cutoffs 1.5-2 SD suggested by MDS) (McDermott K, unpublished data, presented at the International Conference on Dementia, Banff, AB, May 2016). Our classification was more comprehensive taking into account all clinically available information.

S1.2. More information on participants

Participants performed three waves of standardized assessments, including assessment for cognitive function and dementia. In brief, we used patient and caregiver reports to determine clinical dementia rating. We used cognitive and functional assessment to determine if significant cognitive decline was present.[13,14] No single test was used. The mental status assessments included the standardized Mini-Mental Status Examination, the Frontal Assessment Battery and the Clinical Dementia Scale in order to cover a broad range of cognitive function.

S1.3. Uni-variate statistical analysis

In our work, t-test and volcano plot are used for uni-variate statistical analysis.

For the pair-wise comparisons of Control vs. PD and PDND vs. PDID, we conducted "t-tests for two independent samples" for each metabolite in Excel, with the assumption of two-tailed distribution and equal sample variance. The t-test was used to determine if the means of two populations were equal. For example, by analyzing the samples from the control group and the PD group, we were informed whether the mean concentration of a specific metabolite in blood of PD patients is different from that in the blood of the healthy control group. The purpose of doing this is to determine whether a specific metabolite can be used to differentiate the PD patients from healthy controls according to blood concentrations.

Applying multiple tests to a single set of data may result in an increase in false positives. To address this issue, we followed the method described in the work of LeWitt et al.[8]. Briefly, we calculated the q-value, which is the false discovery rate (FDR) analogue of the p-value, for each p-value. The q-values were generated using QVALUE, an R package.[19] Supplemental Table T1 lists the p-values and q-values for Control vs. PD and PDND vs. PDID. A q-value represents the false positive percentile among the metabolites whose q-values are smaller than this value. For the cut-off of FDR, we used a value of 10%. We note that, in our statistical analysis, the t-test was used only as the primary screening of the significant metabolites. The selected significant metabolites were further investigated using fold change, box and whisker diagram, and ROC analysis. Therefore, starting with a relative large FDR would ensure the inclusion of more potential significant metabolites in the subsequent analyses, thereby decreasing the chance of missing some true biomarkers.

The volcano plot is a set of many uni-variate analyses (fold change and p-value/q-value). For each individual metabolite, the fold change is the ratio of the average concentration in one study group to that in the other study group. The t-tests are also individually performed for each metabolite to report the p-value and the corresponding q-value. On the volcano plot, $\log_2$ (fold change) is plotted on the x-axis and – log (q-value) is plotted on the y-axis to visualize these two parameters for all the variables. The volcano plot itself has no data analysis function. Usually there is a cut-off threshold of the fold change to determine the significantly changed variables. The criterion we used was that the fold change should be larger than 1.2 or smaller than 0.83. The red color means the fold change of this metabolite is larger than 1.2 and the q-value of it is smaller than 0.1. The blue color means the fold change of this metabolite is smaller than 0.83 and the q-value of it is smaller than 0.1.

S1.4. Definition of putative identification

Putative identification refers to a structure in the HMDB library and EML database with its mass matched to that of a detected peak pair or metabolite in the samples. Listing these putatively identified metabolites is useful not only in the present study but also for future research. For example, future researchers can consult this list of putatively identified metabolites for information about (or validation of) a specific peak pair or metabolite determined to be a biomarker or related to a specific metabolic pathway of interest. These matched structures can be used as the starting point for future confirmation including the synthesis of standards to positively identify the putative matches.

S1.5. PLS-DA regression model

A total number of 719 metabolites were included in the PLS-DA analysis. It is known that PLS-DA or OPLS-DA models may have over-fitting issues since the number of variables is usually larger than the number of samples. To avoid the case that a model gives a good separation of two groups by random chance, validation methods are needed. We actually used two methods to avoid the over-fitting issue. The first one is cross-validation, which gives the R^2 and the Q^2 values. The second is the permutation test. For the cross-validation approach, the original dataset is separated into two sub-sets. One is the training dataset and the other is the testing dataset. The training dataset is first used to generate the PLS-DA model. Since a few principal components cannot explain the total variance of the whole dataset and there is always a residual, we need a parameter to measure the goodness of the fit. The R^2 value is the ratio of the variance in the training dataset that this model can explain to the total variance in the training dataset. Therefore, R^2 estimates the goodness of fit, and an R^2 closer to 1 is preferred. After that, the testing dataset is substituted into the PLS-DA model and it then predicts the class labels of the samples in the testing dataset. The Q^2 value is the ratio of the variance in the testing dataset that this model can predict to the total variance in the testing dataset. Therefore, Q^2 estimates the goodness of prediction, and a Q^2 closer to 1 is preferred.

Empirically, a very high Q^2 value, which is usually supposed to be higher than 0.9, is believed to represent a good and valid separation. At the same time, other researchers have asserted that the model can be accepted as long as the Q^2 value is larger than 0.5. However, there is no universally accepted cut-off threshold of Q^2 value to determine whether a model should be accepted. The value of Q^2 has no statistical significance as it has no values with which to be compared. For example, it is not easy to interpret the statistical meaning of a Q^2 value of 0.51. In order to prove a Q^2 value that is not that large is not given by random chance, we need to apply a permutation test, in which the class labels of the two groups are permutated. A correlation coefficient, which is the x-axis of the permutation plot, represents how close the permutated group assignment is to the original group assignment. When the correlation coefficient is 0, the group assignment is totally randomized. For each permutated case, the R^2 and the Q^2 are calculated and plotted onto to permutation plot. The rationale behind the permutation test is that with the wrong class labels, the newly calculated classification model should not be able to predict the classes very well. Then the Q^2 of the original dataset can be compared with the Q^2 values of the randomized data. If we find that the Q^2 values of the permutated models are all much lower than the Q^2 value of the original model, we can tell that the separation of the original model is not generated by chance.

S1.6. Receiver operating characteristic curves (ROC) analysis using random forest method and criteria used for selecting the biomarkers and forming the panels

Receiver operating characteristic (ROC) curves are graphical plots that illustrate the performance of a binary classifier system as its discrimination threshold is varied. In our work, ROC analysis was used to show to diagnosis power of one or a group of metabolite candidates. There are several classification models available for building an ROC curve, such as the PLS, random forest, support vector machines, etc. Among them, we have chosen the random forest method for our analysis.

Random forest analysis (from R) was used in this report as the classifier of the ROC analysis. In general, the random forest method begins with splitting the original data set using bootstrapping into many small sub data sets. Some of these small data sets work as training sets and others work as testing sets. For each training set, a decision tree is generated. A random number out of the five biomarker candidates might be involved in one specific decision tree. An example of a decision tree can be: if No. 429 < 0.5, the result is PD; if not, it then examines No. 197; if No. 197 > 1.5, the result is PD, and if not, the result is Control. For each new testing data set input into the random forest model, each decision tree will produce a specific result. After the testing data works through many decision trees, the result with most hits (or votes) is the final output. For the testing sets, the true grouping information is known, so we can calculate the sensitivity (true positive rate) and specificity (1-false positive rate). As the software changes the cut-off thresholds in the decision trees, more pairs of sensitivity and specificity are generated. These are then used to plot the ROC curve. Random forest analysis is a powerful machine-learning-based procedure for predictive biomarker discovery analyses. The advantage of this method is that it can easily cope with missing values, outliers, and relatively small sample sizes.

For building the ROC curves, we did not simply input all 709 variables into the model and then let it find the best five biomarker candidates to use in building the ROC curve. Instead, we manually selected the candidates based on standard procedures. To select the potential biomarkers for differentiating PD vs. control, 5 metabolites were selected according to the following criteria: (1) a large fold change, (2) a q-value of smaller than 0.1 and (3) metabolite identification with high confidence (positive IDs were preferred as they could be immediately used as biomarkers if they could be validated in future studies using large cohorts of samples). The metabolites were first ranked according to their fold change. There were seven putatively identified significant metabolites with fold changes of larger than 10, and each of these generated an ROC curve with very high AUC (the lowest one was 0.914). If these metabolites could be positively identified, they would work as very strong biomarkers for the diagnosis of PD. In order to use more positively identified metabolites to build the classification model, the positively identified metabolites were selected from the top 20 ranked metabolites (according to fold change). We excluded vanillylmandelic acid as it is potentially related to catecholamine metabolism, which can be affected by the dopa medication. The three selected metabolites were vanillic acid, hydroxykynurenine and theophylline. Since the discrimination power of these three positively identified metabolites were not strong (AUC=0.698), two putatively identified metabolites with large fold changes and high-confidence putative identifications, isoleucyl-alanine and 5-acetylamino-6-amino-3-methyluraci, were added to make a 5-metabolites biomarker panel. The ROC curve of this panel of 5 metabolites produced an AUC value of 0.955 with sensitivity of 87.5% and specificity of 93.0%. Adding more metabolites to this panel resulted in only minor increase in sensitivity and specificity. Considering that in real world clinical applications a panel of a few metabolites is preferred over a panel of many metabolites, we concluded that this panel of 5 metabolites was sufficient to illustrate the overall performance of the metabolic profiles for differentiating PD vs. Control. We note that using CIL LC-MS there is no need to select the panel for targeted analysis in a validation study. CIL LC-MS is a quantitative method where thousands of metabolites can be analyzed in one LC-MS run. Thus, the selected biomarkers discussed in this work are only used to illustrate the separation performance. These biomarkers, along with all other labeled metabolites, will be monitored in our future validation studies. This approach will increase the likelihood of finding the high performance biomarkers which may be different from the initial biomarkers determined using a small cohort of discovery samples.

We followed a similar procedure for PDND vs. PDID discrimination. The minor variations were that, although we began with the top 20 metabolites according to the fold change and q-value, the positively identified metabolites did not produce a good classification model. Therefore, we selected a combination of eight positively and putatively identified metabolites with the highest fold changes. This panel gave a very good performance as discussed in the text.

We are aware—and it is generally known—that different selection criteria can result in the inclusion of different biomarker candidates. This, in turn, could lead to small changes in the observed ROC curves. One efficient way for selecting the biomarker candidates is to sort the uni-variate AUCs from high to low and pick the highest-ranked metabolites. Since a large fold change does not necessarily mean a large AUC, the selected biomarker candidates might be slightly different from the list of biomarkers that we are using. However, we followed a standard, efficient and productive procedure. As an illustration, we built another ROC curve with five metabolites (Numbers 429, 562, 563, 135 and 197) according to uni-variate AUC. Among these five, No. 429 and No. 135 are being used in the current panel (of the present report) and No. 562, No. 563 and No. 197 are new. The AUC of the new ROC curve is 0.973 (95% confidence interval: 0.930-0.998). Comparing to the current panel (AUC=0.955), the diagnosis power (AUC) is not greatly improved, but the confidence of metabolite identification is lower (No. 562 and No. 563 can only be matched to the EML library). Therefore, we chose to use more comprehensive criteria for selecting the biomarker candidates in the present study.

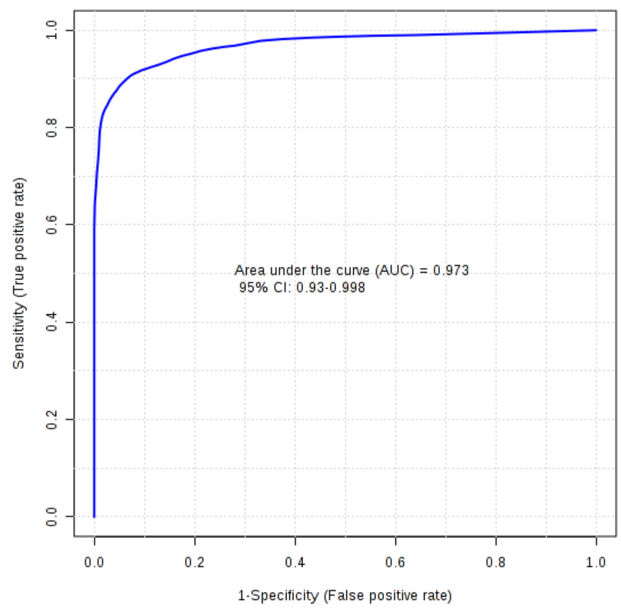


Figure 1. ROC curve generated by random forest model using No. 429, No. 562, No. 563, No. 135 and No. 197.

We also note that random forest models can handle more biomarker candidates and that an optimized number of metabolites can be found by comparing the AUC values of multiple models. For the PDND vs. PDID study, we input all the 36 significantly changed metabolites into Metaboanalyst, and these metabolites were ranked by application of a random forest analysis. Subsequently, different numbers of the top-ranked metabolites were used to generate the ROC curves. Figure 2 (see below) shows a series of ROC curves generated from different numbers of variables. For example, the red ROC curve (AUC = 0.729) is produced by the top two metabolites. Clearly, the remaining curves, each of which reflects the results after including more variables in the system, are associated with increasing discrimination power. The highest discrimination (AUC = 0.904) is produced by the analysis that includes all 36 metabolites. However, for clinical diagnostic purposes, we were trying to balance (1) achieving high sensitivity and specificity with (2) minimizing the required number of metabolites in the diagnosis panel. For real-world applications, a smaller set of biomarkers will be easier to quantify. Moreover, half of the present 36 significant metabolites have not yet been identified. As we noted earlier, we determined a priori that we wanted to include only the identified metabolites in the discrimination panel. For this reason, we did not input all the significant metabolites into the system. For the PDND vs. PDID, we selected 8 metabolites according to our criteria, and the resulting AUC is close to that produced by the 20-metabolite panel.

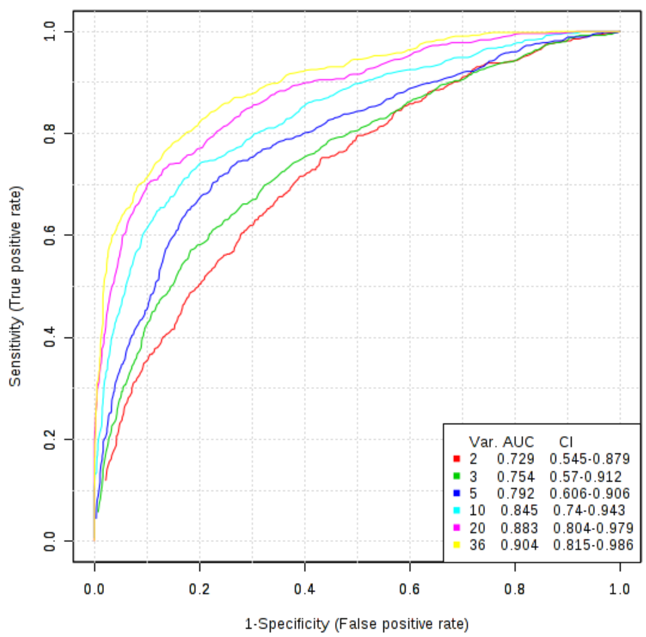


Figure 2. Comparison of ROC curves generated from different numbers of variables (2 variables in red, 3 variables in green, 5 variables in dark blue, 10 variables in sky blue, 20 variables in purple and 36 variables in yellow).

For Control vs. PD, as we mentioned before, seven putatively identified significant metabolites with fold changes of larger than 10, and each of these generated an ROC curve with very high AUC (the lowest one was 0.914). So inputting more metabolites into the system will further increase the discrimination power. However, as more significant metabolites are positively identified, we prioritized the positively identified metabolites when selecting the biomarker candidates. We also generated an ROC curve with all the 11 positively identified metabolites among the 76, including citrulline, methionine mulfoxide, isomer of methionine mulfoxide, pantothenic acid, glycyl-valine, vanillylmandelic acid, pipecolic acid, theophylline, Vanillic acid, hydroxykynurenine and serotonin. The resulting ROC curve is shown in Figure 3. The AUC value is 0.979, and the sensitivity and specificity at the optimal point are 90.0% and 96.0%, respectively. Compared to the current 5-metabolites panel, the performance improvement is not very significant, so we retain the current panel as a smaller panel size is preferred.

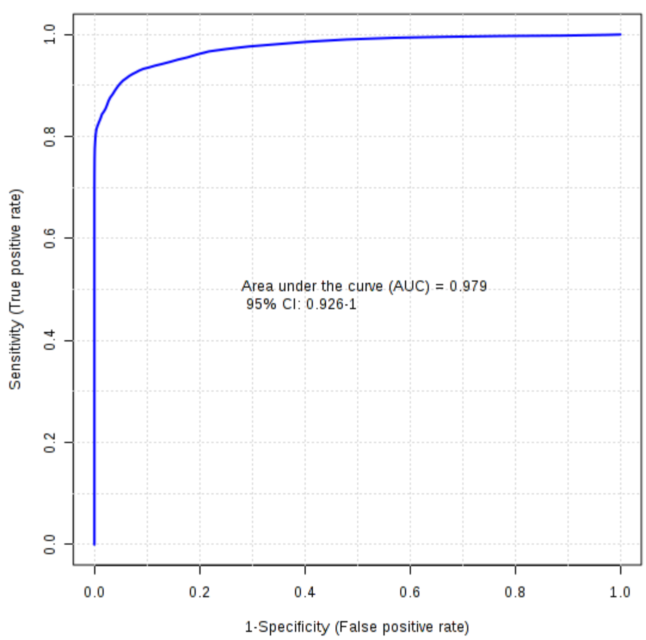


Figure 3. ROC curve generated by the random forest model using 11 positively identified significant metabolites for the Control group and PD group.

S1.7. Permutation tests for ROC curves

To address the issue of potential over-fitting in generating ROC curves from the biomarker panels, we did a permutation test, which can help detect potential over-fitting. The group assignment of the original data set was permutated to generate many other ROC curves, as shown in the graph (see Figure 4 below). In this permutation graph for the ROC curve of Control vs. PD, we can clearly see that the ROC curves generated with the 5-metabolites panel and randomized group assignments are all around the diagonal, representing the random conditions. As the AUC of our curve is much better than those of the permutated curves, we can conclude that there is no significant over-fitting issue. We also show the permutation test result of the biomarker panel for PDND vs. PDID (see Figure 5 below). Although the distance between the original data and the permutated data is not as large as in the first graph (Figure 4), it still shows a clear separation and thus over-fitting is not an issue in this case either.

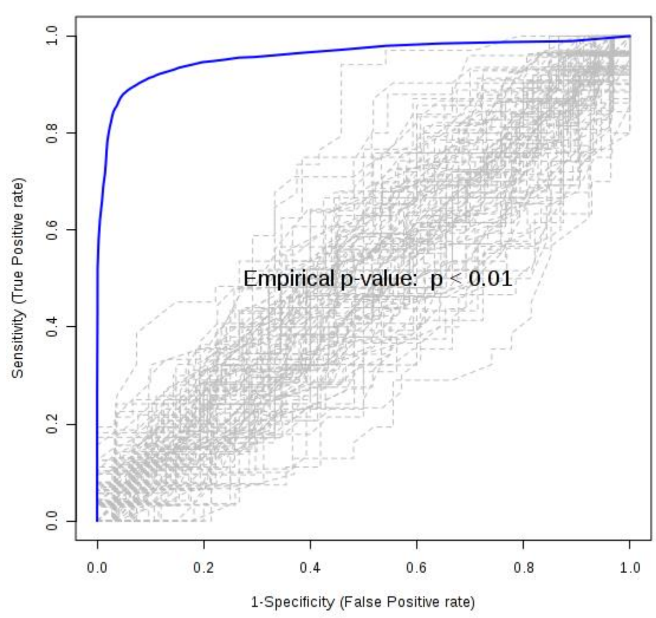


Figure 4. Permutation test result for the ROC curve of Control vs. PD.

