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#### Data article

### LCMD: Lung Cancer Metabolome Database

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#### ABSTRACT

Lung cancer, one of the most common causes of cancer-related death worldwide, has been associated with high treatment cost and imposed great burdens. The 5-year postoperative survival rate of lung cancer (13%) is lower than many other leading cancers indicating the urgent needs to dissect its pathogenic mechanisms and discover specific biomarkers. Although several proteins have been proposed to be potential candidates for the diagnosis of lung cancer, they present low accuracy in clinical settings. Metabolomics has thus emerged as a very promising tool for biomarker discovery. To date, many lung cancer-related metabolites have been highlighted in the literature but no database is available for scientists to retrieve this information. Herein, we construct and introduce the first Lung Cancer Metabolome Database (LCMD), a freely available online database depositing 2013 lung cancer-related metabolites identified from 65 mass spectrometry-based lung cancer metabolomics studies. Researchers are able to explore LCMD via two ways. Firstly, by applying various filters in the "Browse Metabolites" mode, users can access a list of lung cancer-related metabolites that satisfy the filter specifications. For each metabolite, users can acquire the value of the fold change (cancer/normal), statistical significance (p-value) of the fold change, and the comparative research designs of all the mass spectrometry-based lung cancer metabolomics studies that identify this metabolite. Secondly, by applying various filters in the "Browse Studies" mode, users can obtain a list of mass spectrometry-based lung cancer metabolomics studies that satisfy the filter specifications. For each study, users can view the type of studied specimen, mass spectrometry (MS) method, MS data processing software, and differential analysis method, as well as all the identified lung cancer-related metabolites. Furthermore, the overview of each study is clearly illustrated by a graphical summary. The LCMD (http://cosbi7.ee.ncku.edu.tw/LCMD/) is the first database that brings together the meaningful information of lung cancer-related metabolites. The development of the LCMD is envisioned to promote the biomarker discovery of lung cancer.

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#### 1. Introduction

Lung cancer is the leading cause of cancer-related death. It imposes the highest treatment cost and burden among all cancers

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in the United States, Europe, and many other nations [1]. Although the mortality rate of lung cancer was decreasing in recent years, the survival period of fewer than five years was found in 15% of the patients. The possible reason might be the relatively late diagnosis compared with other cancers [2,3]. The five-year average survival rate could be increased to 55% if patients were successfully diagnosed at an early and localized stage [4]. Current diagnostic approaches for lung cancer are based on medical history, X-rays, and sputum cytology, which is costly and the patients without apparent clinical symptoms can be missed by detection [5]. The

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Abbreviations: HMDB, Human Metabolome Database; LCMD, Lung Cancer Metabolome Database; NSCLC, Non-Small-Cell Lung Carcinoma; VIP, Variable Importance in Projection.

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utilization of low-dose chest computed tomography (CT) imaging showed a 20% reduction in lung cancer mortality [6]. Yet enormous challenges remain, such as cost, radiation exposure, and the incidence of high false-positive rates (96%). Other radiologic diagnosis techniques, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) for instance, have been proven with a high capability to detect cancerous lesions in the lung; however, these tests are unsuitable for annual screening of general population due to their high cost [7]. Those limitations initiate the discovery of sensitive/specific complementary biomarkers to be used in conjunction with the existing screening process for more accurate diagnosis [8].

Previous studies focused on the early diagnosis of different types and stages of lung cancer using genomics and proteomics strategies. Some serum proteins such as carcinoembryonic antigens (CEA) [5], cytokeratin-19 fragments (CYFRA 21–1) [9], cancer antigen-125 (CA-125), and neuron-specific enolase (NSE) [10] have been discovered as tumor markers in lung cancer. However, none of them has proceeded to clinical usage due to its low specificity and accuracy. The increasingly high demand of cancer biomarkers necessitates more research endeavor contributing to pathogenic mechanisms and clinically relevant information.

It has been reported that a series of early perturbations in cellular metabolism was involved in the process of tumorigenesis [11]. Aside from genomics and proteomics, metabolomics has opened up new perspectives to provide complementary information regarding cellular metabolic processes that drive tumor formation and progression. Metabolic profiling reveals the current physiological state of an individual in response to disease states and environmental factors [12,13] which cannot be fully predicted from the knowledge of the human genome, transcriptome and proteome [14]. Moreover, because cancer metabolism is highly associated with oncogenic kinase signalling, it has become a vital concept for delineating malignancies and an important hallmark of carcinoma [11,15]. The first application of metabolomics approach to lung cancer research can be traced back to a decade ago. The growing number of dedicated studies is expected to open a new frontier and give in-depth insights to lung cancer research [16]. Using the keywords ((lung cancer[Title/Abstract]) OR (lung adenocarcinoma [Title/Abstract])) AND ((metabolome[Title/Abstract]) OR (metabolomics[Title/Abstract])) to search PubMed on Nov. 15, 2021, a total of 292 papers on the lung cancer metabolomics was found in the period of 2006-2021 in which about 72% (211/292) of papers were published in recent 5 years.

Currently, there are several freely accessible metabolome databases (HMDB [17], MetaboLights [18], Metabolomics WorkBench [19], GMD@CSB.DB [20], and PRIMe [21]) that contain the information of metabolites, metabolomics experiments, and the associated metadata. They aim to be comprehensive in scale and is suitable for general inquiry when looking at a designated metabolite in the molecular biology research field. However, notwithstanding the dramatical accumulation of lung cancer metabolomics data within the past few years, there is still no way to access to an organized collection of lung cancer metabolomics data. To better explore relevant information from the growing massive metabolomics data referring to a specific type/condition of lung cancer, we have constructed the first Lung Cancer Metabolome Database (LCMD) which covers 2013 metabolites collected from 65 mass spectrometry-based lung cancer metabolomics studies. We expect that LCMD will not only facilitate our understanding of lung cancer metabolism but also promote the development of novel therapeutic strategies or diagnostic markers.

#### 2. Materials and methods

## 2.1. Collection of 2013 lung cancer-related metabolites from 65 mass spectrometry-based metabolomics studies

To collect lung cancer-related metabolites from mass spectrometry-based metabolomics studies in the literature, we searched PubMed using the keywords ((lung cancer [Title/ Abstract]) OR (lung adenocarcinoma) [Title/Abstract])) AND (mass spec\* [Title/Abstract]) AND (metabol\* [Title/Abstract]) appeared in the Title/Abstract on Nov. 15, 2021 and found 447 papers. From these 447 papers, we manually checked each paper and kept 65 mass spectrometry-based lung cancer metabolomics studies which aimed to identify metabolite biomarkers for lung cancer in human specimens. For each study (cancer vs. normal), the following information were collected: the type of studied specimen, mass spectrometry (MS) method, MS data processing software, and differential analysis method, as well as all the identified lung cancer-related metabolites. The categorization of these 65 studies based on different characteristics was given in Fig. 1.