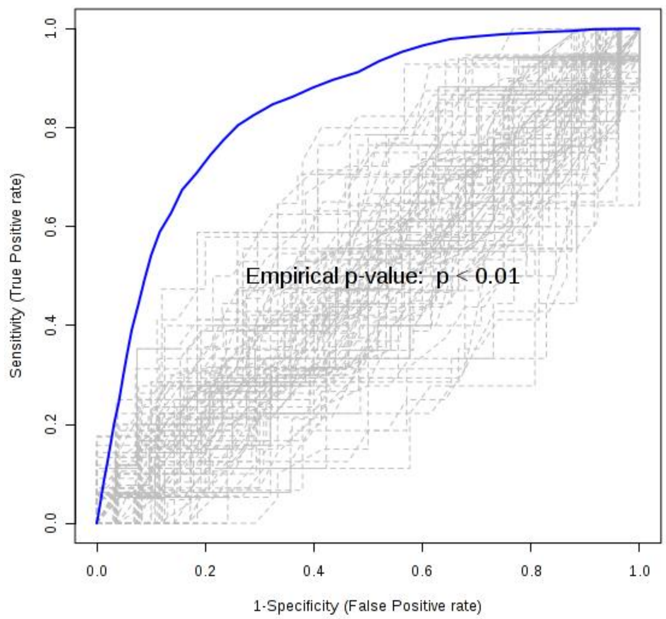


Figure 5. Permutation test result for the ROC curve of PDND vs. PDID.

S1.8. Effect of unidentified metabolites used in the panels on differentiation performance

In the list of significant metabolites, there were 38 detected metabolites that could not be matched to the dansyl standard library or the human metabolome databases. Supplemental Table S6 lists the fold changes and p-values of these unidentified metabolites along with those of the identified (positively or putatively) metabolites used as the current biomarker panels. We list p-values in this table as the p-value is more straight forward when we are comparing uni-variate analysis results, and the variable with smaller p-value always has a smaller q-value.

For Control vs. PD, the five identified metabolites currently used and their fold changes are: vanillic acid (3.48), hydroxykynurenine (2.73), theophylline (0.48), isoleucyl-alanine (0.66) and 5-acetylamino-6-amino-3-methyluracil (0.61). Among the 38 unidentified metabolites, only the fold change of ID506, 1.65, is larger than the worst one in the current panel, which is 5-acetylamino-6-amino-3-methyluracil (0.61). Therefore, we used ID506 to replace 5-acetylamino-

6-amino-3-methyluracil to build a new 5-metabolites panel, and the resulting ROC curve is shown in Figure 6 (see below). The AUC of the new ROC curve is 0.956, which is very close to that of the current 5-metabolites panel (0.955). Based on this analysis, we determined that it was not necessary to use the unidentified metabolites in the current diagnosis panel.

For PDND vs. PDID, none of the 38 unidentified metabolites surpassed the eight metabolites currently being used according to the fold change and p-value. Therefore, there was no need to use the unidentified metabolites to build a new panel.

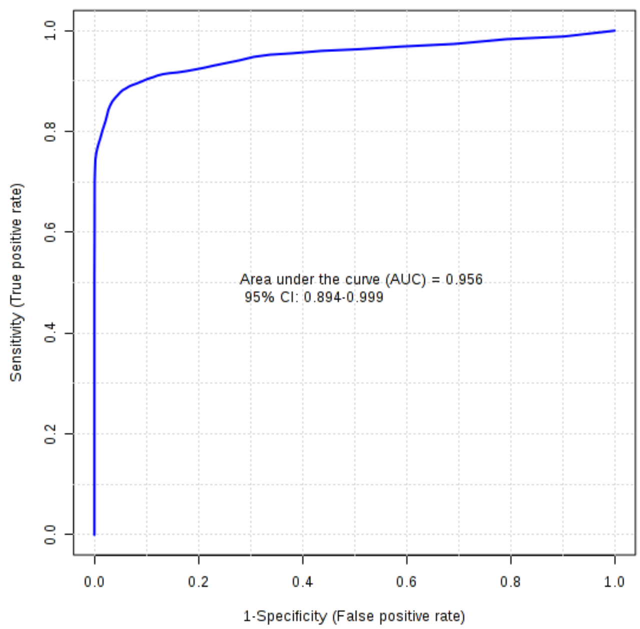


Figure 6. ROC curve generated by the random forest model using 5 metabolite biomarker candidates: vanillic acid, hydroxykynurenine, theophylline, isoleucyl-alanine and unknown ID506.

S1.9. Comparison of biomarkers found using PLS-DA analysis and those by the random forest method.

The PLS method can be used to predict grouping information and to perform ROC analyses. With the PLS-DA model for differentiating between Control and PD groups, we generated a ROC curve with an AUC of 0.936 (see Figure 7 below). However, compared to the random forest method, the PLS-DA approach has some disadvantages. Specifically, it can be more significantly affected by the presence of missing values in the metabolite-intensity data matrix, which may explain the observation of a more "lumpy" curve. In addition, the PLS-DA model is susceptible to the over-fitting problem if validations are not properly performed. Therefore, we chose to use the random forest method to conduct the ROC analyses in this research project.

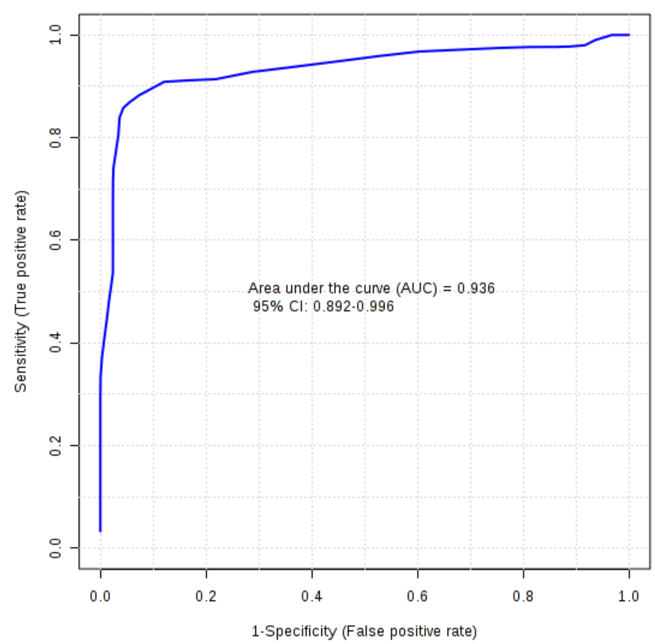


Figure 7. ROC curve generated by the PLS-DA model for Control vs. PD.

Nevertheless, we have investigated the differences in the results generated by the two statistical models: PLS-DA and random forest method. The MetaboAnalyst program assesses the variable importance in terms of a VIP score for the PLS-DA method, or in terms of a Mean

Decrease Accuracy (variables ranked by their contributions to classification accuracy) for the random forest method. In Table 1 (see below), we have listed the top 15 significant metabolites (for Control vs. PD) from both methods, with their VIP scores and Mean Decrease Accuracies, respectively. The metabolites commonly existing in the two lists are labeled in red.

Table 1. List of top 15 significant metabolites (for Control vs. PD) according to the VIP score (from the PLS-DA model) or the Mean Decrease Accuracy (from the random forest model). The common metabolites are shown in red.

PLS-DA		Random Forest	
Variable No.	VIP score	Variable No.	Mean Decrease Accuracy
502	4.2071	502	0.020725
714	3.9855	714	0.017421
429	3.9477	429	0.015893
306	3.8046	306	0.015729
563	3.6543	562	0.010278
562	3.5936	249	0.0091136
712	3.4930	563	0.0084603
249	3.4643	570	0.0077845
570	3.2113	355	0.0060562
355	2.9694	712	0.0050555
612	2.6587	710	0.0043272
135	2.6199	135	0.0031059

292	2.5076	612	0.0030599
295	2.4832	541	0.0028203
294	2.4743	707	0.0027604

As can be seen in the table, 13 metabolites have high rankings in both methods, and the orders of the top 5 metabolites are exactly the same. Based on these results, we conclude that the two statistical models (PLS-DA and random forest analyses) provide equivalent biomarker candidates.

S1.10. Differentiation of the more demented versus less demented subjects

There were relatively few patients within each dementia severity range as this was an incident cohort (subjects were initially non-demented) with relatively short follow up (36 months). When we divided groups according to clinical severity there were 6 with mild dementia and 10 with more moderate to severe dementia at the final time point. While recognizing the sample size was small, we performed the PLS-DA analysis to see if we could differentiate these two groups. The PLS-DA score plot and the permutation test result are shown in Figures 8 and 9 (see below). Although the two group sizes were small, a good separation model with R^2=0.987 and Q^2=0.766 was generated and this model passed the permutation test.

In addition, we did the uni-variate ROC analyses of the metabolome data set for differentiating the two groups. The top five metabolites with the highest AUC values were found to be: ID329 (m/z 163.1034, putatively identified by the EML library with structure matches shown in Supplemental Table T3) (AUC=0.938), 5-acetylamino-6-amino-3-methyluracil (putatively identified by the HMDB library with structure matches shown in Supplemental Table

T3 and used in the panel for differentiating Control vs. PD) (AUC=0.875), theophylline (definitively identified by Dns-library and used in the panel for differentiating Control vs. PD) (AUC=0.867), ID496 (m/z 126.0316, putatively identified by the EML library) (AUC=0.858) and ID478 (m/z 245.0697, putatively identified by the EML library) (AUC=0.825). It is interesting to note that, among the top five metabolites, two of them are related to both the onset of PD and the progression of dementia.

We also examined the AUCs of the eight metabolites used in the diagnosis panel for differentiating PDID from PDND for differentiating the more demented vs. less demented subjects. They are: His-Asn-Asp-Ser (AUC=0.742), 3, 4-dihydroxyphenylacetone (0.625), desaminotyrosine (0.604), hydroxy-isoleucine (0.604), alanyl-alanine (0.571), putrescine [-2H] (0.654), purine [+O] (0.775) and its riboside (0.783). Among these eight metabolites, three metabolites have relatively high discrimination power (AUC> 0.7) for determining dementia severity.

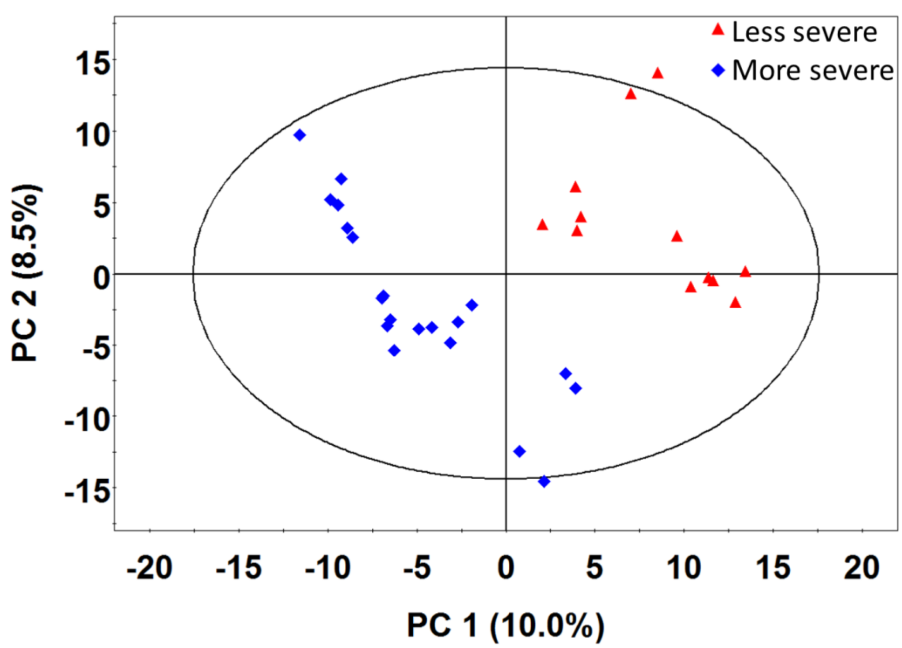


Figure 8. PLS-DA score plot for differentiating PD patients with less severe dementia vs. more severe dementia.

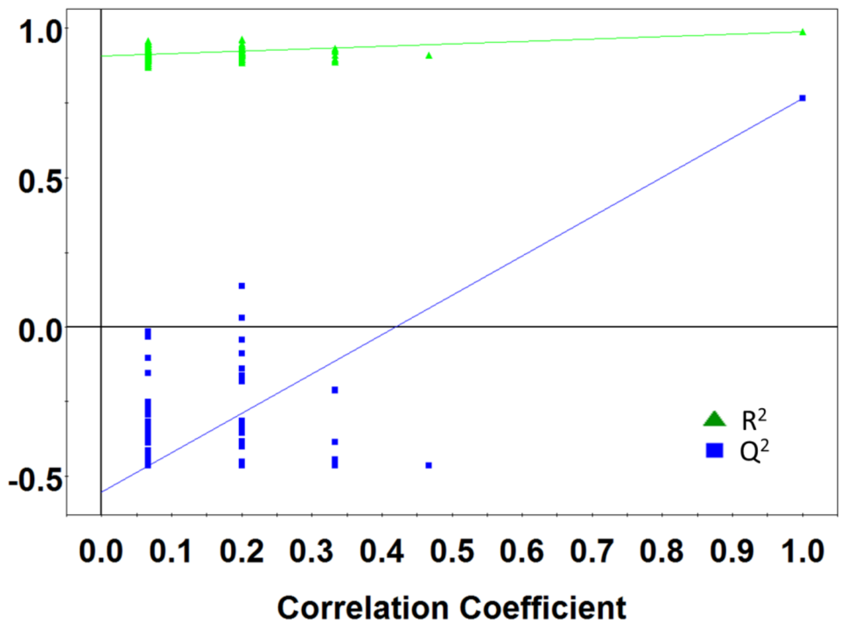


Figure 9. Permutation test result of the PLS-DA model shown in Figure 6.

S1.11. Age effect on group separation

We have examined the effect of age within the healthy control group. The 42 participants at baseline ranged from 65 to 84 years old, with an average of 71. We split the healthy group into two age groups: 22 individuals under 71 and 20 individuals of 71 or older. We used the PLS-DA analysis to investigate the difference between these two groups. The resulting score plot is shown in Figure 10 (see below). Although there is a separation of the two groups in the plot, the Q^2 value of the model is only 0.477, indicating that the separation is not valid.

We also performed the uni-variate ROC analyses of the metabolites used in the two diagnosis panels. The metabolites and their corresponding AUCs are: vanillic acid (0.586), 3-

hydroxykynurenine (0.540), theophylline (0.664), isoleucyl-alanine (0.584), 5-acetylamino-6-amino-3-methyluraci (0.651), His-Asn-Asp-Ser (0.610), 3, 4-dihydroxyphenylacetone (0.584), desaminotyrosine (0.682), hydroxy-isoleucine (0.535), alanyl-alanine (0.510), putrescine [-2H] (0.563), purine [+O] (0.503) and its riboside (0.520). These AUC values are low, indicating that these metabolites do not differ significantly between the two age groups.

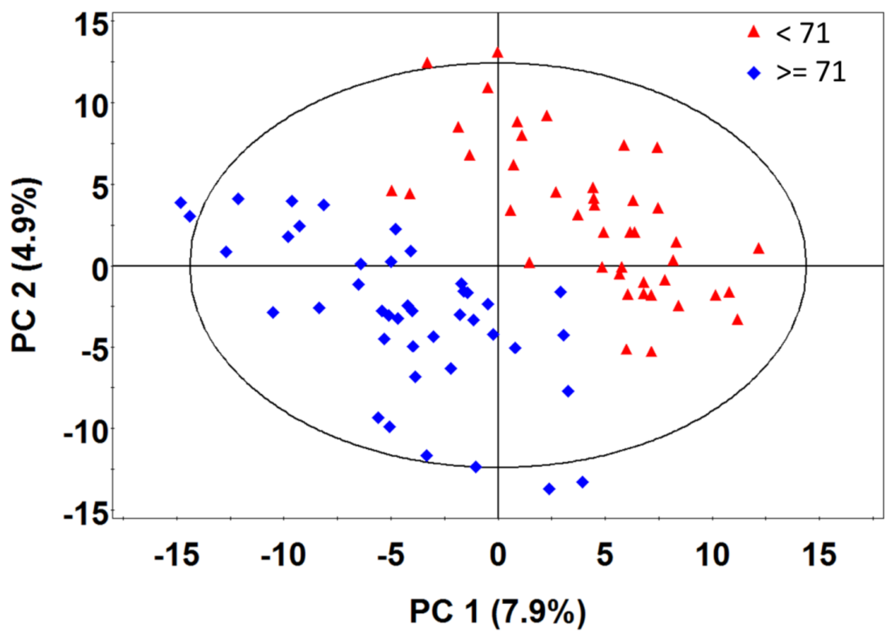


Figure 10. PLS-DA score plot for differentiating healthy people below and above 71 years old.

S1.12. Limitations due to medication, diet and single-time sample collection

In this study, the majority (all but 2) of the patients were on levodopa with few on additional medications. When we compared total levodopa (not equivalents) between those with and without future cognitive impairment there was a difference between groups [cognitively intact mean (SD): 452 (278); dementia mean (SD) 641 (286); $p = 0.049$]. To minimize the influence of medication on group differentiation, we excluded the detected metabolites which are involved in the dopa metabolism pathway. These include dopa-sulfate, dopamine-3-O-sulfate, dopamine-4-O-sufate, 3-methoxytyrosine, 3, 4-dihydroxyphenylethanol, 3, 4-dihydroxyphenylacetic acid, 3-methoxy-4-hydroxyphenylethyleneglycol and homovanillic acid. The pre-analysis exclusion approach has been used in many other studies, such as the work of LeWitt et al.[8] However, it remains possible that levodopa itself may have influenced the results.

On diet effect, in this work, subjects came to the study in the morning after taking morning medication but no food or caffeine. They were given a breakfast after the samples were obtained. While it would have been ideal to take samples before medication this was a symptomatic group of patients and we felt it would be challenging (logistically and ethically) to withdraw patients from medication. Clearly this is something to consider in follow up validation studies.

On sample collection, we collected blood only at baseline, not at multiple time points, and thus intra-patient comparisons of changes in metabolome profiles are not possible. A predictive analysis to check if PD patients without dementia at baseline have specific profiles with respect to the evolution to dementia is not possible either. We would recommend this follow-up blood collection for future research. We note that, in this work, our research goal was to compare PD with PDID, where the PD group was stable for the full period (and thus PDND) and the PDID is PDND at baseline but PDID 3 years later. This is a very interesting challenge, comparing two groups who, for all clinical purposes, were members of the same phenotype at baseline, with one developing dementia during the ensuing three years. We asked whether there would be detectable biomarker differences between these groups prior to their bifurcation into two subgroups. This attempt to discover early biomarkers of incipient dementia in PD patients was successful. Our design did not permit analyses of stable PDND and PDID, as we did not collect blood at the third wave. The patients diagnosed at the onset of cognitive decline; therefore, they were very early in the course of cognitive decline.

S1.12. Correlations of other measures of PD progression with metabolomic changes.

We have not examined correlations of other measures of PD progression with metabolomic changes. Future work using a larger number of subjects might enable us to examine selected correlations. In this work, we avoided examining motor assessments as they may be more directly related to treatment. PD medications can improve motor status, but not cognitive function. No patients were on medications for cognition. We showed in our previous longitudinal study that motor and cognitive decline were correlated (MMSE/UPDRS linear correlation r=0.244, p=0.029).[13,14] Moreover, the motor measures are not readily dichotomized as present/absent. Of course all patients by definition had motor impairment at baseline (not significant cognitive impairment) and our goal of this work was to examine the incidence of cognitive decline.

S1.13 Internal validations for the statistical studies.

An external validation with new samples is essential to this work, and this will be done in the future. With the current data, we took several steps to establish internal validation. We used cross-validation and permutation procedures together with statistical methods. Specifically, for the PLS-DA analysis, the R2 and Q2 values are actually generated by cross-validation. A part of the data was used as the training set and the remaining data were used as the testing set. The good R2 and Q2 values showed that the PLS-DA separation between the two groups was valid. Subsequently, this result was further validated by a permutation test, which rearranged the grouping information. In addition, the ROC curve was validated by a permutation test to avoid over-fitting. Finally, to manually perform a cross-validation for the diagnosis panels, we randomly picked some samples from each study group and label them as "new data" before re-inputting them into the diagnosis model provided by Metaboanalyst. If the output group information of these samples from the diagnosis model can match to their true group information, our diagnosis model can be validated by this small internal set of samples.

For Control vs. PD, we randomly picked 10 control and 10 PD samples and labeled them as "new data" to be the testing set. The current 5-biomarker panel correctly grouped all of them. For the PDND vs. PDID panel, we randomly chose 5 PDND samples and 5 PDID samples to serve as the testing set, and the result also showed very good prediction power. The results are shown in the following tables (Table 2 and Table 3).

Table 2. Prediction results of 10 control samples and 10 PD samples given by the 5-biomarker panel.

Name	Probability	True Class	Output Class
010-New	0.95734	Control	Control
014-New	0.95294	Control	Control
033-New	0.95021	Control	Control
035-New	0.83045	Control	Control
037-New	0.75114	Control	Control
040-New	0.79774	Control	Control
046-New	0.86796	Control	Control
050-New	0.80981	Control	Control

067-New	0.98047	Control	Control
074-New	0.88057	Control	Control
002-New	0.98836	PD	PD
004-New	0.85274	PD	PD
013-New	0.73185	PD	PD
020-New	0.84236	PD	PD
021-New	0.92356	PD	PD
026-New	0.99681	PD	PD
032-New	1	PD	PD
047-New	1	PD	PD
081-New	0.64957	PD	PD
096-New	0.99998	PD	PD

Table 3. Prediction results of 5 control samples and 5 PD samples given by the 8-biomarker panel.

Name	Probability	True Class	Output Class
003-New	0.91	PDND	PDND
017-New	0.94	PDND	PDND
022-New	0.97333	PDND	PDND
029-New	0.99	PDND	PDND
081-New	0.99	PDND	PDND

008-New	0.93667	PDID	PDID
019-New	0.77667	PDID	PDID
028-New	0.77333	PDID	PDID
043-New	0.88333	PDID	PDID
072-New	0.79667	PDID	PDID

Supplemental Note S2. Experimental details.

Dansylation Labeling

Briefly, the frozen serum samples were thawed in an ice-bath and then centrifuged at 14000 rpm for 15 min. 30 µL supernatant was taken into an Eppendorf tube and was mixed with 90 µL methanol. The mixture was then incubated at -20 ^{0}C for 2 hours to precipitate the proteins. After this, the mixture was centrifuged at 14000 rpm for 15 min. 90 µL supernatant was taken and dried using a Speed Vac. The sample was re-dissolved to 75 µL with 2:1 Water/ACN. Then 25 µL of 250 mM sodium carbonate/sodium bicarbonate buffer were added into the sample to make a basic environment for the dansylation reaction. The solution was vortexed, spun down, and mixed with 50 µL of freshly prepared ^{12}C-dansyl chloride solution (18 mg/mL) (for light labeling) or ^{13}C-dansyl chloride solution (18 mg/mL) (for heavy labeling). After 45 min incubation at 40 ^{0}C, 10 µL of 250 mM NaOH was added to the reaction mixture to quench the excess dansyl chloride. The solution was then incubated at 40 ^{0}C for another 10 min. Finally, formic acid (425 mM) in 1:1 ACN/H_2O was added to consume excess NaOH and to make the solution acidic.

LC-UV quantification

To perform the LC-UV quantification, a Waters ACQUITY UPLC system with a photodiode array (PDA) detector was used. Briefly, 4 µL of the labeled serum was injected onto a Phenomenex Kinetex C18 column (2.1 mm × 5 cm, 1.7 µm particle size) for a fast step-gradient run. Solvent A was 0.1% (v/v) formic acid in 5% (v/v) ACN, and solvent B was 0.1% (v/v) formic acid in ACN. The gradient started with 0% B for 1 min and was increased to 95%

within 0.01 min and held at 95% B for 1 min to ensure complete elution of all labeled metabolites. The flow rate used was 0.45 mL/min. The peak area, which can represent the total metabolite concentration in the sample, was integrated using the Empower software (6.00.2154.003). Based on the quantification results, the ^{12}C- and ^{13}C-labeled samples were mixed in equal amounts.

LC-MS

For LC-MS, an Agilent 1100 series binary system (Agilent, Palo Alto, CA) and an Agilent reversed-phase Eclipse plus C18 column (2.1 mm×100 mm, 1.8 µm particle size, 95 A pore size) were used. LC solvent A was 0.1% (v/v) formic acid in 5% (v/v) ACN, and solvent B was 0.1% (v/v) formic acid in ACN. The gradient elution profile was as follows: t = 0 min, 20% B; t = 3.5 min, 35% B; t = 18.0 min, 65% B; t = 24.0 min, 99% B; t = 28.0 min, 99% B. The flow rate was 180 µL/min. After one injection, the column was re-equilibrated with the initial mobile phase conditions for 15 min before injecting the next sample. The flow was loaded to the electrospray ionization (ESI) source of a Bruker maXis impact high-resolution quadrupole time-of-flight (Q-TOF) mass spectrometer (Bruker, Billerica, MA). All MS spectra were obtained in the positive ion mode. According to the UV-quantification result, 1.5 nmol of each labeled and mixed samples were injected into the LC-MS system.

Supplemental Table T1A. List of p-values for Control vs. PD and their corresponding q-values.

Metabolite No.	p-value (Control vs. PD)	q-value
714	4.36723E-25	1.37965E-22
429	2.51001E-22	3.96468E-20
306	1.96549E-21	2.06972E-19
563	3.2338E-21	2.55397E-19
562	2.48068E-18	1.56734E-16
612	2.47553E-10	1.30341E-08
135	4.25845E-10	1.92184E-08
294	6.72466E-10	2.65548E-08
295	8.17867E-10	2.8708E-08
292	9.36915E-10	2.95981E-08
712	2.26622E-09	6.27936E-08
249	2.38525E-09	6.27936E-08
261	3.95641E-09	9.61437E-08
293	4.37211E-09	9.86566E-08
197	4.82678E-09	1.01655E-07
355	1.64753E-08	3.25294E-07
370	2.37768E-08	4.41842E-07
570	2.65643E-07	4.66218E-06
145	3.20163E-07	5.32329E-06
258	3.98612E-07	6.29627E-06
364	4.75583E-07	7.15435E-06
67	5.37216E-07	7.71417E-06
506	5.74752E-07	7.89434E-06
50	1.73198E-06	2.23002E-05
259	1.76476E-06	2.23002E-05
248	2.21932E-06	2.69656E-05
436	2.9605E-06	3.46389E-05
569	4.59489E-06	5.18418E-05
244	5.0635E-06	5.51589E-05
245	5.9434E-06	6.25859E-05
363	7.40308E-06	7.54421E-05
350	9.26915E-06	9.14614E-05
117	9.55408E-06	9.14614E-05
129	1.44768E-05	0.000134511
41	1.99879E-05	0.000173992
95	2.02249E-05	0.000173992
148	2.03783E-05	0.000173992
416	2.4916E-05	0.000207137
127	2.73085E-05	0.000221206
489	3.55633E-05	0.00028087
260	3.842E-05	0.000296031
243	5.03161E-05	0.000378461
26	5.26619E-05	0.000386893

564	5.9969E-05	0.000430563
390	6.6412E-05	0.000457221
568	6.74904E-05	0.000457221
130	6.80239E-05	0.000457221
692	7.27492E-05	0.000478795
468	7.63775E-05	0.000492416
490	8.58988E-05	0.000542725
105	0.000102095	0.000632408
25	0.000120241	0.000730486
459	0.000134715	0.000802977
19	0.000176188	0.001030731
289	0.000217362	0.001248486
42	0.000240283	0.001327066
128	0.000242861	0.001327066
193	0.000243645	0.001327066
299	0.000267846	0.001411479
561	0.000268079	0.001411479
492	0.000294751	0.00152647
467	0.00031634	0.001611853
352	0.000331053	0.001660045
637	0.00035722	0.001763269
222	0.000374031	0.001817846
186	0.000406398	0.001945228
300	0.000458023	0.00215961
525	0.000465929	0.00216458
584	0.000482089	0.002207197
546	0.000494707	0.00223261
100	0.000544488	0.002422662
544	0.000572622	0.002460633
256	0.000577747	0.002460633
171	0.000580274	0.002460633
139	0.000584178	0.002460633
16	0.000594638	0.002465572
567	0.00060096	0.002465572
231	0.000613394	0.002484322
24	0.000636676	0.002545976
485	0.000652464	0.002576496
134	0.000731135	0.002851514
515	0.000762955	0.002914499
237	0.000765736	0.002914499
706	0.000837369	0.003149202
483	0.000955485	0.00355114
635	0.000967734	0.003554843
476	0.001007795	0.00365945
461	0.001037269	0.003723674
710	0.001081556	0.003805328
361	0.001084106	0.003805328

664	0.001193308	0.004104391
538	0.001195291	0.004104391
420	0.001232596	0.004186978
268	0.00132032	0.004437253
668	0.001524925	0.005070932
247	0.001773423	0.005835848
516	0.001857864	0.006050692
165	0.001911013	0.00616028
164	0.001955518	0.006240071
266	0.002050792	0.006456061
402	0.002064078	0.006456061
373	0.002146816	0.006649019
458	0.002266461	0.006951426
376	0.002339369	0.007044226
588	0.002341314	0.007044226
422	0.002398475	0.007148126
423	0.00260853	0.007701493
6	0.002934427	0.008583461
576	0.003021261	0.008680801
693	0.003022662	0.008680801
320	0.003052833	0.008688463
362	0.003393073	0.009570576
585	0.003443416	0.009626622
273	0.003516768	0.009745447
187	0.003649836	0.01002625
541	0.003720251	0.01013158
330	0.003753259	0.01013411
460	0.003951835	0.01057985
340	0.004063158	0.01072691
650	0.004074675	0.01072691
421	0.004253865	0.01109391
369	0.004284315	0.01109391
358	0.004361326	0.01114664
667	0.004431528	0.01114664
374	0.004434946	0.01114664
326	0.004445817	0.01114664
359	0.004527393	0.01126179
478	0.004566157	0.01126948
595	0.004629839	0.01133807
419	0.004861893	0.01181476
346	0.00491172	0.01184473
618	0.005150872	0.01232735
583	0.005302785	0.0125955
271	0.005349705	0.01261212
589	0.005839823	0.0136656
45	0.006165188	0.0143209
121	0.006359416	0.01466424

558	0.006481494	0.01483744
149	0.006705816	0.01524052
160	0.006854083	0.01546622
124	0.006948614	0.01556833
647	0.007078454	0.01574755
303	0.007233981	0.01598101
87	0.007809766	0.01701767
594	0.007810976	0.01701767
536	0.007983025	0.01704753
5	0.008065584	0.01704753
1	0.00808396	0.01704753
49	0.008088121	0.01704753
641	0.008148316	0.01704753
188	0.008148458	0.01704753
120	0.008266799	0.01707095
505	0.008267731	0.01707095
89	0.008459466	0.01735342
168	0.008673011	0.0176767
551	0.009269431	0.01875969
479	0.009323143	0.01875969
40	0.009386477	0.01876759
695	0.009474326	0.01882409
534	0.009550873	0.01885758
191	0.009743173	0.01911778
315	0.009874502	0.01925587
172	0.010050145	0.01947815
571	0.010274025	0.01979063
514	0.010493926	0.02009171
194	0.010736067	0.02043149
10	0.010820579	0.02044418
166	0.010872167	0.02044418
153	0.01111443	0.02072722
511	0.01119717	0.02072722
408	0.01121952	0.02072722
154	0.011422682	0.02097986
661	0.011508735	0.02101573
221	0.011628236	0.02111191
683	0.01178037	0.0212659
465	0.012089209	0.02169942
132	0.012174357	0.0217288
48	0.012415339	0.02192458
126	0.012422857	0.02192458
559	0.012702167	0.02229298
537	0.012914758	0.0224762
22	0.012948855	0.0224762
144	0.013079123	0.02257826
560	0.01376193	0.02362234

623	0.013833489	0.02362234
178	0.014059022	0.02376306
481	0.014128853	0.02376306
590	0.014141559	0.02376306
92	0.014289389	0.023857
634	0.014348504	0.023857
327	0.015207838	0.02515342
94	0.015376995	0.02530073
51	0.015566708	0.02548017
210	0.015730192	0.0255619
624	0.015778469	0.0255619
580	0.015896687	0.02562202
314	0.016423844	0.02630334
401	0.016510223	0.02630334
648	0.016569181	0.02630334
62	0.016935596	0.02675059
452	0.018332302	0.02874236
383	0.018446111	0.02874236
510	0.018470059	0.02874236
246	0.018560502	0.02874236
413	0.018786428	0.02895031
68	0.018917683	0.02901106
615	0.019101233	0.02915103
550	0.019390862	0.02945077
190	0.019958628	0.03016805
604	0.021447777	0.03214988
540	0.021473307	0.03214988
487	0.022065234	0.03284877
274	0.022148067	0.03284877
143	0.02259873	0.03336055
312	0.022893711	0.03363881
170	0.023097414	0.033781
23	0.023221746	0.03380633
549	0.023477551	0.03402195
446	0.023679092	0.03405076
397	0.023713005	0.03405076
349	0.0238892	0.03414855
412	0.024351279	0.03465227
387	0.024533541	0.03475508
625	0.024879447	0.03508776
101	0.025277213	0.03549029
451	0.025985395	0.03632317
334	0.026363525	0.036353
632	0.02644183	0.036353
609	0.026458555	0.036353
707	0.026467029	0.036353
66	0.027206936	0.0372075

183	0.027640172	0.03763706
353	0.028407721	0.03851619
603	0.028558353	0.03855495
174	0.028825476	0.03874998
9	0.029282385	0.03915177
385	0.029372225	0.03915177
407	0.029646856	0.0392949
167	0.029728377	0.0392949
39	0.030229472	0.03954668
156	0.030285366	0.03954668
310	0.030337629	0.03954668
46	0.030419593	0.03954668
555	0.031301964	0.04035115
520	0.031375045	0.04035115
169	0.031421591	0.04035115
473	0.032173385	0.04114932
378	0.032730824	0.04159753
557	0.032787173	0.04159753
675	0.033418721	0.04206207
309	0.033419621	0.04206207
447	0.033748256	0.04230714
417	0.034222456	0.04273203
220	0.034599136	0.04303229
286	0.034911406	0.04325039
86	0.036058742	0.04449728
587	0.036255638	0.04453933
556	0.036374788	0.04453933
654	0.036985418	0.04511216
586	0.037697086	0.04580336
496	0.038526566	0.04663185
36	0.038859947	0.04685585
152	0.039070461	0.04693055
155	0.039240098	0.04695578
480	0.039457896	0.04703823
608	0.040676694	0.04830887
670	0.041004384	0.04851566
456	0.041806951	0.04928067
672	0.043896235	0.05155109
141	0.045458663	0.05318826
102	0.046392028	0.05408003
233	0.046703573	0.05424305
60	0.046947281	0.05432637
116	0.048447274	0.05585752
651	0.049171723	0.05626669
63	0.049236817	0.05626669
691	0.049336494	0.05626669
601	0.050152491	0.05699157

450	0.050809802	0.05753157
543	0.052017218	0.05868836
502	0.05269335	0.05914156
229	0.052947413	0.05914156
607	0.052980537	0.05914156
477	0.054132121	0.06021429
688	0.054645677	0.06057227
633	0.055678782	0.06150162
437	0.056457812	0.06183179
616	0.056487286	0.06183179
72	0.056564864	0.06183179
280	0.058400013	0.06361768
230	0.060195918	0.0652598
218	0.060320607	0.0652598
646	0.06322465	0.06816818
34	0.064008468	0.06860126
705	0.064060636	0.06860126
176	0.064586472	0.06893071
682	0.068715975	0.07299247
173	0.068854359	0.07299247
702	0.069330537	0.07325146
179	0.069650683	0.07334441
606	0.070781764	0.07428785
639	0.07266435	0.07601116
547	0.073581681	0.07671671
322	0.074064856	0.07696646
622	0.074560082	0.07722705
400	0.075314399	0.07731847
288	0.075354978	0.07731847
381	0.075473461	0.07731847
200	0.075804838	0.07731847
75	0.075872087	0.07731847
118	0.076651487	0.07786156
484	0.077540217	0.07851187
494	0.078850129	0.07958312
184	0.079681851	0.08016645
709	0.083547919	0.08378919
403	0.084814376	0.08479013
600	0.085502	0.08520791
392	0.086195978	0.08552235
599	0.086358963	0.08552235
377	0.086652283	0.08554466
238	0.088043103	0.08664693
219	0.088409229	0.08673704
578	0.089261606	0.08730218
448	0.09214682	0.08984589
443	0.093086052	0.09048241

519	0.094514339	0.09158893
388	0.095927612	0.09267418
438	0.096597856	0.09303718
508	0.097086432	0.09322297
133	0.097674586	0.09322297
678	0.097676043	0.09322297
203	0.098648651	0.09386765
391	0.09984426	0.09472002
453	0.100775334	0.09531707
207	0.105777619	0.09948739
638	0.105814315	0.09948739
406	0.10746198	0.1007367
137	0.107793735	0.1007488
628	0.10889888	0.1014814
566	0.111707182	0.1037923
209	0.112779742	0.1042419
189	0.112851063	0.1042419
65	0.113458327	0.1044973
64	0.114675321	0.1053112
701	0.115793628	0.1060299
136	0.118105288	0.1078341
642	0.120334289	0.1095526
276	0.122702462	0.1113876
614	0.125470209	0.1135186
84	0.125768618	0.1135186
267	0.127084323	0.1143361
30	0.127398179	0.1143361
192	0.12800221	0.1145528
356	0.128431105	0.1146013
146	0.128781962	0.1146013
88	0.133178352	0.1181807
301	0.133919638	0.1185056
215	0.137119364	0.1208746
649	0.137362014	0.1208746
242	0.13918263	0.1221224
676	0.13955316	0.1221224
114	0.141340111	0.1233445
319	0.145546085	0.126665
371	0.146257124	0.1269342
214	0.147059647	0.127281
240	0.147675703	0.127465
199	0.148225072	0.1275905
253	0.151012388	0.1296086
527	0.151615372	0.1296086
457	0.151800349	0.1296086
512	0.154474049	0.1311643
548	0.154677712	0.1311643

232	0.154997806	0.1311643
621	0.155283117	0.1311643
69	0.157540053	0.1326664
275	0.157985646	0.1326664
107	0.158321311	0.1326664
498	0.161392265	0.1346538
18	0.161545518	0.1346538
115	0.16330817	0.1356195
698	0.163562668	0.1356195
700	0.164300987	0.135875
304	0.166794466	0.137577
655	0.167775629	0.1380259
225	0.168495692	0.1382582
605	0.169436392	0.1386699
617	0.17006513	0.1388248
518	0.170513922	0.1388325
97	0.171002985	0.1388727
277	0.172665432	0.1398633
360	0.17472124	0.1411666
565	0.175616403	0.1415278
382	0.178790776	0.1437194
656	0.179874455	0.1442235
414	0.18054686	0.1443962
21	0.182267681	0.1454043
59	0.183395513	0.1455823
38	0.183412459	0.1455823
138	0.186140006	0.1468422
216	0.186228851	0.1468422
54	0.18639413	0.1468422
323	0.188690104	0.1482812
211	0.190526351	0.1493303
328	0.190970507	0.1493303
427	0.192159897	0.1498893
122	0.192712122	0.1499498
428	0.193711783	0.1503573
20	0.196319907	0.1520082
674	0.19842923	0.1532658
627	0.19951217	0.1537264
131	0.200318485	0.1537791
104	0.200554145	0.1537791
37	0.203627306	0.1557575
157	0.212897168	0.1624548
432	0.217112665	0.1652723
687	0.218780708	0.165778
345	0.218826567	0.165778
227	0.221241131	0.1672062
482	0.231107262	0.1742459