From these 65 mass spectrometry-based lung cancer metabolomics studies, we extracted 2013 lung cancer-related metabolites which were identified in at least one of these 65 studies. For each metabolite, the following information was collected: the value of the fold change (cancer/normal), the statistical significance (pvalue) of the fold change, and the comparative research designs of all the studies that identify this metabolite. The categorization of these 2013 metabolites based on different characteristics was given in Fig. 2. For each of the 2013 metabolites in LCMD, we provide the number of studies which identify this metabolite (see the download page of LCMD for details). The higher the number, the higher the confidence of a metabolite as a potential lung cancer biomarker. For example, HMDB0000159 (shown as several different names in different studies: L-phenylalanine, phenylalanine or Phe) has been identified as a lung cancer-related metabolite in 21 mass spectrometry-based metabolomics studies (Fig. 2a). Therefore, HMDB0000159 is the most consistent lung cancerrelated metabolite across studies and the most plausible lung cancer biomarker.

#### 2.2. Graphical summaries extracted from the 65 mass spectrometrybased lung cancer metabolomics studies

To allow users to quickly gain an understanding of the comparative research designs (cancer vs. normal) of the collected studies, we provide a concise graphical summary for each study (Fig. 3). The graphical summary contains the following information: (i) sample information, (ii) sample preparation, (iii) instrumental analysis and data acquisition, (iv) data processing and metabolite identification, (v) statistical analysis, and (vi) additional information.

#### 2.3. Implementation of LCMD website

The web interface of the LCMD was developed in Python using the Django MTV framework. The detailed information of the collected 2013 metabolites and 65 mass spectrometry-based lung cancer metabolomics studies were deposited in MySQL. All tables in the website were produced by the JavaScript and feature-rich JavaScript libraries (jQuery and DataTables). Apart from the main website (http://cosbi7.ee.ncku.edu.tw/LCMD/), one backup site (http://cosbi4.ee.ncku.edu.tw/LCMD/) is also available.



Fig. 1. The categorization of the 65 collected mass spectrometry-based lung cancer metabolomics studies. This figure shows the categorization of the 65 collected studies based on different characteristics: (a) publication year, (b) specimen used, (c) chromatography used, and (d) country.





Fig. 2. The categorization of the 2013 collected lung cancer-related metabolites (a) The top 20 most identified lung cancer-related metabolites are shown. (b) The categorization of these 2013 metabolites based on the chemical taxonomy (super class) retrieved from HMDB database is shown.

#### 3. Results and discussion

#### 3.1. Database interface

The LCMD provides two browse modes ("Browse Metabolites" and "Browse Studies"). Using the "Browse Metabolites" mode, users can browse metabolites in LCMD by applying 11 kinds of fil-

ters (metabolite name, chemical taxonomy, participants, specimen, marker function, chromatography, ion source, p-value, FDR, fold change, and VIP; Fig. 4a). Users then can access to a list of lung cancer-related metabolites that satisfy the filter specifications and receive the summary information of each metabolite (Fig. 4b). By clicking on the "HMDB ID" (e.g. HMDB0003403), users will be directed to the HMDB site (Fig. 4c). By clicking on the "Ref-

Sample Information
Sample source: Shanghai Pulmonary Hospital, Tongji University School of Medicine,
Shanghai, P.R. China     Plasma samples
case: 31 lung adenocarcinoma samples with cancer stage I control: 28 healthy controls
4
Sample preparation
<ul> <li>Plasma samples         <ol> <li>Added Methanol, Internal standard: Fmoc-Gly-OH</li> <li>For GC-MS: derivatized by methoxyamine and followed by N-methyl-N-trimethyl-silyl-trifluoroacetamide (MSTFA)</li> </ol> </li> </ul>
Instrumental analysis and data acquisition
LC-MS analysis UPLC/Q-TOF (Agilent), HT zorbax SB-C18 (2.1 x 50 mm, 1.8 μm) Electrospray ionization, positive and negative mode Scan mode: full scan (m/z range 101-1400) GC-MS analysis
<ul> <li>GC-MS (Agilent), fused-silica capillary column HP-5MSI (30 m x 0.25 mm i.d., 0.25 mm film thickness),</li> <li>Ionization: EI</li> <li>Scan mode: full scan (m/z 50-550)</li> </ul>
Determine and an etche literation
Data processing         • LC-MS: Find Compounds by Molecular Feature algorithms (Agilent)         • GC-MS: MassHunter Find Compounds by Chromatogram Deconvolution (Agilent)         • Mass Profiler Professional software (Agilent)         Metabolite identification         • HMDB         • METLIN         • LIPID MAPS libraries         Identification results         • LC-MS: 28 metabolites
¢ Statistical analysis
Differential analysis (Mann–Whitney–Wilcoxon test) <ul> <li>Software: MultiExperiment View V4.6.1 software</li> </ul> <li>Discrimination analysis (OPLS-DA) <ul> <li>Software: SIMCA-P 11.0</li> </ul> </li> <li>Sensitivity analysis (ROC) <ul> <li>Software: Origin 8.0</li> </ul> </li> <li>Other (AUC) <ul> <li>Software: Origin 8.0</li> </ul> </li>
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Additional information
<ul> <li>Main metabolites cluster</li> <li>amino acids, organic and fatty acids, phospholipids, carbohydrates and metabolism of sex hormones</li> </ul>

# Wen et al. 2013 (23857124) Exploratory investigation of plasma metabolomics in human lung adenocarcinoma

Fig. 3. The graphical summary of a mass spectrometry-based lung cancer metabolomics study. The graphical summary contains the following information: (i) sample information, (ii) sample preparation, (iii) instrumental analysis and data acquisition, (iv) data processing and metabolite identification, (v) statistical analysis, and (vi) additional information.