553	0.232572997	0.1749335
513	0.233943842	0.1755466
255	0.23578795	0.1765111
372	0.236888977	0.1769161
71	0.237931247	0.1772754
685	0.238677412	0.1774129
703	0.240121698	0.1780675
354	0.241105312	0.1783782
185	0.245067418	0.1808859
386	0.250858231	0.1847285
202	0.253546716	0.1862741
440	0.25849657	0.18947
32	0.261274152	0.1910626
715	0.264234213	0.1927809
545	0.26594587	0.1935826
302	0.270974263	0.1967894
441	0.274035109	0.1985558
696	0.275233293	0.1989676
472	0.277229853	0.1999534
673	0.278731065	0.2005782
228	0.28080936	0.2009983
679	0.280960609	0.2009983
671	0.281223615	0.2009983
47	0.287112058	0.2047437
665	0.290238589	0.2065071
418	0.293343548	0.2075116
455	0.293592858	0.2075116
241	0.294280224	0.2075116
283	0.294495877	0.2075116
82	0.295069619	0.2075116
662	0.295763084	0.2075116
719	0.296248451	0.2075116
663	0.301242723	0.210127
471	0.301312506	0.210127
177	0.303971825	0.2115146
296	0.305386282	0.2120318
162	0.317613829	0.2200379
198	0.32340188	0.2235575
466	0.328167052	0.2259984
265	0.328540176	0.2259984
611	0.329220159	0.2259984
307	0.330078496	0.2259984
239	0.33106618	0.2259984
652	0.331225216	0.2259984
175	0.333505154	0.2268598
76	0.33392399	0.2268598
159	0.33518434	0.2270668

659	0.33605604	0.2270668
58	0.336421774	0.2270668
324	0.33818944	0.2270668
85	0.338569534	0.2270668
395	0.3387819	0.2270668
311	0.340106271	0.2270668
610	0.34030274	0.2270668
596	0.34069763	0.2270668
405	0.341585171	0.2271791
55	0.349460932	0.2319287
284	0.352610428	0.2335284
298	0.355090511	0.2337051
254	0.355153629	0.2337051
201	0.356131788	0.2337051
74	0.356174539	0.2337051
195	0.356576173	0.2337051
106	0.360033723	0.2350596
83	0.360130953	0.2350596
581	0.365555874	0.2381085
379	0.366349381	0.2381344
264	0.367580701	0.2384441
716	0.369208377	0.2388064
33	0.369651065	0.2388064
217	0.373437007	0.2407599
686	0.37646567	0.2421873
70	0.377605597	0.2421873
351	0.378440253	0.2421873
335	0.378717599	0.2421873
488	0.380156699	0.2426165
409	0.385105957	0.2442876
367	0.385788268	0.2442876
27	0.386340803	0.2442876
677	0.386897666	0.2442876
333	0.387661916	0.2442876
501	0.387835695	0.2442876
619	0.388188179	0.2442876
15	0.38986896	0.2448576
593	0.393221107	0.2462954
108	0.393717537	0.2462954
77	0.394589741	0.2463532
142	0.397787675	0.2478599
297	0.404197987	0.2513584
163	0.408813703	0.2537293
357	0.411111026	0.2546548
150	0.420638962	0.2600468
499	0.422293377	0.2605597
93	0.426461577	0.2626186

380	0.428514267	0.2633692
347	0.43208157	0.2647161
113	0.432381638	0.2647161
208	0.436522564	0.2667344
430	0.441393566	0.2681368
680	0.441425306	0.2681368
493	0.441924858	0.2681368
404	0.44340105	0.2681368
226	0.443473739	0.2681368
389	0.443910347	0.2681368
368	0.446784593	0.2693579
509	0.449118958	0.2702495
507	0.452829882	0.27186
657	0.453516391	0.27186
526	0.456610944	0.2731966
316	0.462787659	0.2763688
475	0.464036702	0.2765918
78	0.469325643	0.2792175
424	0.470824469	0.2795827
464	0.47319549	0.2804635
579	0.475915875	0.2815476
196	0.478747333	0.2822994
53	0.479593365	0.2822994
291	0.479867528	0.2822994
636	0.481011799	0.2824466
658	0.484734802	0.2841046
43	0.48775895	0.2853477
213	0.488814674	0.2854367
574	0.490307354	0.2857801
613	0.49644124	0.2883025
411	0.496460124	0.2883025
486	0.501926883	0.2909423
535	0.502917246	0.2909824
318	0.507867445	0.2933094
689	0.511953891	0.2950115
425	0.512939158	0.2950115
643	0.513616225	0.2950115
620	0.518299409	0.2971611
415	0.520577198	0.2976303
348	0.521002065	0.2976303
644	0.523680969	0.2986207
690	0.526546538	0.2997138
321	0.529460673	0.3008305
140	0.53132334	0.3013468
331	0.532566728	0.3013731
329	0.533790575	0.3013731
433	0.534231647	0.3013731

365	0.537085203	0.3019246
396	0.537120699	0.3019246
491	0.543513627	0.3048445
3	0.544245197	0.3048445
539	0.545995647	0.3052837
305	0.554546608	0.3090419
287	0.554673632	0.3090419
375	0.55651869	0.3094548
325	0.557373897	0.3094548
79	0.559388626	0.3100285
263	0.562309903	0.3111018
500	0.565592346	0.3123708
708	0.568996605	0.3135803
660	0.569767618	0.3135803
495	0.573444914	0.3150553
598	0.578057949	0.3170121
278	0.5790456	0.3170121
61	0.580017094	0.3170121
681	0.583785708	0.3183142
2	0.58441459	0.3183142
250	0.58581375	0.318527
640	0.591587515	0.3211138
317	0.600101227	0.324634
704	0.600128017	0.324634
631	0.60623962	0.3266526
469	0.606525621	0.3266526
111	0.607940111	0.3266526
718	0.607995725	0.3266526
523	0.617269189	0.3310718
697	0.61851117	0.3311757
281	0.620847165	0.3315205
504	0.622949097	0.3315205
474	0.623011228	0.3315205
204	0.623352848	0.3315205
110	0.627797794	0.3333233
645	0.634712654	0.3364293
109	0.636625865	0.3364565
531	0.636894036	0.3364565
251	0.639069238	0.337042
98	0.642280189	0.3381708
28	0.644278786	0.3385556
449	0.645154329	0.3385556
290	0.647526477	0.3392369
112	0.655886111	0.3430476
123	0.662634024	0.3460041
445	0.66436828	0.3463372
224	0.665531005	0.3463718

653	0.668142395	0.3471589
629	0.673809055	0.3483524
151	0.674112802	0.3483524
530	0.674842473	0.3483524
454	0.674850047	0.3483524
181	0.678534483	0.3485289
554	0.679678155	0.3485289
262	0.680474115	0.3485289
81	0.680948209	0.3485289
161	0.681167704	0.3485289
669	0.68181167	0.3485289
342	0.68472464	0.3493267
96	0.68593119	0.3493267
626	0.686689622	0.3493267
80	0.688249346	0.3495572
12	0.695161136	0.352271
575	0.695822708	0.352271
684	0.697741995	0.3526775
529	0.699523622	0.3530132
180	0.707047751	0.3562412
711	0.708293668	0.3563006
532	0.717446741	0.3603312
119	0.720633866	0.3613574
11	0.725824328	0.3633834
393	0.737911723	0.3681786
332	0.738564247	0.3681786
442	0.738898662	0.3681786
308	0.740340455	0.3683161
103	0.746595561	0.3705731
542	0.747223307	0.3705731
337	0.752043904	0.3723792
14	0.75332929	0.3724319
90	0.755807689	0.3730733
524	0.760567318	0.3743969
73	0.760859296	0.3743969
158	0.763431069	0.3750781
470	0.76653051	0.3759271
8	0.767538942	0.3759271
29	0.769407024	0.3762587
597	0.772737361	0.3773032
91	0.776178753	0.3783987
384	0.777466746	0.3784426
521	0.779498194	0.3785197
212	0.780021522	0.3785197
35	0.784082743	0.3799069
13	0.789143038	0.3817732
285	0.79102707	0.3820995

223	0.792575398	0.3822629
717	0.801773478	0.3856901
444	0.802123013	0.3856901
630	0.803840646	0.3859286
577	0.805689816	0.3862294
517	0.808910381	0.3871857
272	0.813681676	0.3888511
394	0.815462143	0.3888511
552	0.816082384	0.3888511
572	0.817571705	0.3889741
279	0.81972588	0.3892349
591	0.82058408	0.3892349
205	0.824702431	0.3906019
533	0.826998571	0.391103
366	0.830590313	0.3922145
56	0.837928345	0.3940528
270	0.838044331	0.3940528
602	0.838225268	0.3940528
7	0.842522008	0.3954841
522	0.847983614	0.3974573
4	0.853962991	0.3992512
410	0.854338711	0.3992512
269	0.856689204	0.3997583
338	0.857991412	0.3997755
343	0.863039133	0.4015352
592	0.866904398	0.4027404
463	0.872110832	0.4045642
699	0.883590722	0.4092886
257	0.897231261	0.4144191
497	0.897290216	0.4144191
344	0.901109535	0.4155755
666	0.905733579	0.4170991
582	0.907540116	0.4172166
462	0.909125344	0.4172166
435	0.909950743	0.4172166
336	0.91721518	0.4180192
182	0.919282613	0.4180192
234	0.919427788	0.4180192
282	0.919848691	0.4180192
426	0.920242792	0.4180192
31	0.920817235	0.4180192
44	0.920963809	0.4180192
528	0.92376355	0.4186884
503	0.927635356	0.4189812
399	0.927741594	0.4189812
439	0.928388379	0.4189812
99	0.934072429	0.4209451

252	0.935414961	0.4209496
694	0.938094165	0.4215548
125	0.942012096	0.4227141
339	0.948074395	0.4242799
17	0.948187567	0.4242799
713	0.955667198	0.4270219
236	0.977289314	0.4352836
52	0.977929816	0.4352836
206	0.978632732	0.4352836
313	0.980811844	0.4352836
341	0.981046039	0.4352836
235	0.984029424	0.4359949
573	0.985986018	0.43625
57	0.989211233	0.4370649
147	0.991415401	0.4374269
434	0.994650556	0.4378427
398	0.995129572	0.4378427
431	0.996979856	0.4380467

Supplemental Table T1B. List of p-values for PDND vs. PDID and their corresponding q-values.

Metabolite No.	p-value (PDND vs. PDID)	q-value
125	1.86402E-06	0.000773113
110	4.94976E-06	0.001028739
53	0.00013578	0.0164299
575	0.000208232	0.0164299
545	0.000227485	0.0164299
389	0.000243703	0.0164299
265	0.000276696	0.0164299
574	0.000458329	0.02381318
508	0.000709799	0.03278105
318	0.000798743	0.03319992
331	0.001053582	0.03964362
509	0.001144523	0.03964362
597	0.00148035	0.04332602
439	0.001536389	0.04332602
464	0.001644052	0.04332602
628	0.00166778	0.04332602
90	0.001979466	0.04839819
297	0.002135635	0.04931562
418	0.00298143	0.06217146
476	0.002991514	0.06423357
552	0.003245274	0.06217146
714	0.003517943	0.06646547
484	0.004067655	0.07350997
532	0.004448402	0.07547055
32	0.004539286	0.07547055
328	0.005030985	0.07941083
711	0.005158382	0.07941083
646	0.005683827	0.08171254
533	0.006013529	0.08204441
300	0.006380901	0.08171254
223	0.006494991	0.08204441
290	0.006669449	0.08171254
367	0.006889291	0.08171254
627	0.007245799	0.08171254
562	0.007252845	0.08204441
624	0.007345375	0.08171254
639	0.007386817	0.08171254
382	0.007654037	0.08468801
561	0.007707153	0.08171254
469	0.008256216	0.08171254
379	0.008346631	0.08171254
210	0.008399807	0.08171254
34	0.008453317	0.08630174

548	0.008749455	0.08171254
623	0.009077961	0.08669168
470	0.009079812	0.08171254
716	0.009576125	0.08171254
208	0.009966227	0.08669168
230	0.01037188	0.08753455
598	0.010695545	0.08669168
271	0.010696358	0.08171254
108	0.01084553	0.08171254
473	0.011161573	0.08669168
440	0.011600716	0.0891129
632	0.011874246	0.08916158
128	0.012006007	0.08916158
151	0.012309001	0.0891129
372	0.012453041	0.0891129
479	0.012656096	0.08916158
249	0.01330204	0.09215035
50	0.01387765	0.09456188
412	0.014345406	0.09567577
296	0.014579504	0.09567577
596	0.014731669	0.09567577
183	0.01520958	0.09725991
166	0.016007122	0.100809
160	0.016286277	0.1010362
595	0.01658644	0.1013851
386	0.017139332	0.1032464
129	0.01773027	0.1052803
334	0.01849724	0.1058742
77	0.018702254	0.1065938
351	0.018770142	0.1065938
560	0.018849149	0.1058742
696	0.019606334	0.1065938
523	0.019627614	0.1065938
117	0.019815982	0.1065938
345	0.020474683	0.1065938
531	0.020883102	0.1075342
511	0.020987328	0.1076488
253	0.021065527	0.1076488
275	0.021359841	0.1077096
673	0.021924866	0.1065938
444	0.021930802	0.1058742
385	0.022105513	0.1065938
570	0.022321099	0.1065938
498	0.022364417	0.1065938
83	0.022716486	0.1058742
558	0.022892118	0.1065938
667	0.023080465	0.1076488

291	0.023542795	0.1065938
82	0.024033298	0.1065938
45	0.024093674	0.1065938
637	0.024344849	0.1094531
134	0.02461772	0.1095457
392	0.025279546	0.1095545
306	0.025703571	0.1095457
712	0.025847578	0.1065938
46	0.026282419	0.1065938
204	0.026355142	0.1095457
429	0.026620836	0.1103336
622	0.027075582	0.1095457
218	0.027918527	0.1105793
258	0.028057043	0.1105793
192	0.028546056	0.1117421
89	0.028845014	0.1105793
594	0.029088965	0.1105793
615	0.029115822	0.1105793
609	0.029216119	0.1105793
298	0.029264179	0.1105793
466	0.029840767	0.1105793
79	0.030879246	0.1145984
245	0.031683415	0.1150564
229	0.032034722	0.1154375
572	0.032425939	0.1150564
544	0.032532796	0.1150564
65	0.032578267	0.1150564
502	0.032663517	0.1150564
589	0.033049416	0.1150564
678	0.034050406	0.1179427
608	0.035110203	0.1206085
522	0.035611211	0.1213268
654	0.036217979	0.1222462
243	0.036576502	0.1222462
625	0.036763371	0.1225336
186	0.037158928	0.1225336
355	0.037502754	0.1222462
69	0.037734214	0.1225336
567	0.038105057	0.1227787
40	0.038501406	0.1231015
80	0.038993397	0.1237228
6	0.039834959	0.1251664
391	0.040050648	0.1251664
411	0.040567619	0.1255218
590	0.040860937	0.1255218
417	0.041070313	0.1255218
144	0.041847529	0.1267137

581	0.042070026	0.1267137
198	0.042704547	0.1272095
424	0.042846722	0.1272956
384	0.043426739	0.1272095
612	0.043690614	0.1272956
388	0.043794472	0.1272956
86	0.044516912	0.1282145
505	0.044727552	0.1282145
556	0.045693989	0.1292194
573	0.045699867	0.1292194
244	0.046845021	0.1315624
357	0.047197008	0.131604
200	0.047504144	0.131604
686	0.047809694	0.131604
642	0.049385659	0.1335115
525	0.049591371	0.1335332
468	0.049612397	0.1335115
310	0.050388033	0.1339318
157	0.050617011	0.1335115
510	0.05072198	0.1335115
287	0.050751121	0.1335115
390	0.051080634	0.1335115
175	0.051555352	0.1335115
658	0.052423276	0.1353407
217	0.052992445	0.1355669
197	0.053163237	0.1355669
402	0.055619864	0.1409665
703	0.056675054	0.1427703
240	0.057177678	0.1431688
383	0.05762704	0.1434299
187	0.059089783	0.1459714
709	0.059725995	0.1459714
239	0.059954095	0.1459714
87	0.060439446	0.1459714
114	0.060970311	0.1459714
333	0.061000153	0.1459714
405	0.061106437	0.1459714
313	0.062432142	0.148286
616	0.064334595	0.1519364
282	0.064828806	0.1522386
162	0.06878744	0.1606272
442	0.070044231	0.1626482
378	0.070519537	0.1627181
702	0.071292421	0.1627181
695	0.07129302	0.1627181
233	0.071640245	0.1627181
29	0.074902231	0.1684537

363	0.07497602	0.1684537
707	0.076014201	0.1694194
329	0.076220999	0.1694194
220	0.077030381	0.1703077
483	0.078047042	0.1716424
528	0.078494888	0.1717188
202	0.081058668	0.1757555
387	0.082256026	0.1757555
330	0.082343076	0.1757555
449	0.082948712	0.1757555
547	0.08312133	0.1757555
123	0.083501815	0.1757555
557	0.083617579	0.1757555
153	0.083722887	0.1757555
462	0.085765543	0.1791388
550	0.086440003	0.1796448
127	0.087722157	0.1814025
126	0.088360335	0.1818176
72	0.089095285	0.1824268
421	0.091536778	0.1854641
694	0.092157368	0.1854641
100	0.092724589	0.1854641
536	0.092959793	0.1854641
221	0.093016465	0.1854641
199	0.093412066	0.1854641
521	0.093702047	0.1854641
277	0.095646814	0.1884161
529	0.096630878	0.1890553
650	0.096880954	0.1890553
377	0.099243126	0.1927599
94	0.100770291	0.1934684
58	0.101075495	0.1934684
433	0.101629164	0.1934684
540	0.101818617	0.1934684
604	0.101935176	0.1934684
395	0.103230244	0.1950358
327	0.105301833	0.1980495
214	0.105821012	0.1981169
599	0.107679404	0.198128
139	0.10812076	0.1981169
490	0.108556448	0.1986438
216	0.10885934	0.1981169
146	0.109207437	0.1981169
507	0.109210588	0.1981169
364	0.109471034	0.1981169
649	0.109627459	0.2002339
322	0.110110297	0.2003713

587	0.110874827	0.1981169
142	0.112244111	0.1981169
516	0.112803188	0.1981169
656	0.11669271	0.2038081
1	0.116942585	0.2038081
61	0.117046096	0.2038081
171	0.117449956	0.2038081
435	0.117656431	0.2038081
641	0.117848291	0.2038081
56	0.119388605	0.2038081
184	0.119405325	0.2052557
371	0.119569041	0.2038081
105	0.119758166	0.2052557
420	0.120131671	0.2038081
683	0.121763089	0.2038081
286	0.121972566	0.2038081
687	0.123989681	0.2078088
99	0.125035691	0.208184
319	0.125215296	0.2083159
174	0.126188449	0.208184
668	0.126296965	0.2083159
132	0.127305049	0.2091487
593	0.1281876	0.2097695
626	0.129229459	0.2102028
163	0.129463816	0.2102028
430	0.131627131	0.2128836
203	0.133200177	0.2142482
189	0.134054804	0.2142482
168	0.134396831	0.2146258
569	0.134532624	0.2142482
353	0.135286091	0.2142482
178	0.137135313	0.2154732
428	0.137189855	0.2155122
422	0.137589235	0.2154732
406	0.137893824	0.2154732
165	0.139185114	0.2155122
55	0.139361889	0.2155122
699	0.13947426	0.2154732
643	0.140915309	0.2169324
674	0.143984208	0.2208389
130	0.147450416	0.2253238
155	0.150525968	0.2264521
64	0.151369541	0.2264521
12	0.151422333	0.2264521
179	0.152684852	0.2279098
169	0.15271447	0.2279098
73	0.153000016	0.2264521

708	0.153166388	0.2279098
698	0.153271946	0.2264521
662	0.153376438	0.2264521
88	0.153636905	0.2264521
84	0.155495698	0.2264521
485	0.15579091	0.2264521
416	0.156270843	0.2296281
119	0.158353778	0.2297968
657	0.15855393	0.2264521
131	0.160307356	0.2297968
400	0.160638766	0.2296281
295	0.160689489	0.2297968
517	0.161040259	0.2297968
312	0.161434644	0.2297968
360	0.164359897	0.2331622
359	0.165094401	0.2334076
307	0.166429024	0.2337579
453	0.166466942	0.2343573
285	0.167457626	0.2344377
257	0.16807908	0.2337579
138	0.169416288	0.2347885
539	0.169757907	0.2347885
568	0.17014747	0.2347885
2	0.170590061	0.2352296
135	0.171476497	0.2347885
606	0.172691161	0.2361166
489	0.174178615	0.236536
586	0.174612445	0.236536
542	0.175272	0.236536
663	0.175274178	0.236536
576	0.185487854	0.2495094
106	0.189768138	0.2544436
248	0.190995836	0.2552663
410	0.195475749	0.2604164
225	0.198165913	0.2612431
92	0.198328756	0.2612431
136	0.198462357	0.2612431
317	0.198610371	0.2612431
167	0.201943441	0.2647893
13	0.203266524	0.2649224
207	0.203319646	0.2649224
368	0.206217412	0.2678584
607	0.209238945	0.2709365
356	0.210637744	0.2719007
281	0.213268428	0.274214
316	0.213749307	0.274214
267	0.215295005	0.2753472

362	0.216195787	0.275651
54	0.218275902	0.2774521
141	0.220341614	0.279224
354	0.223775981	0.281025
241	0.225446067	0.281025
465	0.226093723	0.281025
369	0.22652319	0.2822329
85	0.228112456	0.2823579
78	0.228829925	0.281025
212	0.228899909	0.281025
427	0.22922947	0.281025
680	0.229342012	0.281025
644	0.230463373	0.281025
255	0.23061733	0.281025
456	0.230744813	0.2837761
3	0.230919513	0.2838634
361	0.231228361	0.281025
467	0.232901217	0.2839456
26	0.23368369	0.281025
474	0.236603326	0.281025
425	0.237351243	0.2839456
76	0.238622786	0.2839456
555	0.238674883	0.2837761
688	0.23887984	0.2839456
309	0.238953736	0.281025
349	0.239710217	0.281025
159	0.241840777	0.2837761
374	0.242120123	0.2839456
170	0.242487352	0.2837761
408	0.243466008	0.2839456
438	0.243484827	0.2837761
543	0.243948787	0.2851859
621	0.244561582	0.2854804
293	0.246315973	0.2839456
205	0.247257089	0.2837761
583	0.249124079	0.2868392
263	0.251761751	0.2890754
209	0.253163566	0.2898013
37	0.253788391	0.2898013
268	0.255926858	0.2914426
515	0.259117485	0.2932601
156	0.25958914	0.2932601
452	0.259639559	0.2932601
710	0.26170023	0.294515
358	0.26216765	0.294515
482	0.265455537	0.2965409
398	0.265782649	0.2965409

659	0.266111412	0.2972227
81	0.267561815	0.2972227
399	0.268153386	0.2965409
648	0.271434336	0.2993138
666	0.27277971	0.2993138
496	0.272967128	0.2993138
477	0.274133045	0.2993138
600	0.274390032	0.2993138
133	0.274851067	0.2993138
582	0.27641779	0.2993138
120	0.276427381	0.2993138
448	0.276699649	0.2993138
320	0.277612746	0.2993138
526	0.278578908	0.2993138
661	0.279308739	0.2993138
564	0.279957141	0.2993138
340	0.280121483	0.2993138
488	0.286619357	0.3054716
122	0.288290163	0.3062591
559	0.288956866	0.3062591
514	0.289568646	0.3062591
492	0.293006151	0.3090618
44	0.294584243	0.3090618
36	0.294838669	0.3090618
459	0.295563981	0.3090618
74	0.29593646	0.3095295
213	0.297128971	0.3090618
461	0.302447509	0.313876
370	0.303109959	0.313876
404	0.304309775	0.313876
206	0.304564859	0.313876
326	0.305076968	0.313876
494	0.31195744	0.3197496
512	0.312324472	0.3198969
380	0.313310118	0.3198969
292	0.314047299	0.3198969
653	0.314777226	0.3197496
25	0.317417304	0.3215799
228	0.317980717	0.3215799
350	0.32480822	0.3276874
264	0.326164328	0.3282588
481	0.327005379	0.3283103
580	0.332034476	0.3325562
713	0.333423586	0.3331448
219	0.336748665	0.3351759
348	0.337069186	0.3351759
684	0.343848681	0.3411013

534	0.346364811	0.3420534
232	0.346809434	0.3420534
14	0.347277247	0.3420534
181	0.350443213	0.3443557
256	0.352056748	0.3448227
426	0.352577655	0.3448227
500	0.35615888	0.3475075
365	0.36102466	0.3502144
701	0.362310253	0.3502144
95	0.362418801	0.3506825
638	0.362707462	0.3502144
341	0.363146055	0.3502144
718	0.364475088	0.3502144
640	0.367308731	0.3525927
677	0.368629168	0.3530449
394	0.371127459	0.3546205
584	0.375074245	0.3575697
373	0.378744273	0.35998
513	0.379347691	0.35998
66	0.380366043	0.35998
446	0.381715862	0.35998
164	0.382670082	0.35998
262	0.382798905	0.35998
437	0.38637868	0.3625262
52	0.388479609	0.3636765
665	0.390326022	0.3645839
149	0.393216897	0.3664606
685	0.394822836	0.3671341
499	0.396002687	0.3674093
614	0.396924647	0.3674445
176	0.400089273	0.3676826
67	0.400730936	0.3683872
31	0.40078519	0.3676826
339	0.401560851	0.3676826
419	0.402450548	0.3676826
692	0.403320514	0.3676826
266	0.403374018	0.3683872
39	0.405448079	0.3676826
269	0.40591958	0.3676826
571	0.412003938	0.3730944
376	0.419151062	0.3779957
57	0.419235294	0.3780741
332	0.420231812	0.3779957
121	0.425402923	0.3818998
107	0.428188848	0.3830543
423	0.428762459	0.3830936
501	0.429453598	0.3830543

601	0.430419389	0.3830543
445	0.432094862	0.3837631
432	0.433492628	0.3841836
124	0.436460458	0.3859909
311	0.439935223	0.3879323
283	0.440933349	0.3879323
338	0.441455617	0.3879323
215	0.446816236	0.390494
226	0.447968804	0.390494
33	0.448897241	0.390494
527	0.450504528	0.390494
611	0.451459246	0.390494
30	0.451973684	0.390494
158	0.452104033	0.390494
431	0.453202851	0.390494
471	0.45342363	0.3924453
335	0.453765492	0.390494
201	0.457311188	0.390494
273	0.457921277	0.3924453
104	0.461400757	0.394089
671	0.461735476	0.394089
506	0.475339202	0.4048683
308	0.478006997	0.406308
602	0.482377572	0.4088012
375	0.482988489	0.4088012
280	0.483890722	0.4088012
71	0.486293696	0.409998
193	0.48734237	0.4100504
115	0.489676279	0.4105263
137	0.489883361	0.4105263
472	0.494933097	0.4139235
366	0.497566913	0.4152906
147	0.50051252	0.416912
549	0.501544655	0.4169362
270	0.504950072	0.4182536
259	0.505141969	0.4182536
610	0.507925244	0.4191887
222	0.508341794	0.4191887
645	0.509900597	0.4191887
495	0.511719118	0.4191887
403	0.511873701	0.4191887
518	0.512322369	0.4191887
443	0.515655354	0.4210869
315	0.518673326	0.4227209
182	0.521540265	0.4236963
28	0.521908845	0.4236963
5	0.526478434	0.4265729

381	0.528724374	0.4266953
109	0.529107849	0.4266953
617	0.530756665	0.4266953
238	0.531559781	0.4266953
447	0.53244322	0.4266953
97	0.532788966	0.4266953
250	0.535614766	0.4281044
276	0.537161865	0.4281044
672	0.537638343	0.4281044
352	0.541942454	0.4301396
8	0.542263875	0.4301396
305	0.544590533	0.4307285
49	0.545078842	0.4307285
636	0.548635056	0.432716
681	0.555762998	0.4375077
475	0.561531573	0.4405069
145	0.561692411	0.4405069
118	0.571173334	0.4455754
651	0.571226341	0.4455754
603	0.571889104	0.4455754
272	0.57244323	0.4455754
579	0.575522597	0.4471349
242	0.581935189	0.4512731
4	0.583020435	0.4512731
247	0.584276139	0.4514045
236	0.58639953	0.4517421
24	0.586886726	0.4517421
605	0.589889239	0.4532139
719	0.592841945	0.4546421
294	0.595082527	0.4555199
16	0.601858437	0.4597027
588	0.602758749	0.4597027
676	0.605994358	0.4609347
191	0.606592078	0.4609347
337	0.610114663	0.4627654
535	0.612902717	0.4640334
413	0.618250773	0.4658693
102	0.618996356	0.4663744
347	0.619363852	0.4658693
304	0.619810934	0.4663744
91	0.623671708	0.4658693
323	0.625097182	0.4663744
697	0.625102357	0.4663744
96	0.625804315	0.4658693
634	0.62710172	0.4663744
7	0.627329405	0.4663744
194	0.628337123	0.4663744

342	0.638248375	0.4728864
21	0.644039896	0.4763284
112	0.647057368	0.4772305
618	0.647918789	0.4772305
289	0.649290992	0.4772305
592	0.654125395	0.4772305
47	0.654996031	0.4772305
631	0.656082972	0.4772305
578	0.656136557	0.4785526
441	0.657146324	0.4785526
251	0.657284786	0.4791335
254	0.657377059	0.4772305
172	0.657889237	0.4785526
38	0.663592354	0.4772305
111	0.664273249	0.4785526
530	0.665143915	0.4785526
152	0.665318574	0.4785526
497	0.668037967	0.4772305
565	0.668765778	0.4772305
177	0.66899817	0.4785526
717	0.66927509	0.4772305
22	0.670073867	0.4785526
493	0.672039966	0.4785526
15	0.678276505	0.4821026
27	0.678524274	0.4821026
224	0.682164199	0.483241
520	0.682792042	0.483241
504	0.683820711	0.483241
563	0.684776819	0.4837228
63	0.686623414	0.483241
237	0.689991199	0.4850839
278	0.690889475	0.4850839
288	0.692597333	0.485463
705	0.699694845	0.4896122
491	0.702513127	0.4907581
613	0.705798549	0.4922259
60	0.710534925	0.4946991
173	0.712617953	0.4953197
93	0.716043737	0.4968699
20	0.718931638	0.4980424
706	0.72636518	0.5007408
336	0.72693891	0.5008132
234	0.726950678	0.5007408
690	0.728643516	0.5007408
591	0.728850348	0.5007408
487	0.730160653	0.5019721
682	0.734990246	0.5007408

652	0.735885849	0.5025064
150	0.737178775	0.5025064
231	0.737790407	0.5019721
227	0.737888658	0.5029385
260	0.740017405	0.5019721
18	0.741091977	0.5019721
211	0.743898629	0.5019721
700	0.744149124	0.5029385
486	0.746449723	0.5036744
458	0.750363254	0.5054944
48	0.755391112	0.5080581
551	0.761106616	0.5110752
454	0.763246732	0.5116857
704	0.766131092	0.5127923
101	0.767434036	0.5128386
59	0.772261953	0.5152365
407	0.775537161	0.5165924
401	0.776873697	0.5166547
480	0.779845748	0.5178028
19	0.782331256	0.5186246
325	0.786702911	0.5200024
566	0.787207986	0.5200024
299	0.78913155	0.5200024
154	0.789413811	0.5200024
303	0.792114369	0.5209557
397	0.794697305	0.5218288
457	0.796791317	0.5220912
630	0.799616475	0.5220912
396	0.800720632	0.5220912
11	0.800841859	0.5220912
541	0.801377295	0.5220912
344	0.809958505	0.5248839
246	0.811180721	0.5250328
635	0.81272124	0.5248839
620	0.813652487	0.5260319
503	0.814479694	0.5248839
554	0.815878563	0.5248839
252	0.816464355	0.5248839
23	0.816497969	0.5248839
116	0.817029124	0.5248839
196	0.81852403	0.5248839
629	0.821347265	0.5248839
103	0.829351413	0.5298157
647	0.830551876	0.5298157
450	0.831391619	0.5298157
655	0.832353917	0.5298157
619	0.835178379	0.5308007

301	0.841752823	0.5336754
43	0.842269459	0.5336754
664	0.845934502	0.5351818
633	0.852297406	0.5378505
414	0.852740705	0.5378505
75	0.85673701	0.5395523
42	0.858672659	0.5399533
235	0.864803095	0.5412538
41	0.866380003	0.5412538
188	0.866492226	0.5412538
302	0.866735727	0.5412538
434	0.867251836	0.5412538
455	0.873137064	0.5441098
346	0.876740354	0.5448252
10	0.876906494	0.5448344
679	0.880328893	0.5448344
35	0.880612768	0.5448252
463	0.880853736	0.5458993
143	0.883888691	0.5448344
537	0.895166592	0.5520443
274	0.898776885	0.5529532
546	0.900458423	0.5529532
538	0.900722523	0.5529532
478	0.90196173	0.5536451
261	0.904422211	0.5529532
17	0.907171096	0.5545112
460	0.909284863	0.554987
343	0.911448655	0.555492
415	0.913184444	0.5557351
691	0.915231083	0.5561663
185	0.917891292	0.5567723
113	0.918907385	0.5567723
180	0.924531822	0.5573554
324	0.924560483	0.5573554
68	0.924868829	0.5573554
70	0.925879801	0.5573554
675	0.926957597	0.5582241
393	0.92791521	0.5582241
321	0.930937349	0.5573554
436	0.932952212	0.5582241
577	0.933390553	0.5573554
161	0.937431733	0.5598355
669	0.939640391	0.5603494
51	0.941773562	0.5608169
451	0.943686618	0.5608357
190	0.9452697	0.5608357
524	0.948650886	0.5608357

9	0.949278826	0.5608357
140	0.949505239	0.5608357
284	0.950428734	0.5608357
195	0.951397641	0.5608357
314	0.952599467	0.5608357
670	0.956839109	0.5625349
62	0.959707231	0.5634242
553	0.962781903	0.5634983
715	0.963832519	0.5638588
660	0.963900562	0.5634983
585	0.965873759	0.5634983
409	0.971545427	0.5663743
689	0.973803676	0.5668957
693	0.975798782	0.5672627
148	0.98096118	0.5690767
519	0.981657449	0.5690767
98	0.994555557	0.5757509
279	0.998012995	0.5769488

Supplemental Table T2. List of positively identified metabolites based on accurate mass and retention time match to the dansyl standard library.

Name	HMDB ID	Accurate mass (Da)	Dansylated mass (Da)	Library retention time (min)	Average Peak Pair Ratio (Control)	Average Peak Pair Ratio (PD)	Fold change	p value
Hypoxanthine + H2O	HMDB 00157	136.0385	388.1098	2.12	0.9237	0.9384	1.0159	0.7675
1-Methylhistidine	HMDB 00001	169.0851	403.1434	2.17	0.9770	0.8759	0.8965	0.0108
Taurine	HMDB 00251	125.0147	359.0730	2.24	0.9298	0.9171	0.9864	0.7258
L-Arginine	HMDB 00517	174.1117	408.1700	2.44	0.9233	0.8127	0.8802	0.0001
L-Asparagine	HMDB 00168	132.0535	366.1118	3.00	0.9257	0.8979	0.9700	0.2036
L-Glutamine	HMDB 00641	146.0691	380.1275	3.32	0.9519	0.9470	0.9948	0.4878
Citrulline	HMDB 00904	175.0957	409.1540	3.74	0.9669	0.7978	0.8251	0.0000
Methionine Sulfoxide	HMDB 02005	165.0460	399.1043	3.72	0.7405	0.8977	1.2123	0.0156
L-Homoserine	HMDB 00719	119.0582	353.1166	4.05	0.9410	0.9120	0.9692	0.5800
Methionine Sulfoxide - Isomer	HMDB 02005	165.0460	399.1043	4.20	0.7219	0.8937	1.2380	0.0169
L-Serine	HMDB 00187	105.0426	339.1009	4.40	0.8962	0.8587	0.9582	0.1135
L-Glutamic Acid	HMDB 00148	147.0532	381.1115	5.05	0.8538	0.8957	1.0491	0.3946
L-Aspartic Acid	HMDB 00191	133.0375	367.0958	5.16	0.8495	0.8933	1.0515	0.2951
Trans-4-Hydroxyl-L-Proline	HMDB 00725	131.0582	365.1166	5.17	0.9888	1.0471	1.0589	0.3601
N6-Acetyl-L-Lysine	HMDB 00206	188.1161	422.1744	5.71	0.9186	0.8535	0.9291	0.0143
L-Threonine	HMDB 00167	119.0582	353.1166	5.79	0.8498	0.9167	1.0788	0.0154
Aminoadipic acid	HMDB 00510	161.0688	395.1271	5.97	0.8971	0.8938	0.9963	0.9341
Ethanolamine	HMDB	61.0528	295.1111	6.00	0.9027	0.9592	1.0625	0.0253

	00149							
Glycine	HMDB 00123	75.0320	309.0903	6.59	0.9358	0.9748	1.0416	0.0064
L-Alanine	HMDB 00161	89.0477	323.1060	7.57	0.9713	0.9564	0.9846	0.0391
Gamma-Aminobutyric acid	HMDB 00112	103.0633	337.1216	7.79	0.9509	0.9260	0.9738	0.3352
Uridine	HMDB 00296	244.0695	478.1279	7.84	0.9395	0.8480	0.9026	0.0019
Pantothenic acid	HMDB 00210	219.1107	453.1690	8.37	0.9102	0.6891	0.7571	0.0101
Hypoxanthine	HMDB 00157	136.0385	370.0968	8.73	0.8842	0.9770	1.1049	0.0797
2-Aminoisobutyric acid	HMDB 01906	103.0633	337.1216	8.91	0.8451	0.9158	1.0837	0.2451
Uridine - H2O	HMDB 00296	244.0695	460.1173	8.67	0.9371	0.8309	0.8867	0.0004
Xanthine	HMDB 00292	152.0334	386.0917	8.95	0.9850	0.8390	0.8517	0.0200
Glycyl-Valine	HMDB 28854	174.1004	408.1588	9.19	0.6544	0.9510	1.4532	0.0097
L-Alpha-aminobutyric acid	HMDB 00452	103.0633	337.1216	9.13	0.8280	0.8610	1.0399	0.3566
L-Glutamic Acid - H2O	HMDB 00148	147.0532	363.1009	9.46	0.9513	0.9914	1.0421	0.4365
Methylamine	HMDB 00164	31.0422	265.1005	9.82	1.6430	1.6264	0.9899	0.7800
L-Aspartyl-L-phenylalanine	HMDB 00706	280.1059	514.1642	10.07	0.7760	0.8530	1.0992	0.1685
L-Proline	HMDB 00162	115.0633	349.1216	10.18	0.9725	0.9828	1.0106	0.2212
L-Valine	HMDB 00883	117.0790	351.1373	10.81	0.9161	0.8850	0.9661	0.0880
L-Methionine	HMDB 00696	149.0510	383.1094	10.89	1.4577	1.1860	0.8136	0.1392
L-Tryptophan	HMDB 00929	204.0899	438.1482	11.44	0.8661	0.7359	0.8497	0.0000
L-Kynurenine	HMDB 00684	208.0848	442.1431	11.44	1.7386	1.5041	0.8651	0.0000
Glycyl-Phenylalanine	HMDB 28848	222.1004	456.1588	11.65	0.8488	0.8380	0.9873	0.8137
L-Phenylalanine	HMDB 00159	165.0790	399.1373	12.74	0.8073	0.7703	0.9543	0.1339