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fl Chemical	taxonomy:									
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	Case Check all				Con	trol 🗆 check all				
	benign lung disease	□ lung cancer_unspe	cified		0	at-risk controls				
	✓ <u>NSCLC</u> adenocarcinoma	NSCLC_adenosqua	mous carcinoma		0	before vs. after treatment				
	□ <u>NSCLC</u> large cell carcino	ma <u>NSCLC</u> squamous	cell carcinoma			healthy controls				
	□ <u>NSCLC</u> unspecified	□ other types of lung	g cancer		vs	NSCLC_unspecified				
	⊔ <u>scic</u>					J <u>NSCLC_</u> squamous cell carc	inoma			
	Cancer stage					) tumor vs. adiacent normal	tissue			
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pleural effus	ion serum	🗆 sputum	🗆 tissue 🛛 🗆 urin	e	📋 P-valu	e: e.g. 0.01				
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Apply filter  Ap	APPI       AFADESI       EI       ESI         that satisfy the filter so         Show 25 entries       Previous         Ite name       See Figures 88.9          coyle ethanolamide       See Figures 58.6         i       Ite name         oryle ethanolamide       Ite name         is See Figures 58.6       Ite name         i       Ite name	Nano-55!           etting           1         Next           Reference         0           Wen et al. 2013         0	<ul> <li>Chromatography</li> <li>LC</li> <li>LC<td>Lon source () ESI ESI ESI ESI ESI ESI ESI ESI</td><td>VIP ≥              plasma           plasma</td><td>Marker function     diagnosis     diagnosis</td><td>Fold change           709.18           290.02           61.82           19.03           5.54           5.54           4.26           2.84           2.41</td><td>P-value 2.4.09e-11 3.15e-10 4.35e-09 2.43e-10 1.15e-09 1.15e-09 1.15e-09 1.15e-09 1.75e-08 3.80e-03</td><td>FDR </td><td>1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1</td></li></ul>	Lon source () ESI ESI ESI ESI ESI ESI ESI ESI	VIP ≥              plasma	Marker function     diagnosis	Fold change           709.18           290.02           61.82           19.03           5.54           5.54           4.26           2.84           2.41	P-value 2.4.09e-11 3.15e-10 4.35e-09 2.43e-10 1.15e-09 1.15e-09 1.15e-09 1.15e-09 1.75e-08 3.80e-03	FDR 	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1
Apply filter  Apply filter  wing metabolites  ing 1 to 11 of 11 entries H#00 ID  Metabol: ADB00002034  ADB00002034  ADB00002037  ADB0000203  ADB0000203  ADB0000203  ADB00002037  ADB0000203  ADB0000203  ADB0000203  ADB0000203  ADB0000203  ADB0000203  ADB0000203  ADB00000203  ADB00000203  ADB00000203  ADB0000003  ADB0000003  ADB0000000  ADB0000000  ADB0000000  ADB0000000  ADB000000  ADB000000  ADB000000  ADB000000  ADB000000  ADB000000  ADB000000  ADB000000  ADB000000  ADB0000000  ADB000000  ADB000000  ADB000000  ADB000000  ADB000000  ADB000000  ADB000000  ADB000000  ADB000000  ADB00000  ADB00000  ADB00000  ADB000000  ADB00000  ADB0  ADB00000  ADB0  ADB0000  ADB0  ADB0	APP1       AFADESI       EI       ESI         that satisfy the filter so         Show 25 • entries       Previous         ite name         See Figures 8&9          coyle ethanolamide         • See Figures 5&6         i        <	Nano-55!         etting         1       Next         Reference       0         Wen et al. 2013       0         Wen et al. 2014       0         Wen et al. 2014       0	<ul> <li>Chromatography</li> <li>LC</li> <li>LC<td>Lon source () ESI () ES</td><td>v₽≥ Specimen plasma</td><td>Marker function     diagnosis     diagnosis</td><td>Fold change           709.18           290.02           61.82           19.03           5.67           7.46           5.54           4.26           2.84           2.41</td><td><ul> <li>P-value</li> <li>A.09e-11</li> <li>3.15e-10</li> <li>4.35e-09</li> <li>5.14e-09</li> <li>5.14e-09</li> <li>2.43e-10</li> <li>4.41e-10</li> <li>1.15e-09</li> <li>1.15e-09</li> <li>1.15e-09</li> <li>1.58e-09</li> <li>1.79e-08</li> <li>7.00e-04</li> <li>3.80e-03</li> </ul></td><td>FDR </td><td>1</td></li></ul>	Lon source () ESI () ES	v₽≥ Specimen plasma	Marker function     diagnosis	Fold change           709.18           290.02           61.82           19.03           5.67           7.46           5.54           4.26           2.84           2.41	<ul> <li>P-value</li> <li>A.09e-11</li> <li>3.15e-10</li> <li>4.35e-09</li> <li>5.14e-09</li> <li>5.14e-09</li> <li>2.43e-10</li> <li>4.41e-10</li> <li>1.15e-09</li> <li>1.15e-09</li> <li>1.15e-09</li> <li>1.58e-09</li> <li>1.79e-08</li> <li>7.00e-04</li> <li>3.80e-03</li> </ul>	FDR 	1
Apply filter  Apply filter  wing metabolites  ing 1 to 11 of 11 entries Hell08 ID  ADBROX2503 Amylose ADBROX2504 bilirubin ADBROX2503 Entries  ADBROX2507 Celec acid ADBROX2507 Celec acid ADBROX2507 Ubiquinol ADBROX2507 Ubiquinol ADBROX2507 Uric acid ADBROX2507 Uric acid ADBROX2537 3-hydroxyb  Celec acid ADBROX2	APP1       AFADESI       EI       ESI         that satisfy the filter so         Show       Ei       Previous         tte name       See Figures 8&9          soyl ethanolamide       See Figures 5&6         i       I         d       Unyric add	Nano-5SI         etting         1       Next         Reference       0         (Wen et al. 2013)       0         Wen et al. 2013       0         Hori et al. 2011       0         Hori et al. 2011       0	<ul> <li>Chromatography</li> <li>LC</li> <li>LC<td>Lon source ESI</td><td>VIP ≥           Specimen           plasma           plasma</td><td>Narker function     diagnosis     diagnosis</td><td>Fold change           709.18           290.02           61.82           19.03           15.67           7.46           5.54           4.26           2.84           2.41</td><td><ul> <li>P-value</li> <li>4.09e-11</li> <li>3.15e-10</li> <li>4.35e-09</li> <li>5.14e-09</li> <li>2.45e-10</li> <li>4.41e-10</li> <li>1.15e-09</li> <li>1.53e-09</li> <li>1.53e-09</li> <li>1.53e-09</li> <li>3.50e-03</li> </ul></td><td>FDR </td><td></td></li></ul>	Lon source ESI	VIP ≥           Specimen           plasma	Narker function     diagnosis	Fold change           709.18           290.02           61.82           19.03           15.67           7.46           5.54           4.26           2.84           2.41	<ul> <li>P-value</li> <li>4.09e-11</li> <li>3.15e-10</li> <li>4.35e-09</li> <li>5.14e-09</li> <li>2.45e-10</li> <li>4.41e-10</li> <li>1.15e-09</li> <li>1.53e-09</li> <li>1.53e-09</li> <li>1.53e-09</li> <li>3.50e-03</li> </ul>	FDR 	
Apply filter  Apply filter  wing metabolites  ing 1 to 11 of 11 entries  Hello ID  ADBRO003403  attry/ose  ADBR0003403  attry/ose  ADBR0003503  attry/ose  ADBR0003503  attry/ose  ADBR0003503  attry/ose  ADBR0003503  attry/ose  ADBR0003503  attry/ose  at	APP2       AFADESI       EI       ESI         that satisfy the filter so         Show       Simple entries       Previous         tte name       See Figures 38.0        Image: See Figures 58.6         i       See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Image: See Figures 58.6         i       Image: See Figures 58.6       Im	Nano-55           etting           1         Next           Reference         0           (Wen et al. 2013)         0           Wen et al. 2013         0           Hori et al. 2014		Lon source () ESI ESI ESI ESI ESI ESI ESI ESI ESI ESI	vip ≥           specimen           plasma	Parker function     diagnosis	Fold change 700.18 290.02 61.82 19.03 13.67 7.46 5.52 5.54 4.26 2.84 2.41 5.54 5.54 5.54 5.54 5.54 5.54 5.54 5	<ul> <li>P-value</li> <li>A.09e-11</li> <li>3.15e-10</li> <li>4.35e-09</li> <li>5.14e-09</li> <li>2.43e-10</li> <li>4.41e-10</li> <li>1.15e-09</li> <li>1.53e-09</li> <li>1.53e-09</li> <li>3.80e-03</li> <li>metabol</li> </ul>	FDR 	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1
Apply filter Wing metabolites ing 1 to 11 of 11 entries Hello ID Hetabol: Absocozso2 Abs	APP2       AFADESI       Ei       ESI         that satisfy the filter so         Show ES       entries       Previous         the name       See Figures 38.0        Image: Comparison of the source of the sour	Nano-55       etting       1     Next       Reference       (Wen et al. 2013)       Wen et al. 2013       Wen et al. 2014       Wen et al. 2014       Wen et al. 2014		Lon source ESI ESI ESI ESI ESI ESI ESI ESI	viP ≥ Specimen  plasma plas	Marker function     diagnosis     diagnosis	Fold change 709.18 290.02 61.82 19.03 13.67 7.46 5.62 5.54 4.26 5.54 2.84 2.84 2.84 2.84 2.84 2.84	<ul> <li>P-value</li> <li>A-09e-11</li> <li>3.15e-10</li> <li>4.35e-09</li> <li>5.14e-09</li> <li>5.14e-09</li> <li>2.45e-10</li> <li>4.41e-10</li> <li>1.15e-09</li> <li>1.53e-09</li> <li>1.53e-09</li> <li>3.80e-03</li> <li>metabol</li> </ul>	FDR 	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1

Fig. 4. The "Browse Metabolites" mode. (a) Users can browse metabolites in LCMD by applying 11 kinds of filters. (b) Users then can access to a list of lung cancer-related metabolites that satisfy the filter specifications and receive the summary information of each metabolite. (c) By clicking on the "HMDB ID" (e.g. HMDB0003403), users will be directed to the HMDB website.

erence" (e.g. Wen et al. 2013), users will be directed to a page containing the detailed information of the selected mass spectrometry-based lung cancer metabolomics studies. The details of this page will be introduced later.

By clicking on the metabolite name (e.g. oleic acid), users will be directed to a page containing the detailed information of this metabolite. This page can be divided into three parts. The first part is the metabolite's basic information including HMDB ID, synonyms, chemical formula, monoisotopic molecular weight, chemical taxonomy, and pathways (Fig. 5a). The second part refers to the studies that particularly mentioned that this metabolite could serve as a lung cancer biomarker (Fig. 5b). The third part refers to all the mass spectrometry-based lung cancer metabolomics studies that have identified this metabolite. Users can know the detailed (cancer vs. normal) comparative design of each study including (i) sample information (Fig. 6a), (ii) analytical methods (Fig. 6b), (iii) data processing (Fig. 6c), and (iv) statistical analysis (Fig. 6d). It should be noted that the identification of a metabolite does not necessarily mean that this metabolite is a useful biomarker. However, users can still judge whether this metabolite may be a potential biomarker based on the detailed comparative research designs and differential analysis results provided by the LCMD.

The second way for exploring the LCMD is using "Browse Studies" mode. Users can browse studies in the LCMD by applying 5 kinds of filters (participants, specimen, chromatography, ion source, and year of publication; Fig. 7a). Users then can obtain a list of mass spectrometry-based metabolomics studies that satisfy the filter specifications (Fig. 7b). By clicking on the "Reference" (e.g. Wen et al. 2013), users will be directed to a page containing the detailed information of the selected study. This page can be divided into 7 parts. First, "Citation information" provides the authors' names, paper titles, journal names, and links to the PubMed (Fig. 8a). Second, "Analytical methods" provides the details of the mass spectrometry being used (Fig. 8b). Third, "Sample information" provides the details of the specimen and participants (Fig. 8c). Fourth, "Data processing and metabolite identification" provides the details of the software and database search engines being used to identify the metabolites from the mass spectrometry data (Fig. 9a). Fifth, "Statistical analysis" provides the details of the differential analysis, classification, and survival analysis methods being used (Fig. 9b). Sixth, "Lung cancer-related metabolites identified in the paper" provides the details of all the metabolites identified in the paper derived from the differential analysis and classification analysis (Fig. 9c). Seventh, "Paper graphical summary" provides a summary of the study design of the paper (Fig. 9d or Fig. 3).