Vanillylmandelic acid	HMDB 00291	198.0528	432.1111	12.81	0.3532	1.3415	3.7981	0.0000
L-Isoleucine	HMDB 00172	131.0946	365.1529	13.06	0.8894	0.8572	0.9638	0.3301
L-Pipecolic acid	HMDB 00716	129.0790	363.1373	13.45	0.8705	0.6964	0.8000	0.0099
L-leucine	HMDB 00687	131.0946	365.1529	13.36	0.8830	0.8433	0.9550	0.1455
Urocanic acid	HMDB 00301	138.0429	372.1012	13.52	0.7015	0.7643	1.0894	0.1887
L-Cystathionine - Isomer	HMDB 00099	222.0674	345.0920	13.69	0.9857	1.0544	1.0697	0.5574
5-Hydroxylysine	HMDB 00450	162.1004	315.1085	13.88	0.8719	0.9307	1.0674	0.1910
L-Cystine	HMDB 00192	240.0238	354.0702	14.11	0.8501	0.8544	1.0051	0.8630
Theophylline	HMDB 01889	180.0647	414.1230	15.42	1.2695	0.6073	0.4784	0.0000
Phenyl-Leucine	NA	278.1631	512.2214	15.90	0.7490	0.7936	1.0596	0.4285
Ornithine	HMDB 00214	132.0899	300.1033	16.58	0.8229	0.8848	1.0752	0.0862
3-Aminoisobutanoic acid - H2O	HMDB 03911	103.0633	319.1110	16.29	0.9512	0.9735	1.0234	0.7379
Phenylalanylphenylalanine	HMDB 13302	312.1474	546.2057	16.55	0.8044	0.7615	0.9467	0.3388
3-Hydroxyphenylacetic acid	HMDB 00440	152.0473	386.1057	16.72	0.9189	0.9056	0.9855	0.8543
p-Hydroxyphenylacetic acid	HMDB 00020	152.0473	386.1057	16.91	0.9656	1.0179	1.0542	0.4965
L-Lysine	HMDB 00182	146.1055	307.1111	17.47	0.8595	0.8241	0.9588	0.1922
Vanillic acid	HMDB 00484	168.0423	402.1006	17.34	0.4441	1.5441	3.4770	0.0000
4-Hydroxybenzoic acid	HMDB 00500	138.0317	372.0900	17.57	0.9440	0.9065	0.9602	0.2171
Desaminotyrosine	HMDB 02199	166.0630	400.1213	18.04	0.9563	0.8265	0.8643	0.2585
L-Histidine	HMDB 00177	155.0695	389.1278	18.09	0.9064	0.8699	0.9597	0.0931
Indole-3-	HMDB	161.0477	395.1060	19.27	0.9570	0.8733	0.9126	0.0093

carboxylic acid	03320							
1,4-diaminobutane	HMDB 01414	88.1000	278.1083	21.27	1.0035	0.9671	0.9638	0.5029
3-Hydroxymandelic acid - COOH	HMDB 00750	168.0423	356.0951	21.64	0.9627	0.9094	0.9446	0.0235
L-Tyrosine	HMDB 00158	181.0739	324.5953	22.65	0.8215	0.7283	0.8864	0.0034
Hydroxykynurenine	HMDB 00732	224.0797	346.0985	24.00	0.5755	0.9479	2.7326	0.0000
Phenol	HMDB 00228	94.0419	328.1002	23.16	0.6177	0.5513	0.8926	0.0565
Serotonin	HMDB 00259	176.0950	322.1058	24.65	1.2032	0.9554	0.7941	0.0041

Supplemental Table T3. Metabolites putatively identified based on accurate mass searches against the human metabolites in HMDB and the predicted human metabolites with one metabolic reaction.

Retention time (second)	Accurate mass (Da)	Dansylated mass (Da)	matches in HMDB*	matches in EML Library*
124.05	155.0685	389.1268	1	14
125.42	141.0184	375.0767	1	7
126.56	169.0038	403.0621	1	9
136.25	132.0895	366.1479	2	19
136.40	117.0778	351.1361	5	38
142.45	261.0301	495.0885	0	19
147.28	179.0788	413.1371	3	42
148.82	42.0213	276.0796	0	3
153.06	180.0625	414.1208	17	87
153.56	240.0227	474.0810	1	3
154.28	121.0187	355.0770	2	15
156.32	146.1051	380.1634	4	23
159.10	198.0746	432.1329	1	33
159.79	132.0888	366.1472	2	17
162.27	179.0789	413.1372	3	42
162.86	116.0704	350.1287	0	1
163.27	87.0317	321.0900	1	18
164.40	151.0296	385.0879	0	17
167.64	121.0187	355.0770	2	15
167.99	297.0446	531.1029	1	5
168.72	180.0625	414.1208	17	87
169.92	115.0624	349.1207	2	33
172.25	275.1111	509.1694	2	19
172.51	129.0422	363.1005	5	28
173.49	149.0679	383.1262	4	36
177.49	148.0477	382.1061	2	37
183.26	190.0578	424.1162	1	15
186.62	234.0840	468.1423	1	13
188.75	188.1518	422.2101	1	5
192.23	268.0802	502.1385	4	25
194.90	222.0672	456.1255	3	32
195.01	146.1047	380.1630	4	23
203.36	281.1114	515.1698	4	42
204.96	180.0625	414.1208	17	87
214.46	188.1263	422.1846	1	7
214.75	237.0839	471.1422	6	57
218.55	202.1421	436.2004	2	6

224.99	87.0324	321.0907	1	18
228.95	162.0523	396.1106	5	81
228.98	221.0893	455.1476	7	53
229.40	276.1314	510.1897	1	19
230.72	248.0996	482.1579	0	20
233.19	204.0741	438.1324	2	22
249.83	558.0881	513.1024	0	1
252.16	164.0681	398.1264	6	74
253.23	554.0776	511.0971	0	1
254.95	505.1514	739.2098	0	2
255.62	114.0085	291.0626	0	1
256.26	132.0219	300.0693	0	4
259.37	527.1553	994.2646	0	5
259.88	204.0742	438.1325	2	22
261.97	180.0629	414.1212	17	87
277.04	180.0625	414.1209	17	87
277.57	91.0269	325.0852	0	4
288.09	158.0433	392.1017	1	3
294.18	176.0789	410.1372	0	18
294.67	189.1103	423.1687	1	7
308.91	243.0709	477.1292	0	17
310.15	221.0918	455.1501	7	54
310.46	119.0577	353.1160	3	36
311.82	417.1849	651.2433	0	2
312.31	218.0897	452.1480	2	15
321.40	188.0789	422.1372	2	22
322.70	128.0579	362.1162	1	18
324.22	133.0724	367.1307	0	40
326.83	132.0533	366.1116	5	20
327.11	164.0676	398.1259	6	74
330.48	75.0322	309.0905	1	21
331.08	170.0685	404.1268	0	17
333.02	180.0628	414.1211	17	87
339.55	188.0795	422.1378	2	22
345.03	221.0893	455.1476	7	53
345.82	168.0273	402.0856	1	9
351.49	180.0628	414.1211	17	87
356.78	129.0893	363.1476	0	4
357.94	328.1736	562.2320	0	3
361.48	161.0674	395.1257	1	48
362.31	145.0733	379.1316	6	54
367.36	128.1056	362.1639	0	4
367.84	267.0953	501.1536	3	56

371.33	243.1208	477.1791	0	8
374.82	145.0727	379.1310	6	54
378.90	174.0632	408.1215	2	22
381.68	103.0995	337.1578	0	5
383.26	228.1101	462.1684	1	10
387.61	181.0403	415.0986	1	27
389.26	223.0298	457.0881	0	4
390.71	277.1155	511.1738	2	26
392.98	155.0692	389.1275	1	14
395.10	202.1057	436.1640	0	10
402.41	100.0640	334.1223	0	3
402.44	164.0675	398.1259	6	74
402.96	170.1162	404.1745	0	1
403.14	368.1914	602.2497	0	3
403.55	155.0688	389.1271	1	14
405.06	114.0426	348.1009	2	12
405.13	277.1145	511.1728	2	28
407.37	244.0687	478.1270	3	31
408.47	181.0733	415.1316	5	46
410.37	288.1427	522.2011	0	1
410.62	202.0945	436.1528	0	20
411.80	147.0881	381.1464	0	40
416.29	240.0087	707.1180	0	0
418.43	120.0050	354.0634	0	4
425.29	147.0886	381.1469	0	40
432.13	164.0677	398.1260	6	74
433.13	184.0228	418.0811	0	3
433.96	513.2125	747.2708	0	4
434.85	515.2181	749.2764	1	5
435.20	151.0712	385.1296	0	6
436.16	167.0456	401.1039	2	11
438.62	133.0368	367.0951	3	28
438.98	222.0734	456.1317	1	53
439.75	168.0274	402.0857	1	9
440.66	114.0788	348.1371	1	4
444.17	202.1311	436.1894	0	14
444.75	110.0474	344.1057	1	8
444.85	517.0723	751.1307	0	0
444.96	246.0847	480.1430	2	31
450.63	129.1147	363.1730	0	10
452.84	162.0520	396.1103	5	81
453.42	216.1106	450.1689	0	16
454.72	128.0582	362.1166	1	18

454.87	164.0654	398.1237	6	77
457.36	222.0730	456.1313	2	53
457.99	75.0685	309.1269	2	13
458.05	246.1210	480.1793	2	20
459.44	89.0478	323.1061	4	38
460.55	203.0354	437.0938	0	2
464.98	231.1209	465.1792	0	5
466.01	162.0519	396.1102	5	81
470.46	174.0632	408.1215	2	22
475.37	222.0726	456.1309	2	53
478.04	203.0888	437.1471	0	11
480.61	83.0727	317.1311	0	2
481.93	110.0477	344.1060	1	8
484.24	162.0530	396.1114	5	82
484.80	124.0632	358.1216	1	10
486.39	172.0837	406.1420	2	9
486.68	243.1036	477.1620	1	9
487.23	69.0570	303.1153	0	2
488.30	114.0788	348.1371	1	4
489.78	132.0417	366.1000	7	69
492.51	181.0731	415.1314	5	46
494.16	117.0812	351.1395	5	38
495.94	168.0275	402.0858	1	9
503.19	162.0518	396.1102	5	81
509.52	223.0066	457.0650	0	2
510.77	252.1106	486.1689	0	11
515.02	225.1099	459.1683	0	29
515.71	162.0517	396.1100	5	81
523.63	203.0776	437.1359	0	36
523.92	45.0207	279.0791	1	8
526.00	221.0727	455.1310	0	39
526.31	87.0689	321.1272	1	29
527.42	168.0275	402.0859	1	9
527.67	104.0659	338.1242	0	5
536.20	165.0430	399.1013	4	24
537.22	186.0994	420.1578	0	15
538.28	162.0517	396.1101	5	81
547.85	157.0844	391.1427	0	13
550.09	117.0780	351.1363	5	38
551.08	87.0690	321.1274	1	29
560.76	260.1370	494.1953	2	13
566.51	165.0089	399.0672	0	9
568.03	247.0684	481.1267	0	17

570.04	316.1992	550.2575	6	57
571.45	73.0533	307.1116	3	18
575.10	203.0776	437.1359	0	36
577.06	87.0316	321.0899	1	18
577.68	142.0370	376.0953	1	12
580.36	117.0419	351.1003	3	35
584.12	459.1191	693.1774	0	14
586.39	105.0774	339.1357	1	15
586.84	294.1220	528.1803	2	15
587.05	145.0735	379.1318	6	54
587.60	156.0529	390.1112	3	18
588.52	240.0076	354.0621	0	6
593.50	87.0682	321.1266	1	29
594.38	162.0518	396.1101	5	81
596.37	135.0346	369.0929	2	20
603.16	136.0375	370.0958	3	24
604.34	105.0794	339.1377	1	14
609.69	247.0673	481.1256	0	22
611.35	76.0160	310.0743	1	16
614.72	62.0363	296.0946	0	19
615.54	162.0519	396.1102	5	81
616.40	87.0679	321.1262	1	29
616.93	428.0880	448.1023	0	2
617.57	426.0857	447.1012	1	5
618.50	128.0939	362.1522	0	8
622.64	147.0883	381.1466	0	40
624.84	153.0284	387.0867	0	2
628.86	206.0414	440.0997	4	21
633.66	51.1007	285.1590	0	0
639.25	292.1865	526.2448	0	3
641.02	101.0474	335.1058	0	29
645.49	202.1299	436.1882	0	14
647.95	575.2579	809.3162	0	4
655.43	438.1760	672.2344	0	5
655.91	371.0651	419.5908	0	13
658.87	185.0340	419.0923	1	9
659.09	369.0657	418.5912	0	8
667.26	101.0845	335.1428	0	20
673.55	472.2629	470.1898	0	25
674.54	473.2685	470.6925	0	4
675.54	146.0572	380.1155	7	60
684.51	176.1110	322.1138	0	0
685.12	174.1112	321.1139	3	11

685.55	175.1137	642.2230	1	3
689.65	131.0571	365.1155	8	60
690.94	101.0847	335.1430	0	20
691.16	177.0338	411.0921	0	0
694.85	196.0363	430.0946	0	37
698.99	89.0781	323.1364	0	0
700.67	154.0505	311.0836	0	14
701.51	153.0404	387.0987	2	20
701.95	117.0734	351.1317	0	0
702.84	146.0591	380.1174	7	60
706.05	275.1460	371.6313	2	10
706.09	166.0470	400.1053	5	35
711.16	154.0992	388.1575	0	5
711.35	43.0421	277.1004	0	4
711.70	115.0262	349.0845	0	13
712.34	166.0254	400.0838	3	22
713.11	144.0077	378.0660	0	7
714.82	90.0311	324.0894	5	41
716.10	146.0567	380.1150	7	60
717.32	101.0842	335.1425	0	20
720.69	103.0265	337.0848	2	15
720.92	166.0483	400.1066	5	36
723.20	106.0097	340.0680	0	10
726.11	163.0660	397.1243	3	36
729.11	261.1324	364.6245	3	3
731.51	101.0833	335.1416	0	20
734.14	274.1645	371.1406	0	4
736.00	144.0427	378.1010	3	44
739.27	72.0569	306.1152	3	22
741.11	188.1261	328.1214	1	7
742.34	214.1318	448.1901	1	7
748.07	271.1633	369.6400	0	1
753.28	101.0837	335.1420	0	20
754.11	356.2273	590.2856	0	0
755.65	102.0315	336.0899	6	52
758.63	325.1865	559.2448	0	0
759.50	430.2390	664.2974	0	2
760.48	261.1326	364.6246	3	3
762.60	130.0249	364.0832	4	40
763.39	133.0186	367.0769	0	4
768.50	273.1796	370.6481	0	0
768.70	101.0849	335.1432	0	20
772.12	129.0777	363.1360	4	30

772.47	156.0522	390.1106	3	18
773.17	149.0239	383.0822	0	1
773.77	297.0434	382.5800	1	5
774.10	297.0439	531.1023	1	5
774.33	299.0419	383.5793	0	17
777.36	275.1477	371.6322	2	13
778.20	276.1505	372.1336	0	5
783.06	129.0779	363.1362	4	30
783.54	101.0837	335.1420	0	20
785.41	242.1499	476.2082	0	5
791.89	63.0085	297.0668	0	1
792.66	295.0305	381.5736	0	1
794.40	125.0170	296.5668	1	5
795.27	127.0156	297.5661	0	1
810.11	486.1741	720.2324	0	17
810.21	101.0845	335.1428	0	20
814.33	223.0062	457.0646	0	2
815.98	208.0510	338.0838	0	12
816.56	187.0833	421.1416	1	32
817.18	85.0521	319.1104	1	16
819.30	145.0726	379.1310	6	54
820.74	121.0307	355.0891	0	2
824.05	151.0601	385.1184	3	35
824.69	117.0417	351.1000	3	35
831.85	101.0848	335.1432	0	20
833.51	187.0947	327.6057	0	7
836.34	322.1279	395.1223	0	8
842.54	356.0618	590.1201	0	8
848.66	446.0119	457.0643	0	4
850.19	144.0533	306.0850	3	15
852.03	163.1034	315.6100	0	16
852.22	144.0587	306.0877	3	0
854.60	144.0419	378.1002	3	44
855.00	153.0419	387.1002	2	24
855.51	137.0469	371.1052	5	20
859.78	203.0784	437.1367	0	36
860.83	43.0414	277.0997	0	4
863.82	155.0514	622.1607	0	1
863.85	153.0398	387.0981	2	20
864.08	154.0499	311.0833	0	14
865.75	154.0491	621.1585	0	14
865.84	115.0995	349.1579	0	21
866.47	349.1993	583.2577	0	0

867.68	242.0210	355.0688	1	35
868.45	240.0239	474.0822	1	3
869.23	132.0528	300.0847	5	20
876.51	200.1156	434.1739	0	11
881.61	147.0339	381.0922	1	8
882.08	71.0362	305.0945	1	9
896.10	34.0046	501.1140	1	8
896.12	146.0671	307.0919	4	29
896.65	144.0408	378.0992	3	43
898.05	148.0691	308.0929	2	45
898.18	133.1091	367.1674	0	9
901.08	114.1017	581.2110	3	12
903.27	198.0518	432.1101	3	20
905.90	112.0967	579.2060	0	0
906.00	88.0167	322.0750	2	30
907.55	115.0996	349.1579	0	21
909.44	168.0409	402.0992	7	25
909.94	180.0588	324.0877	14	90
928.93	133.1092	367.1675	0	9
933.08	115.0991	349.1574	0	21
934.75	256.0378	362.0772	0	11
935.66	254.0406	361.0786	0	9
936.91	202.1054	335.1110	0	5
942.24	204.1112	336.1139	0	12
945.76	126.0314	360.0897	0	15
951.10	155.0677	389.1260	1	14
951.19	115.0983	349.1566	0	21
952.86	159.0886	393.1469	6	43
953.11	190.1306	329.1236	0	8
954.57	240.0076	474.0659	0	6
961.81	115.0995	349.1579	0	21
962.48	104.0829	338.1413	0	11
963.03	135.0434	369.1017	0	0
963.30	180.0657	324.0912	17	88
968.23	100.0169	334.0753	0	16
970.81	144.0411	378.0994	3	43
977.73	351.1571	585.2154	0	16
977.87	583.2814	817.3397	0	6
980.29	159.0881	393.1464	6	43
985.11	129.0773	363.1356	4	30
993.27	32.0282	266.0865	1	37
994.36	446.2273	680.2856	0	6
999.45	133.0935	600.2028	0	6

1001.55	134.0902	301.1034	0	11
1002.80	493.1550	727.2133	0	12
1002.99	246.0994	480.1578	0	12
1004.67	132.0906	366.1490	2	19
1011.83	436.1623	670.2206	0	12
1014.22	161.0495	395.1078	3	19
1015.78	188.0297	422.0880	1	18
1015.88	221.0881	688.1975	7	56
1018.88	112.0515	346.1098	1	16
1020.68	120.0572	354.1155	2	18
1020.70	180.0624	324.0895	17	87
1022.18	191.0565	425.1148	1	19
1022.22	182.0641	325.0904	0	1
1022.29	162.0519	396.1102	5	81
1027.21	145.0723	379.1306	6	54
1027.82	363.1691	597.2274	0	7
1028.02	57.0205	291.0788	0	5
1028.87	574.2754	808.3337	0	1
1030.25	243.1578	355.6372	0	3
1050.90	188.0302	422.0886	1	18
1051.52	230.1466	349.1316	0	6
1054.65	71.0725	305.1308	0	6
1054.65	132.0533	366.1116	5	20
1054.97	243.1210	355.6188	0	8
1056.90	189.0402	423.0985	1	10
1058.28	144.0407	378.0990	3	43
1064.67	182.0632	325.0899	0	3
1064.96	180.0617	324.0892	17	94
1065.33	162.0524	396.1107	5	81
1065.97	138.0305	372.0888	4	21
1066.60	181.0667	324.5917	0	0
1067.09	147.1081	614.2175	0	3
1068.09	131.0728	365.1311	2	10
1070.18	260.1147	494.1730	0	13
1072.35	148.1052	308.1109	0	2
1079.43	173.1035	407.1618	4	29
1081.75	147.1122	307.6144	0	1
1092.79	187.1666	327.6416	2	3
1093.74	243.1563	355.6365	0	2
1095.07	207.0888	441.1471	3	34
1102.21	96.2056	563.3149	0	0
1102.25	155.0673	622.1767	1	14
1103.18	157.0685	624.1779	0	0