## 3.2. A case study: using LCMD to find metabolites associated with early diagnosis of lung adenocarcinoma

The feasibility of the LCMD was demonstrated by searching potential biomarkers for a case of early diagnosis of lung adenocarcinoma. By studying this case, we are able to systematically sieve out the metabolites from the comprehensive results of the literature according to the customized needs. Using the "Browse Metabolites" mode, we focused on finding out the differentially expressed (fold change  $\geq 2$ ) metabolites between early-stage (I and II) lung adenocarcinoma patients and healthy controls (Fig. 4a). Based on these criteria, a total of 11 metabolites were found (Fig. 4b). Among them, we are interested in two metabolites, namely amylose and bilirubin, of which plasma abundance expressed 709 and 290 times higher in lung adenocarcinoma patients compared to that of healthy controls (Fig. 4b). Checking

the metabolite detail page of amylose (Fig. 10a), we observed that amylose was identified in only one lung cancer metabolomics study [22]. It is known that the increase of amylose level has been associated with Alzheimer's disease [23] but such phenomenon has not yet been well reported in other diseases or cancers. The possible reason for the elevation of plasma amylose is the activation of glucose metabolism found in lung cancer. One of amylose synthesis pathway occurs in starch and sucrose metabolism as well as glycolysis/gluconeogenesis [24]. The growth of non-small-cell lung carcinoma (NSCLC) cells rely on the energy offered by the active glycolysis [25], which may give rise to the amylose level. Besides, amylase, an enzyme that can catalyze the hydrolysis of amylose, was considered to be a sensitive tumor marker for amylase-producing lung adenocarcinoma [26]. Above information suggests that amylose may function as a small-molecule indicator for lung cancer. Since the role of amylose in other lung cancer types remains unclear, it will be worthy to conduct the experiments to address these issues.

Another metabolite caught our attention is bilirubin. Bilirubin showed 290 times the abundance in plasma from stage I lung adenocarcinoma patients compared to that from healthy controls (Fig. 4b). Checking the metabolite detail page of bilirubin (Fig. 10b), we noticed that, for the squamous cell carcinoma (stage I, II, and III), bilirubin showed higher level (6-fold) in tumor tissues than in adjacent normal tissues [27]. The above two studies [22,27] indicated that a higher level of bilirubin may be related to the pathogenesis of lung cancer especially the early stage (stage I) of lung adenocarcinoma. Although in the previous clinical studies, increased serum bilirubin has been associated with lower incidence of lung cancer, chronic obstructive lung disease, and lung cancer mortality [28,29], their result did not take the cancer stage into consideration. It has been reported that the increase level of bilirubin measured at the early stage in NSCLC may due to its antioxidant and anti-inflammatory properties [30], which suggested that biomarkers are associated with specific cancer stages. Besides, the bilirubin level in lung cancer patients was found to be higher (2.7 fold) than that in the patients after treatment (operation) [2]. Moreover, the bilirubin level does not change between adenocarcinoma/squamous cell carcinoma patients (stage I, II, and III) and at-risk controls [31]. Therefore, for the application of this marker, further targeted analysis should be conducted to verify the association between bilirubin and different stages of different lung cancer types. To sum up, checking all the mass spectrometry-based metabolomics studies of a lung cancerrelated metabolite provided by LCMD can not only help researchers quickly judge whether this metabolite is a potential biomarker but also disclose which knowledge of this metabolite have been known and which still needs further investigation.

#### 3.3. Comparison with existing metabolome databases

Curated databases with reference data and chemical structures are critical for studying biological metabolites. Major resources such as Human Metabolome Database (HMDB) [17], MetaboLights [18], Metabolomics workbench [19], Golm Metabolome Database (GMD@CSB.DB) [20], and PRIMe [21] provide general information about metabolites and metabolomics researches. However, these databases are not useful for lung cancer researchers. The reasons are as follows. First, users have no way to retrieve any lung cancer-related metabolites from Metabolomics workbench, GMD@CSB.DB, and PRIMe. Second, MetaboLights does not clearly annotate any metabolites as lung cancer-related metabolites. Despite using "lung cancer" as a keyword in compound search returns 192 metabolites where descriptions contain "lung cancer",

Showing information for HMDB0000207 ('oleic acid', 'oleate')

Metabolite information	
HMDB ID	H/D8000207
Synonyms	(92)-9-Octadecenoate (92)-9-Octadecenoate (92)-9-Octadecenoate (92)-Octadecenoate (92)-Octadecenoate (92)-Octadecanoate (2)-9-Octadecanoate (2)-9-0ctadecanoate (2)-9-
Chemical formula	C18H3402
IUPAC name	(9Z)-octadec-9-enoic acid
CAS registry number	112-80-1
Monoisotopic molecular weight	282.255888332
Chemical taxonomy	
Super class	Lipids and lipid-like molecules
Class	Fatty Acyls
Sub class	Fatty acids and conjugates
Biological properties	

Pathways

#### (b)

(0)								
The p	The paper(s) that report HMDB0000207 as a lung cancer biomarker							
Chen et a	al. 20156; al. 20156;							

#### Showing paper detailed information

**Citation Information** 

Biomed Res Int. 2015;2015:183624. doi: 10.1155/2015/183624. Epub 2015 Apr 16. Biomarker identification and pathway analysis by serum metabolomics of lung cancer. Chen Y, Ma Z, Min L, Li H, Wang B, Zhong J, Dai L.

Analytical methods					
Comparative study	#1	#2		. #3	#4
Chromatography	ιc	ιc		GC	GC
Ion source	ESI	ESI		-	-
Positive/Negative mode	positive	positive		-	-
Mass analyzer	Q-TOF	Q-TOF		-	-
Identification level	-	-		-	-
Sample information					
Comparative study	#1	#2		#3	#4
Country	China	China		China	China
Spacimon	seriim	seriim		serum	senim

Fig. 5. The metabolite detail page (the first two parts). (a) The first part is the metabolite's basic information including HMDB ID, synonyms, chemical formula, monoisotopic molecular weight, chemical taxonomy, and pathways. (b) The second part refers to the studies that particularly mentioned that this metabolite could serve as a lung cancer biomarker.

The studies that id	dentify H	HMDB0000207 as a l	lung cancer-rel	ated metabolite					
Sample information	Sample Information Analytical methods Data processing Statistical analysis								
Reference	Reference Country Specimen Marker function Participants (Case)								
				Cancer type 🕴	Stage	0 Number 0	Gender (M,F) 🕴	Age mean (range) (M/F)	Smoking
Callejon-Leblic et al. 2016	Spain	bronchoalveolar lavage fluid	diagnosis	lung cancer	-	24	16, 8	66±11	-
Callejon-Leblic et al. 2019	Spain	bronchoalveolar lavage fluid	diagnosis	NSCLC, SCLC	-	24	16, 8	65±12	former,
Callejón-Leblic et al. 2019	Spain	blood	diagnosis	NSCLC, SCLC	11, 111, TV	30	25, 5	67±12	former, current
Chen et al. 2015a	China	serum	diagnosis	adenocarcinoma, squamous cell carcinoma, large cell carcinoma	1, 11, 111	30	9, 21	61.53 ± 10.67	-
Chen et al. 2015a	China	serum	diagnosis	adenocarcinoma, squamous cell carcinoma, large cell carcinoma	1, 11, 111	30	9, 21	61.58 ± 10.67	-

#### (b)

The studies that	identify	HMDB0	000207 as a lu	ng can	cer-related me	etaboli	ite			
Sample information	Analytical	methods	Data processing	Statisti	ical analysis					
Reference		<b>^</b> (	Chromatography		Ion source 0		Positive/Negative mode	Mass analyzer	Identification level	0
Callejon-Leblic et a	1. 2016		GC		EI		-	ion trap	-	
Callejon-Leblic et a	1. 2019		GC		EI		-	ion trap	-	
Callejón-Leblic et a	1. 2019		DI		ESI		negative	Q-TOF	MS/MS	
Chen et al. 201	Sa		GC		-		-	-	÷.	
Chen et al. 201	5a		GC		-		-	-	-	
Chen et al. 201	56		GC		EI		-	quadrupole	-	

#### (C)

The studies that identify HMDB0000207 as a lung cancer-related metabolite

Sample information Analytical methods	Data processing	Statistical analysis	
Reference	*	Data processing software	Database search 0
Callejon-Leblic et al. 2016		XCMS	NIST Mass Spectral Library
Callejon-Leblic et al. 2019		XCMS	NIST Mass Spectral Library
Callejón-Leblic et al. 2019		-	HMDB, Metlin
Chen et al. 2015a		GC/MSD ChemStation software (Agilent Technologies)	NIST
Chen et al. 2015a		GC/MSD ChemStation software (Agilent Technologies)	NIST

(d)

Sample information	Analytical methods	Data processing	Statistical analys	5						
Differential analysis	Classification analysis									
Reference	•	Difference	method		Mean concentration (case)	Mean concentration (control)	Fold change (case/control)	P-value 0	FDR 0	VIR
allejon-Leblic et al. 2016		PLS-LDA, one-	ay ANOVA		-	-	0.78	0.02	-	1.4
illejon-Leblic et al. 2019		PLS-LDA, one-	ay ANOVA		-	-	0.78	0.02	-	1.4
llejón-Leblic et al. 2019		PCA, PLS-DA, one	-way ANOVA		-	-	1.68	0.01	-	1.4
Chen et al. 2015a		independe	nt t-test		605.66 ± 361.44	244.99 ± 131.32	2.47	1.00e-03	-	-
	independent verst									
Chen et al. 2015a e studies that	identify HMDB00	independe 000207 as a lui	nt t-test	ted metabolit	605.66±361.44	346.53 ± 164.66	1.75	1.00e-03	-	
chen et al. 2015a ne studies that ample information	identify HMDB0( Analytical methods	independe 000207 as a lui Data processing	ng cancer-rel Statistical analys	ted metabolit	603.66±361.44 e	34653±164.66	1.75	1.00e-03	-	-
Chen et al. 2015a en studies that iample information Differential analysis Reference	identify HMDB00 Analytical methods Classification analysis	Independe	ng cancer-rel Statistical analys	ted metabolit	605.66 ± 361.44	34653±164.66	1.75 Specificity (%)	1.00e-03	- uracy (%)	-
Chen et al. 2015a e studies that ample information tifferential analysis Reference Catlejon-Lebic et.	identify HMDB00 Analytical methods Classification analysis e 4 al. 2016	Independe	ethod	ted metabolit	605.66 ± 361.44 e auroc 95%c1 0.54	34653±164.66	1.75 Specificity (%)	1.00e-03	- iracy (%;	-
Chen et al. 2015a e studies that ample information ifferential analysis Reference Categon-Lebic et. Categon-Lebic et. Categon-Lebic et.	identify HMDB00 Analytical methods Classification analysis e 4 al. 2016 al. 2019	independe 000207 as a lun Data processing Classification m ROC curve analy ROC curve analy	ethod	ted metabolit s cutoff value	605.66 ± 361.44 e auroc 95%CI 0.54 0.54	34653±164.66	1.75 Specificity (%)	1.00e-03	- inacy (%) -	-
chen et al. 2015a e studies that ample information ifferential analysis Reference Callejon-Leblic et. Callejon-Leblic et. Callejon-Leblic et. Callejon-Leblic et.	identify HMDB00 Analytical methods Classification analysis e 4 al. 2016 al. 2019 al. 2019	Independe D000207 as a lun Data processing Classification m ROC curve analy ROC curve analy ROC curve analy ROC curve	nt t-test ag cancer-rel Statistical analys ethod • is is	ted metabolit s Cutoff value	605.66 ± 361.44 e e AUROC 95%CI 0.54 0.54 0.54	34653±164.66	1.75 Specificity (%)	1.00e-03	- iracy (%) - -	-
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Fig. 6. The metabolite detail page (the third part). The third part refers to all the mass spectrometry-based lung cancer metabolomics studies that have identified this metabolite. Users can know the detailed (cancer vs. normal) comparative research design of each study including (a) sample information, (b) analytical methods, (c) data processing, and (d) statistical analysis (including differential analysis and classification analysis).