1103.45	193.0721	427.1304	3	28
1105.70	157.0684	312.5925	0	0
1106.06	268.0155	368.0661	0	2
1106.51	270.0152	369.0659	1	4
1106.58	156.0681	312.0924	1	3
1107.17	155.0698	311.5932	1	14
1107.32	27.0111	261.0694	0	0
1107.77	156.0709	623.1802	1	0
1112.05	48.0034	282.0617	1	4
1114.56	93.0323	327.0906	0	0
1114.72	180.0674	324.0920	17	88
1115.70	173.1032	407.1615	4	29
1122.10	90.0479	324.1063	0	6
1124.10	102.0814	285.0990	0	10
1124.93	310.1231	389.1199	1	20
1127.36	173.1034	407.1617	4	29
1128.86	120.0038	354.0621	0	4
1132.02	111.0796	345.1379	1	4
1132.30	42.0220	276.0803	0	3
1133.28	128.1045	298.1106	0	4
1134.28	128.1055	595.2148	0	4
1135.23	280.1194	514.1778	0	19
1137.40	175.0658	409.1241	2	20
1140.13	438.0025	672.0609	0	0
1142.61	240.0089	354.0628	0	0
1143.04	310.1324	544.1908	0	5
1143.21	227.0589	347.5878	0	17
1143.40	226.0577	347.0872	1	26
1145.35	136.0379	370.0962	3	24
1145.93	159.0881	393.1464	6	43
1148.92	175.0648	409.1231	2	19
1156.35	240.0070	354.0618	0	6
1161.00	32.0242	266.0826	1	37
1167.58	324.0440	396.0803	0	12
1169.51	73.0882	307.1465	0	8
1171.79	175.0620	409.1203	3	22
1177.41	221.1050	455.1633	0	24
1182.06	245.0697	356.5932	0	14
1182.59	244.0668	356.0917	2	33
1186.17	160.1213	314.1190	2	12
1195.62	276.1466	510.2050	0	8
1197.14	136.0519	370.1102	1	43
1201.39	164.0685	316.0926	6	74

1205.77	129.0620	596.1713	1	3
1209.66	424.2327	658.2910	0	13
1210.58	166.0032	317.0599	0	5
1212.32	187.1190	421.1773	0	22
1212.61	128.0576	298.0871	1	18
1212.96	130.0575	299.0871	0	1
1213.16	202.0941	335.1054	0	19
1213.61	128.0571	362.1154	1	16
1218.48	174.1034	321.1100	1	35
1219.04	246.1361	480.1944	0	12
1219.73	112.0150	346.0734	2	9
1220.00	126.0317	360.0900	0	15
1220.05	174.0977	321.1072	1	35
1223.28	121.0180	294.5673	2	15
1223.62	187.1190	421.1773	0	22
1223.88	246.1466	480.2049	1	7
1224.34	61.0110	295.0693	0	1
1225.99	180.0781	414.1364	1	31
1233.86	102.0798	285.0982	0	10
1237.44	246.1456	480.2040	1	7
1248.42	99.1044	333.1627	0	1
1249.09	305.2608	539.3191	0	0
1249.72	310.1296	544.1879	0	14
1250.04	160.0862	314.1014	1	37
1250.68	162.0837	315.1002	1	6
1251.90	77.0313	272.5740	1	5
1253.75	75.0304	271.5735	1	22
1255.66	144.0871	306.1019	0	17
1255.84	144.0925	306.1046	0	17
1259.16	161.1239	628.2332	0	0
1260.09	160.1193	314.1180	2	12
1260.53	162.1193	315.1180	2	7
1260.67	282.1382	516.1965	0	1
1262.70	190.1205	329.1186	0	3
1264.17	188.1190	328.1178	3	25
1264.69	188.1126	328.1146	3	24
1267.40	136.0507	370.1090	1	43
1270.00	131.0615	299.5891	8	60
1270.58	131.0563	299.5865	8	60
1270.59	90.0138	324.0721	0	2
1272.61	157.0840	312.6003	0	12
1273.47	167.0695	317.5931	0	20
1274.85	868.0080	668.0623	0	0

1275.69	162.0538	315.0852	5	82
1280.79	167.0675	401.1259	0	20
1283.33	85.0888	319.1471	0	5
1284.91	175.1046	642.2139	0	7
1285.81	174.0995	321.1081	1	35
1286.03	176.0997	322.1082	2	20
1289.61	362.2099	596.2682	3	44
1291.02	83.0737	317.1320	0	2
1298.89	188.1253	328.1210	1	7
1300.23	188.1168	328.1167	3	25
1301.21	61.0512	264.5839	1	15
1301.83	189.1170	328.6168	0	1
1304.77	152.0456	386.1039	9	32
1305.94	115.0984	349.1567	0	21
1306.02	241.0087	354.5627	1	7
1308.08	116.0960	292.1063	1	9
1308.21	162.0553	315.0860	5	82
1308.47	118.0931	293.1049	0	0
1309.03	240.0062	354.0614	0	7
1312.80	168.0282	318.0724	1	9
1314.96	216.1115	342.1141	0	16
1315.01	83.0724	317.1307	0	2
1320.35	164.0681	316.0924	6	74
1320.46	114.0780	291.0973	1	4
1320.66	116.0798	292.0982	2	45
1325.65	120.0055	354.0639	0	4
1327.94	169.0315	636.1408	0	2
1329.70	117.0999	292.6083	0	1
1329.76	168.0274	318.0720	1	9
1330.10	170.0265	319.0716	1	11
1330.29	105.0782	286.5974	1	15
1331.79	170.0140	404.0723	1	3
1332.41	106.0446	340.1030	1	13
1332.48	208.0885	338.1026	3	32
1332.83	117.0977	584.2070	0	0
1333.81	204.1353	336.1260	0	4
1334.49	202.1332	335.1249	0	14
1335.45	118.0932	293.1049	0	0
1335.59	98.0836	565.1930	0	1
1335.96	116.0933	292.1050	1	9
1336.69	212.0873	679.1967	0	16
1338.95	118.0978	293.1072	0	10
1344.00	183.0626	650.1719	0	15

1344.25	183.0627	417.1210	0	15
1345.10	69.0571	303.1154	0	2
1345.79	86.0834	277.1000	0	1
1347.22	99.0445	283.5806	0	4
1353.78	90.0133	324.0717	0	2
1357.98	119.0355	353.0938	0	8
1364.40	154.0511	311.0838	0	14
1367.09	104.0297	338.0880	0	7
1367.93	162.0509	315.0838	5	84
1370.03	274.1764	508.2347	1	2
1377.60	169.0301	636.1394	0	3
1378.07	182.0769	649.1862	4	40
1380.74	247.0671	357.5918	0	21
1381.28	167.0211	401.0794	2	13
1382.02	183.0761	325.5964	1	12
1382.10	168.0279	318.0723	1	9
1382.43	170.0304	319.0735	0	13
1383.66	126.0551	297.0859	2	3
1384.49	92.0467	280.0817	1	25
1385.31	82.0383	275.0775	0	8
1385.53	80.0375	547.1468	1	0
1386.46	80.0375	274.0771	1	0
1386.56	162.0508	315.0837	5	84
1387.25	114.0799	291.0983	1	4
1388.30	116.0788	292.0977	2	45
1389.94	245.1037	479.1620	0	20
1391.07	126.0222	360.0806	0	1
1392.64	211.1339	339.6253	0	1
1396.01	222.0115	345.0641	0	3
1396.23	159.0670	393.1253	1	16
1401.26	163.0567	630.1660	0	0
1401.49	145.0514	379.1097	0	12
1402.23	527.1872	994.2966	0	9
1403.52	144.0424	378.1007	3	44
1404.11	162.0519	315.0843	5	81
1404.18	164.0516	316.0841	5	39
1404.51	195.0051	331.5609	0	4
1404.94	197.0031	332.5598	0	6
1407.90	72.0580	306.1164	3	22
1410.45	159.0669	393.1252	1	16
1412.01	163.0563	315.5865	0	0
1424.01	188.0197	328.0682	0	4
1425.02	188.0259	328.0712	0	7

1430.86	83.0749	317.1332	0	2
1435.96	129.1156	363.1739	0	10
1438.02	101.1039	568.2132	0	0
1440.60	138.0580	605.1674	1	4
1441.82	83.0742	317.1325	0	2
1441.92	100.0988	284.1077	0	2
1442.39	102.0989	285.1078	0	0
1442.74	329.0411	398.5789	0	10
1443.52	123.0864	590.1957	0	3
1443.66	158.1520	625.2613	0	4
1445.30	195.0016	331.5591	0	4
1445.36	197.0001	332.5584	1	7
1446.02	56.0503	290.1086	0	0
1447.02	100.1006	567.2100	0	2
1453.90	152.0336	310.0751	3	13
1454.65	128.0925	298.1046	0	8
1455.21	151.0077	385.0660	0	7
1457.92	264.1346	498.1929	0	17
1462.64	136.0538	302.0852	1	41
1463.03	216.1461	342.1314	0	15
1466.84	82.0526	275.0846	0	4
1470.08	223.1311	345.6239	0	2
1481.38	136.0515	302.0841	1	43
1482.51	130.0260	299.0713	4	40
1489.56	138.0401	303.0784	2	17
1489.95	136.0393	302.0780	3	24
1491.04	136.0391	370.0974	3	24
1495.16	209.0675	338.5921	1	49
1501.25	151.0080	385.0663	0	7
1501.85	177.0974	644.2068	0	22
1502.67	178.0962	323.1064	1	24
1505.42	120.0567	354.1150	2	18
1505.90	56.0946	290.1530	0	0
1506.97	136.0506	302.0836	1	43
1507.38	116.0141	292.0654	2	18
1507.79	101.0851	284.6009	0	20
1508.25	118.0106	293.0636	0	5
1523.17	138.0400	303.0783	2	18
1524.30	136.0392	302.0779	3	24
1524.43	182.0590	325.0878	6	48
1529.23	237.0969	352.6068	0	13
1541.49	120.0331	354.0915	0	4
1543.35	110.0462	577.1556	1	8

1543.49	110.0484	344.1068	1	8
1547.56	127.0608	297.5887	2	20
1549.56	159.0673	313.5920	1	16
1550.34	158.0604	392.1187	2	30
1551.89	108.0415	288.0791	0	10
1553.06	107.0418	574.1512	0	5
1556.88	143.0255	305.5711	0	5
1559.05	45.0282	256.5724	0	1
1559.06	110.0501	289.0834	1	8
1559.28	44.0248	256.0707	1	16
1559.31	110.0480	344.1063	1	8
1570.31	110.0461	577.1554	1	8
1571.07	154.0175	388.0758	0	2
1571.69	90.0560	324.1143	0	0
1572.06	111.0483	578.1576	1	10
1572.70	110.0472	344.1055	1	8
1573.23	170.0717	404.1300	0	19
1574.20	110.0457	289.0812	1	8
1582.37	244.0836	478.1419	2	18
1588.20	154.0175	388.0759	0	2
1590.84	414.2054	648.2637	0	6
1591.51	138.0372	303.0769	0	1
1592.89	220.1829	454.2412	0	3
1593.16	112.0471	290.0819	0	0
1593.22	110.0471	344.1054	1	8
1593.72	110.0470	289.0818	1	8
1597.07	111.0528	578.1621	0	0
1606.82	188.0594	328.0880	0	4
1611.64	220.1816	454.2400	0	3
1619.07	270.0842	369.1004	0	33
1625.83	163.2363	397.2946	0	0
1630.44	234.1969	468.2552	0	2
1635.67	142.0180	305.0673	0	2
1637.39	144.0128	306.0647	0	3
1638.09	377.0559	611.1142	0	8
1638.69	270.0865	369.1016	0	34
1639.20	379.0806	613.1390	0	3
1640.08	403.0547	637.1130	0	4
1640.89	144.0075	306.0621	0	7
1641.67	144.0076	378.0659	0	7
1642.09	146.0057	307.0612	0	1
1642.12	203.0762	437.1345	0	36
1643.36	205.0818	439.1401	0	13

1646.71	148.0877	382.1460	1	26
1648.67	211.0677	304.4142	0	22
1651.08	297.0594	531.1177	0	4
1652.09	54.0192	288.0775	0	0
1652.15	140.0485	304.0826	0	18
1653.62	160.0366	394.0949	2	39
1664.27	165.0551	399.1134	0	3
1664.72	271.0926	369.6046	0	21
1665.45	166.0655	317.0911	7	49
1666.09	272.0944	370.1055	0	11
1669.09	222.1618	456.2201	0	3
1671.60	137.0559	604.1653	0	9
1673.41	301.2090	535.2673	0	3
1676.09	43.0255	277.0838	0	1

*Click each matched number will link to a list of matches in www.mycompoundid.org.

Supplemental Table T4. List of 46 identified significant metabolites found in human serum samples that differentiate the PD group and the healthy control group.

Retention time (min)	Mass of dansylated metabolite (Da)	Mass of metabolite (Da)	Metabolite	HMDB ID	ID	Fold change	q-value
2.65	432.1329	198.0746	5-Acetylamino-6-amino-3-methyluracil	HMDB04400	Putative	0.61	2.47E-03
3.20	502.1385	268.0802	Inosine	HMDB00195	Putative	0.74	6.86E-02
3.58	471.1422	237.0839	Biopterin	HMDB00468	Putative	1.36	1.74E-04
3.90	409.1534	175.0951	Citrulline	HMDB00904	Library	0.83	2.23E-05
4.08	399.1035	165.0452	Methionine Sulfoxide	HMDB02005	Library	1.21	2.55E-02
4.60	399.1037	165.0454	Methionine Sulfoxide - Isomer	HMDB02005	Library	1.24	2.68E-02
4.90	410.1372	176.0789	Ornithine [+CO2]	HMDB00214	Putative	0.78	7.71E-06
6.81	415.1316	181.0733	L-Threo-3-Phenylserine	HMDB02184	Putative	0.76	9.15E-05
7.40	436.1894	202.1311	Isoleucyl-Alanine	HMDB28900	Putative	0.66	1.92E-08
7.63	309.1269	75.0685	1-Amino-propan-2-ol	HMDB12136	Putative	1.90	5.32E-06
7.75	465.1792	231.1209	Norophthalmic acid [-CO2]	HMDB05766	Putative	1.34	1.51E-02
8.21	415.1314	181.0731	L-Threo-3-Phenylserine	HMDB02184	Putative	0.82	2.04E-02
8.56	453.1683	219.1100	Pantothenic acid	HMDB00210	Library	0.76	1.95E-02
9.34	408.1574	174.0991	Glycyl-Valine	HMDB28854	Library	1.45	1.91E-02
9.52	307.1116	73.0533	Aminoacetone	HMDB02134	Putative	1.48	1.02E-07
11.58	430.0946	196.0363	4-Hydroxy-benzenepropanedioate	HMDB59809	Putative	179.70	6.28E-08
11.77	400.1053	166.0470	Methylxanthine	HMDB10738	Putative	0.62	2.46E-03
12.02	400.1066	166.0483	3-Methylxanthine	HMDB01866	Putative	0.65	4.44E-03
12.90	382.5800	297.0434	L-Cysteinylglycine disulfide	HMDB00709	Putative	0.83	9.87E-08
13.27	432.1101	198.0518	Vanillylmandelic acid	HMDB00291	Library	3.80	2.07E-19
13.66	363.1361	129.0778	L-Pipecolic acid	HMDB00716	Library	0.80	1.93E-02
14.61	434.1739	200.1156	Glycylproline [+C2H4]	HMDB00721	Putative	0.82	1.18E-02
15.05	432.1101	198.0518	Isovanillymandelic acid	NA	Putative	164.05	3.25E-07

15.87	414.1232	180.0649	Theophylline	HMDB01889	Library	0.48	4.42E-07
17.58	355.6188	243.1210	Aspartylysine [-H2O]	HMDB04985	Putative	1.24	2.07E-04
17.77	372.0888	138.0305	4-Hydroxybenzoic acid	HMDB00500	Putative	0.80	7.15E-03
17.88	402.1001	168.0418	Vanillic acid	HMDB00484	Library	3.48	3.96E-20
20.43	414.1364	180.0781	p-Hydroxyphenylacetic acid [+C2H4]	HMDB00020	Putative	3.75	5.91E-02
20.81	333.1627	99.1044	Cyclohexylamine	HMDB31404	Putative	0.60	1.71E-02
20.82	539.3191	305.2608	Capsaicin	HMDB02227	Putative	1.65	7.89E-06
21.00	314.1180	160.1193	N(6)-Methyllysine	HMDB02038	Putative	0.65	2.91E-03
21.01	315.1180	162.1193	Tryptamine [+2H]	HMDB00303	Putative	0.68	6.05E-03
21.75	386.1039	152.0456	Vanillin	HMDB12308	Putative	1.27	1.01E-02
22.21	338.1026	208.0885	5-Hydroxyindoleacetic acid [+NH3]	HMDB00763	Putative	0.61	2.55E-19
22.28	679.1967	212.0873	Histidinyl-Glycine	HMDB28885	Putative	29.32	4.66E-06
23.42	346.0986	224.0805	Hydroxykynurenine	HMDB00732	Library	2.73	1.30E-08
23.75	328.0712	188.0259	L-Homocysteine sulfonic acid [+NH3]	HMDB02238	Putative	0.82	1.23E-02
24.23	310.0751	152.0336	6,8-Dihydroxypurine	HMDB01182	Putative	0.59	6.15E-02
24.38	302.0852	136.0538	Dopamine [-NH3]	HMDB00073	Putative	0.75	1.76E-03
24.38	342.1314	216.1461	Valyl-Valine	NA	Putative	0.82	9.95E-02
24.69	302.0841	136.0515	Dopamine [-NH3]	HMDB00074	Putative	0.83	1.70E-02
25.06	322.1050	176.0933	Serotonin	HMDB00259	Library	0.79	1.07E-02
27.48	304.4142	211.0677	a-Methyldopa	HMDB11754	Putative	231.42	3.64E-02
27.54	304.0826	140.0485	Vanillic acid [-CO]	HMDB00484	Putative	11.77	3.81E-03
27.74	399.1134	165.0551	Methylguanine	HMDB03282	Putative	240.60	6.28E-08
27.76	317.0911	166.0655	3,4-Dihydroxyphenylacetone	HMDB31132	Putative	208.33	1.38E-22

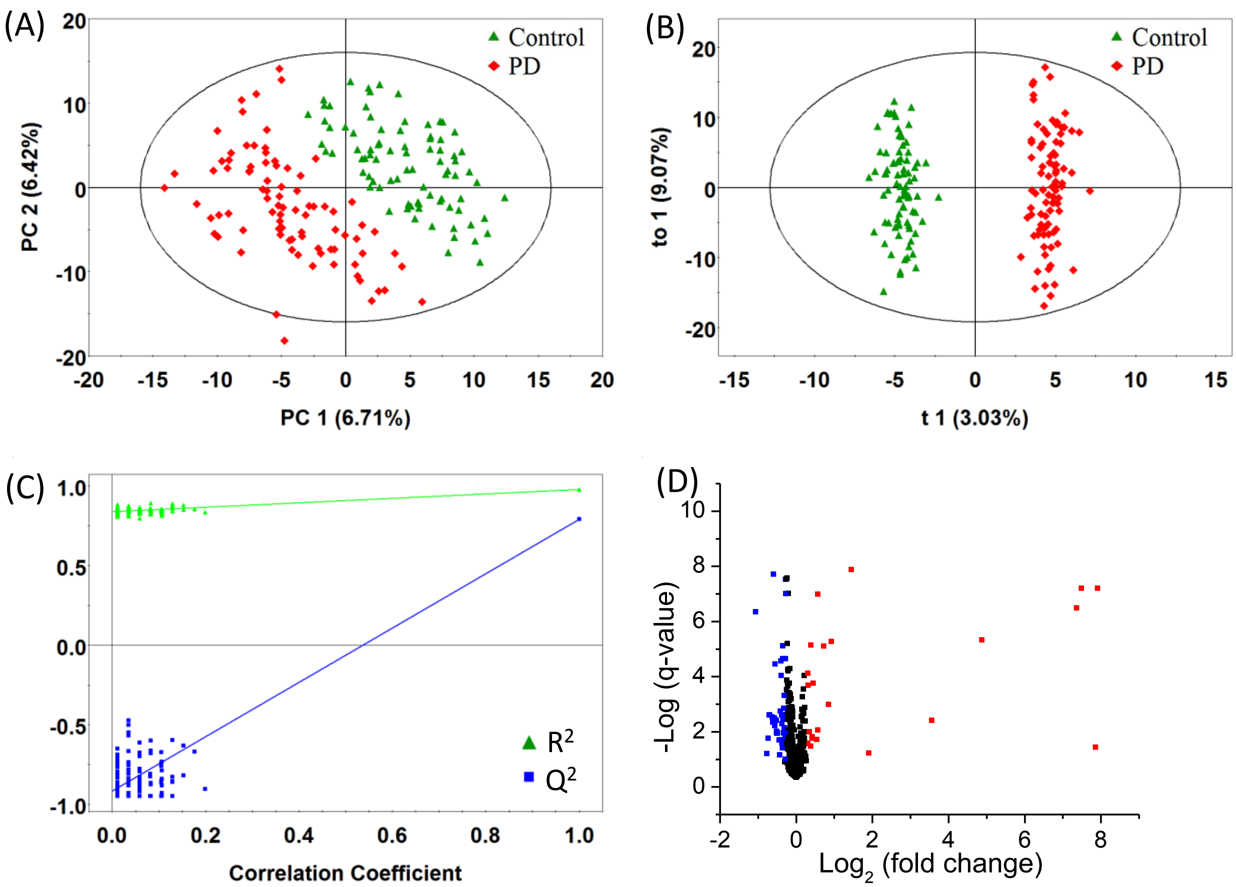
Supplemental Table T5. List of 18 identified significant metabolites found in human serum samples that differentiate the PDND subgroup and the PDID subgroup.