Care Car	a di all			Control Catal	
Case 🗆 ch	eck all				
🗆 benign	lung disease 🛛 lung cancer_u	unspecified		at-risk controls	
✓ NSCLC	_adenocarcinoma  _ <u>NSCLC_</u> adeno	osquamous carcinoma		before vs. after treatment	
	_large cell carcinoma _ <u>NSCLC_</u> squan	mous cell carcinoma		healthy controls <u>NSCLC_</u> unspecified <u>NSCLC_</u> squamous cell carcinoma      noncancerous lung diseases      tumor us_adiacent normal tiscue	
	_unspecified □ other types o	of lung cancer	vs		
U <u>sele</u>					
Cancers	stage				
<b>2</b> 1	🖬 I, II	□ 1, 11, 111			
01,11,1	IV 🗆 II, III, IV	🗆 I, II, III, IV			
Specimen: Check all blood bronchoal	veolar lavage fluid 🛛 dried blood spot 🗌 sputum	t Dexhaled breath Dplasma			
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Specimen: Check all blood bronchoal pleural effusion serum Chromatography: Di Flow infusion GC Ion source:	veolar lavage fluid	t exhaled breath plasma			
Specimen: check all blood bronchoal pleural effusion serum Chromatography: DI Flow infusion <u>CC</u> Ion source: <u>APC</u> <u>AFADES</u>	veolar lavage fluid O dried blood spot O sputum	t exhaled breath plasma			
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Specimen: Check all blood bronchoal pleural effusion serum Chromatography: DI Flow infusion GC Ion source: APCI APPI AFADESI Ion source: APCI APPI AFADESI	veolar lavage fluid O dried blood spot Sputum DLC IEI OESI O Nano-ESI	t exhaled breath plasma			
Specimen:       check all         blood       bronchoal         pleural effusion       serum         Chromatography:	veolar lavage fluid O dried blood spot Sputum DLC IEI OESI O Nano-ESI	t exhaled breath plasma ttssue urine			
Specimen: check all blood bronchoal pleural effusion serum Chromatography: DI Flow infusion GC Ion source: APCI APPI AFADESI Vana of authinitia	veolar lavage fluid O dried blood spot O sputum	t exhaled breath plasma			

(b)

ihowing 1 to 4 of 4 entries Show 10 v entries Previous 1 Next											
Year of publication	Reference	Comparative study	Chromatography	Ion source	Specimen	Participants (Case)			Participants (Control)		
	Î					Cancer type	Stage 🕴	Number 🕴	Туре 🕴	Number	
2011	Hori et al. 2011	#2	GC	-	serum	adenocarcinoma, squamous cell carcinoma, SCLC	1, 11	11	healthy	29	
2017	Klupczynska et al. 2017	#1	LC	ESI	serum	adenocarcinoma, squamous cell carcinoma	1, 11	50	healthy	25	
2013	Wen et al. 2013	#1	GC	EI	plasma	adenocarcinoma	T.	31	healthy	28	
2013	Wen et al. 2013	#2	LC	ESI	plasma	adenocarcinoma	1	31	healthy	28	

Fig. 7. The "Browse Studies" mode. (a) Users can browse studies in the LCMD by applying 5 kinds of filters (participants, specimen, chromatography, ion source, and year of publication). (b) Users then can obtain a list of mass spectrometry-based metabolomics studies that satisfy the filter specifications.

MetaboLights does not provide any further information to explain why these metabolites may be related to lung cancer. Third, users can only find 42 metabolites related to lung cancer in HMDB by browsing lung cancer diseases in HMDB. Although HMDB points out the lung cancer studies for these 42 metabolites, HMDB does not outline the detailed comparative research designs of these lung cancer studies.

On the contrary, our LCMD is a very useful resource for lung cancer researchers. The LCMD collected 2013 lung cancer-related metabolites from 65 mass spectrometry-based lung cancer metabolomics studies. Using the "Browse Metabolites" mode, users

can browse the lung cancer-related metabolites of interest by applying 11 kinds of filters (metabolite name, chemical taxonomy, participants, specimen, marker function, chromatography, ion source, p-value, FDR, fold change, and VIP; Fig. 4a). Using the "Browse Studies" mode, users can browse lung cancer metabolomics studies of interest by applying 5 kinds of filters (participants, specimen, chromatography, ion source, and year of publication; Fig. 7a). In summary, the LCMD is the most comprehensive repository for lung cancer-related metabolites and provides various advanced filters for users to retrieve both the metabolites and studies of interest.

#### Showing paper detailed information

#### **Citation Information**

Mol Biosyst. 2013 Sep;9(9):2370-8. doi: 10.1039/c3mb70138g. Exploratory investigation of plasma metabolomics in human lung adenocarcinoma. Wen T, Gao L, Wen Z, Wu C, Tan CS, Toh WZ, Ong CN.

#### (b)

Analytical methods		
Comparative study	#1	#2
Chromatography	GC	ιc
Ion source	EI	ESI
Positive/Negative mode	-	-
Mass analyzer	-	Q-TOF
Identification level	-	MS/MS

#### (C)

Sample information					
Comparative study		#1	#2		
Country		China	China		
Specimen		plasma	plasma		
Marker function		diagnosis	diagnosis		
Participants(Case)	Cancer type	adenocarcinoma	adenocarcinoma		
	Stage	1	1		
	Number	31	31		
	Gender (M,F)	15. 16	15, 16		
	Mean age (range) (M,F)	median: 63 (40-81)	median: 63 (40-81)		
	Smoking status	smoker, non-smoker	smoker, non-smoker		
Participants(Control)	Туре	healthy	healthy		
	Number	28	28		
	Gender (M,F)	20.8	20, 8		
	Mean age (range) (M,F)	median: 37 (29-50)	median: 37 (29-50)		
	Smoking status	smoker, non-smoker	smoker, non-smoker		

**Fig. 8.** The study detail page (the first three parts). (a) The first part "Citation information" provides the authors' names, paper titles, journal names, and links to the PubMed. (b) The second part "Analytical methods" provides the details of the mass spectrometry being used. (c) The third part "Sample information" provides the details of the specimen and participants.

#### 4. Conclusion

In this study, we constructed the first Lung Cancer Metabolome Database (LCMD) which deposits 2013 lung cancer-related metabolites retrieved from 65 mass spectrometry-based lung cancer metabolomics studies in the literature. The LCMD provides various filters for users to efficiently browse both the lung cancerrelated metabolites and metabolomics studies of interest. In the case study, we showed that by using several filters, users can easily find 11 metabolites that are differentially expressed (fold change  $\geq$  2) between early-stage (I and II) lung adenocarcinoma patients and healthy controls. Among these 11 metabolites, two metabolites (amylose and bilirubin) were further discussed and suggested to be potential biomarkers for early diagnosis of lung adenocarcinoma. We believe that the LCMD is a useful resource for lung cancer research. Our research group will keep updating the LCMD to include any newly published mass spectrometry-based lung cancer metabolomics studies in the future.

(a)						
Data processing and metabolite identification						
Data processing software	MassHunter, Mass Profiler Professional software (Agilent)					
Database search	NIST 08, HMDB, METLIN, LIPID MAPS					
(b)						
Statistical analysis						
Differential analysis method	Mann-Whitney-Wilcoxon test, OPLS-DA					
Classification method	ROC curve analysis					
Survival analysis method						

#### (c)

Lung cancer-related metabolites identified in the paper									
Differential analysis method Classification method Show 10 $\stackrel{\circ}{=}$ entries									
Metabolite 0	Author-emphasized biomarkers	Mean concentration (case)	Mean concentration (control)	Fold change (case/control)	P-value	O FOR O	VIP 0		
3.4.5-trimethoxycinnamic acid	-	-	-	-	0.0000000000316	-	1.62		
5-methoxytryptophan	-	-	-	-	0.000000000316	-	1.61		
amylose	-	-	-	709.176047672794	0.000000000409	-	1.34		
linoleic acid	-	-	-	7.46426393229446	0.00000000441	-	1.25		
maltitol	-	-	-	61.8199250511901	0.0000000435	-	1.25		
ubiquinone	-	-	-	5.61777950295199	0.0000000115	-	1.29		
ubiquinol	-	-	-	5.5404378724437	0.0000000153	-	1.23		
palmitic acid	-	-	-	4.25748072981344	0.000000179	-	1.16		
bilirubin	-	-	-	290.018274635724	0.00000000315	-	1.23		
N-Palmitoleoyl ethanolamide	-	-	-	19.0273138400435	0.0000000514	-	1.03		
					Previous 1 2	3 4	Next		

Lung cancer-related metabolites identified in the paper								
Differential analysis method Classification method Show 10 v entries								
Metabolite	Author-emphasized biomarkers	Cutoff value	AUROC (95%CI)	Sensitivity (%)	<pre>\$ Specificity (%)</pre>	Accuracy (%)		
5-hydroxytryptophan	-	-	0.7	-	-	-		
amylose	-	-	0.98	-	-	-		
bilirubin	-	-	0.96	-	-	-		
maltitol	-	-	0.93	-	-	-		
N-Palmitoleoyl ethanolamide	-	-	0.93	-	-	-		
oleic acid	-	-	0.98	-	-	-		
linoleic acid	-	-	0.97	-	-	-		
ubiquinone	-	-	0.96	-	-	-		
ubiquinol	-	-	0.96	-	-	-		
palmitic acid	-	-	0.93	-	-	-		
					Previous 1	2 3 4 Next		



**Fig. 9.** The study detail page (the last four parts). The last four parts of the study detail page are as follows. (a) "Data processing and metabolite identification" provides the details of the software and database search engines being used to identify the metabolites from the mass spectrometry data. (b) "Statistical analysis" provides the details of the differential analysis, classification, and survival analysis methods being used. (c) "Lung cancer-related metabolites identified in the paper" provides the details of all the metabolites identified in the paper derived from the differential analysis. (d) "Paper graphical summary" provides a summary of the comparative research design of the paper.

(a)		
The studies that identify HMDB0003403 as a lu	g cancer-related metabolite	
Sample information Analytical methods Data processing	Statistical analysis	
Differential analysis Classification analysis		
Reference * Difference method	Mean concentration (case) # Mean concentration (control) # Fold change (case/control) # P-value # FDR # VIP	0
Wen et al. 2013 Mann–Whitney–Wilcoxon test, OPLS-DA	709.18 4.09e-11 - 1.34	_

#### (b)

The studies that identify HMDB0000054 as a lung cancer-related metabolite									
Sample information	Analytical methods Data processing	Statistical analysis							
Differential analysis	Classification analysis								
Reference	Difference method	Mean concentration (case)	Mean concentration (control)	Fold change (case/control)	P-value 0	FDR 0	VIP 0		
Wen et al. 2013	Mann-Whitney-Wilcoxon test, OPLS-DA	-	-	290.02	3.15e-10	-	1.23		
Moreno et al. 2018	paired two-sample t-test, PLS-DA	-	-	6.59	1.35e-17	2.16e-15	-		
Chen et al. 2015b	PCA, PLS-DA, independent t test	-	-	2.70	1.00e-03	-	1.42		
Moreno et al. 2018	paired two-sample t-test, PLS-DA	-	-	1.43	0.05	0.07	-		
Mazzone et al. 2016	two- sample independent t test	1.278786± 1.0961254	1.218406±0.9363659	1.05	0.63	0.66	-		
Mazzone et al. 2016	two-sample independent t test	1.147686±1.116875	1.150153±0.5770102	1.00	0.98	0.80	-		
Chen et al. 2015b	PCA, PLS-DA, independent t test	-	-	0.57	1.00e-03	-	1.30		

Fig. 10. The metabolite detail page of amylose and bilirubin. (a) The metabolomics study that identify amylose as a lung cancer-related metabolite is shown. (b) The metabolomics studies that identify bilirubin as a lung cancer-related metabolite are shown.

#### **CRediT** authorship contribution statement

Wei-Sheng Wu: Conceptualization, Investigation, Supervision, Project administration, Visualization, Writing – original draft, Writing – review & editing. Hsin-Yi Wu: Investigation, Writing – original draft. Pin-Hsuan Wang: Investigation. Ting-Yu Chen: Investigation, Software, Visualization. Kuan-Ru Chen: Software, Visualization. Chih-Wei Chang: Investigation. Dong-En Lee: Visualization. Bo-Heng Lin: Software, Visualization. William Chih-Wei Chang: Investigation, Writing – review & editing. Pao-Chi Liao: Conceptualization, Investigation, Supervision, Project administration.

#### **Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Authors' contributions

WSW and PCL conceived the research topic and provided essential guidance. PHW and CWC collected the 2013 metabolite information from the 65 mass spectrometry-based lung cancer metabolomics studies and prepared the graphical summaries. TYC, KRC, BHL, and DEL constructed the website. KRC and DEL prepared all the figures in the manuscript. WSW, CWC and HYW wrote the manuscript. WSW, HYW, PHW, and CWC tested the website. CWC prepared the demo video. All authors read, edited and approved the final manuscript.

#### Data availability

LCMD is freely available at http://cosbi7.ee.ncku.edu.tw/LCMD/ or http://cosbi4.ee.ncku.edu.tw/LCMD/. The complete metabolite tables and study tables can be downloaded from the Download page of LCMD website. We also deposit all the downloadable files in a public repository at Github (https://github.com/cosbi-nckuee/ LCMD). Demo video can be accessed at https://youtu.be/ xUb1nHDMxyY.

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