Retention time (min)	Mass of dansylated metabolite (Da)	Mass of metabolite (Da)	Metabolite	HMDB ID	ID	Fold change	q value
3.20	502.1385	268.0802	Riboside of Purine [+O]	NA	Putative	0.51	8.63E-02
10.38	381.1466	147.0883	Hydroxyisoleucine	NA	Putative	1.47	8.20E-02
11.58	430.0946	196.0363	4-Hydroxy-benzenepropanedioate	HMDB59809	Putative	1.33	9.22E-02
12.87	363.1360	129.0777	L-Proline [+CH2]	HMDB00612	Putative	0.81	8.17E-02
13.74	351.1000	117.0417	L-2-Amino-3-oxobutanoic acid	HMDB06454	Putative	1.35	3.32E-02
14.18	315.1080	162.0995	5-Hydroxylysine	HMDB00450	Library	1.23	7.94E-02
16.71	727.2133	493.1550	His-Asn-Asp-Ser	NA	Putative	1.72	1.64E-02
18.39	427.1304	193.0721	Phenylacetylglycine	HMDB00821	Putative	1.27	4.33E-02
18.41	400.1196	166.0612	Desaminotyrosine	HMDB02199	Library	0.64	8.91E-02
19.09	370.0962	136.0379	Purine [+O]	HMDB01366	Putative	0.44	8.17E-02
20.83	314.1014	160.0862	Alanyl-alanine	NA	Putative	1.44	3.28E-02
21.43	321.1081	174.0995	Ornithine [+C2H2O]	HMDB00214	Putative	1.37	7.55E-02
21.43	322.1082	176.0997	Tryptamine [+O]	HMDB00303	Putative	1.33	8.20E-02
22.42	303.1154	69.0571	1-Pyrroline-2-carboxylic acid [-CO2]	HMDB06875	Putative	1.32	2.38E-02
22.43	277.1000	86.0834	Putrescine [-2H]	HMDB01414	Putative	1.41	1.64E-02
24.03	284.1077	100.0988	Cadaverine [-2H]	HMDB02322	Putative	1.20	8.17E-02
24.92	338.5921	209.0675	Hydroxyphenylacetylglycine	HMDB00735	Putative	1.23	8.17E-02
27.76	317.0911	166.0655	3,4-Dihydroxyphenylacetone	HMDB31132	Putative	1.54	6.65E-02

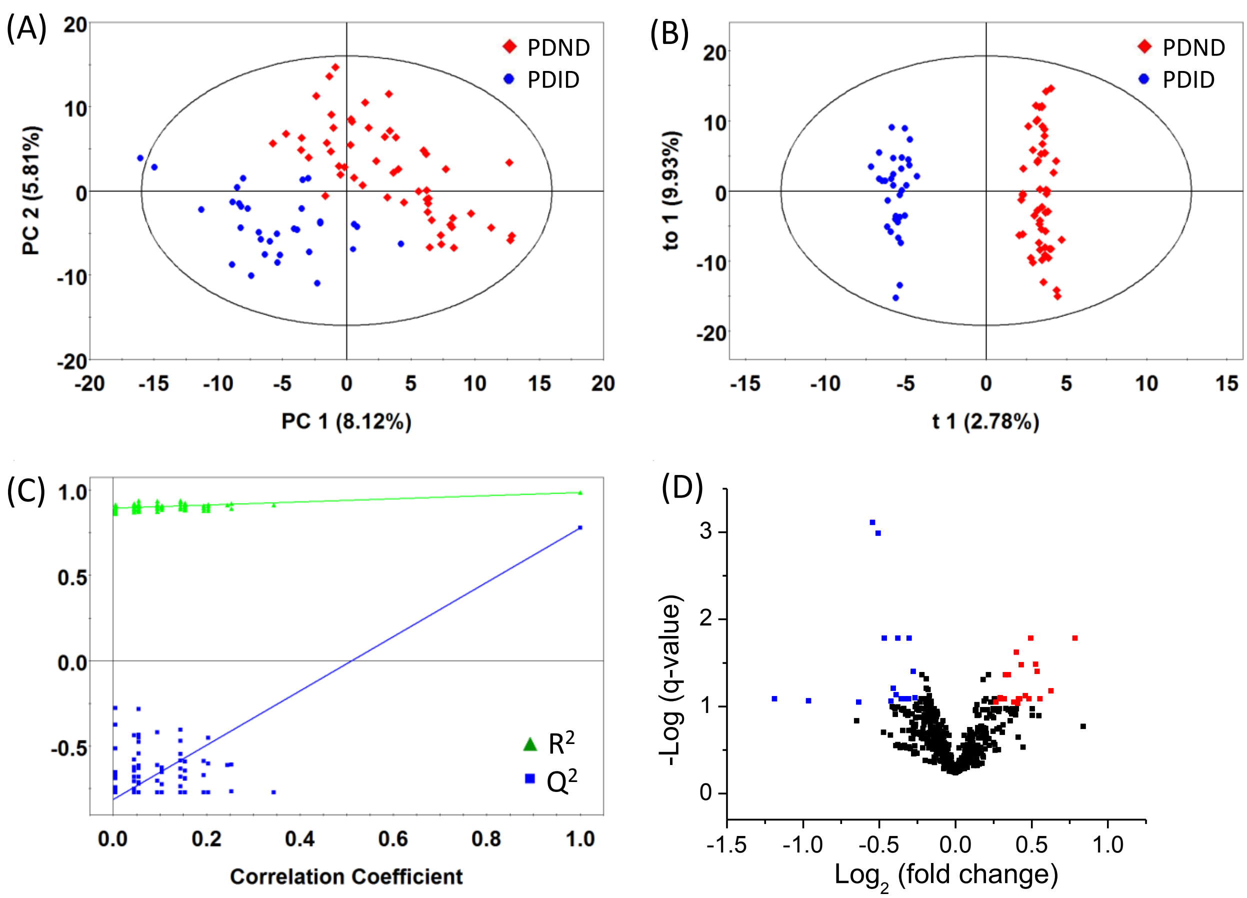
Supplemental Table T6. List of 38 unidentified metabolites with their fold changes (FC) and p-values for both Control vs. PD and PDND vs. PDID. The identified metabolites are listed at the end of the table for comparison.

ID	Retention time (second)	m/z	FC (Control vs. PD)	p-value (Control vs. PD)	FC (PDND vs. PDID)	p-value (PDND vs. PDID)
122	416.3	240.0087	1.03	1.93E-01	0.97	2.88E-01
137	444.8	517.0723	0.94	1.08E-01	0.96	4.90E-01
228	633.7	51.1007	1.04	2.81E-01	0.95	3.18E-01
243	684.5	176.1110	0.88	5.03E-05	0.90	3.66E-02
248	691.2	177.0338	0.76	2.22E-06	0.90	1.91E-01
250	699.0	89.0781	1.03	5.86E-01	1.05	5.36E-01
253	701.9	117.0734	1.10	1.51E-01	1.28	2.11E-02
281	754.1	356.2273	1.03	6.21E-01	0.92	2.13E-01
283	758.6	325.1865	1.05	2.94E-01	0.95	4.41E-01
288	768.5	273.1796	0.89	7.54E-02	0.96	6.93E-01
341	866.5	349.1993	1.00	9.81E-01	1.06	3.63E-01
356	905.9	112.0967	1.03	1.28E-01	0.96	2.11E-01
376	963.0	135.0434	0.91	2.34E-03	1.04	4.19E-01
423	1066.6	181.0667	0.90	2.61E-03	0.96	4.29E-01
436	1102.2	96.2056	0.68	2.96E-06	0.99	9.33E-01
438	1103.2	157.0685	0.96	9.66E-02	0.96	2.43E-01
441	1105.7	157.0684	0.97	2.74E-01	0.98	6.57E-01
447	1107.3	27.0111	0.95	3.37E-02	0.98	5.32E-01
450	1114.6	93.0323	1.10	5.08E-02	0.99	8.31E-01
464	1140.1	438.0025	0.97	4.73E-01	0.86	1.64E-03
465	1142.6	240.0089	1.10	1.21E-02	0.93	2.26E-01
506	1249.1	305.2608	1.65	5.75E-07	1.10	4.75E-01
514	1259.2	161.1239	0.73	1.05E-02	0.81	2.90E-01
527	1274.8	868.0080	1.08	1.52E-01	0.94	4.51E-01
546	1308.5	118.0931	0.88	4.95E-04	0.99	9.00E-01
564	1332.8	117.0977	0.90	6.00E-05	0.96	2.80E-01

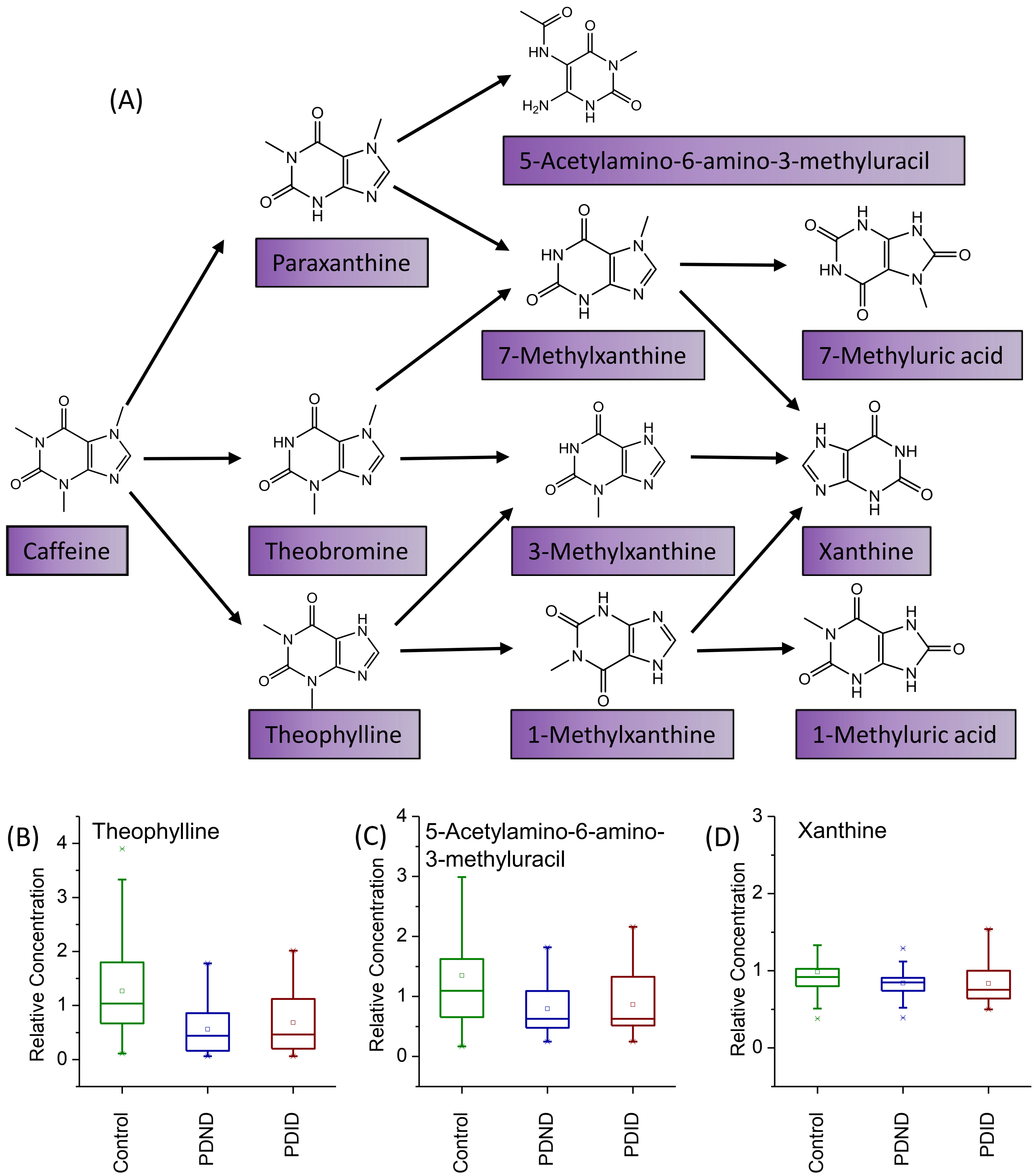
567	1335.4	118.0932	0.92	6.01E-04	0.92	3.81E-02
604	1401.3	163.0567	0.93	2.14E-02	0.92	1.02E-01
615	1412.0	163.0563	0.92	1.91E-02	0.88	2.91E-02
621	1438.0	101.1039	0.92	1.55E-01	1.10	2.45E-01
625	1442.4	102.0989	0.90	2.49E-02	1.17	3.68E-02
631	1446.0	56.0503	0.99	6.06E-01	1.02	6.56E-01
652	1505.9	56.0946	1.03	3.31E-01	0.99	7.36E-01
676	1571.7	90.0560	1.03	1.40E-01	1.02	6.06E-01
686	1593.2	112.0471	1.03	3.76E-01	0.92	4.78E-02
689	1597.1	111.0528	1.02	5.12E-01	1.00	9.74E-01
693	1625.8	163.2363	1.48	3.02E-03	0.99	9.76E-01
709	1652.1	54.0192	1.09	8.35E-02	0.87	5.97E-02
5-Acetylamino-6-amino-3-methyluracil	159.1	198.0746	0.61	5.95E-04		
Hydroxykynurenine	1405.4	224.0805	2.73	2.48E-10		
Theophylline	952.0	180.0649	0.48	2.38E-08		
Vanillic acid	1072.6	168.0418	3.48	2.51E-22		
Isoleucyl-Alanine	444.2	202.1311	0.66	4.26E-10		
3,4-Dihydroxy-phenylacetone	1665.5	166.0655			1.54	3.52E-03
alanyl-alanine	1250.0	160.0862			1.44	7.10E-04
Cyclohexylamine	1248.4	99.1044			1.46	4.47E-02
Desaminotyrosine	1104.6	166.0612			0.64	1.16E-02
His Asn Asp Ser	1002.8	493.1550			1.72	2.44E-04
Hydroxyisoleucine	622.6	147.0883			1.47	6.49E-03
Purine [+O]	1145.3	136.0379			0.44	8.26E-03
Riboside of Purine [+O]	192.2	268.0802			0.51	8.45E-03



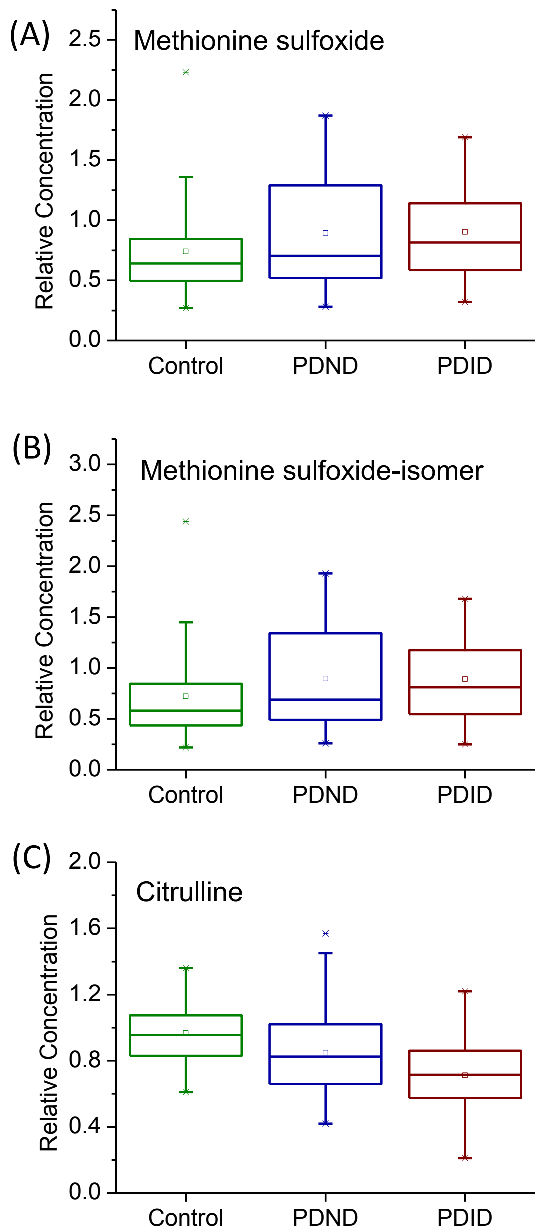
Supplemental Figure S1. (A) PLS-DA and (B) OPLS-DA score plots of dansylation LC-MS data obtained from 42 healthy controls (in green) and 43 PD patients (in red). (“PC” represents for “principal component” and the corresponding percentage is the percentage of the variance among all the data points that this principal component covers.) R^2 and Q^2 values given by cross-validation are: 0.977 and 0.791 for PLS-DA; 0.974 and 0.866 for OPLS-DA. (C) Response permutation test result of the PLS-DA model in Figure S1A. (D) Volcano plot of the comparison between healthy control and PD showing 28 variables with FC > 1.2, q < 0.1 (in red) and 48 variables with FC < 0.83, q < 0.1 (in blue).



Supplemental Figure S2. (A) PLS-DA and (B) OPLS-DA score plots of dansylation LC-MS data obtained from 27 PD patients without dementia (PDND in red) and 16 PD patients with incipient dementia (PDID in blue). R^2 and Q^2 values given by cross-validation are: 0.974 and 0.866 for PLS-DA; 0.982 and 0.813 for OPLS-DA. (C) Response permutation test result of the PLS-DA model in Figure S2A. (D) Volcano plot of the comparison between the PDND subgroup and the PDID subgroup showing 21 variables with $FC > 1.2$, $q < 0.1$ (in red) and 15 variables with $FC < 0.83$, $q < 0.1$ (in blue).



Supplemental Figure S3. (A) A simplified schematic of the caffeine metabolism pathway. Box plots of the relative concentrations of theophylline (B), 5-acetylamino-6-amino-3-methyluracil (C) and xanthine (D) in the control group, the PDND subgroup and the PDID subgroup.



Supplemental Figure S4. Box plots of the relative concentrations of methionine sulfoxide (A), methionine sulfoxide-isomer (B) and citrulline (C) in the control group, the PDND subgroup and the PDID subgroup.