Metabolomics Research Conducted by Nurse Scientists: A Systematic Scoping Review

Laura P. Kimble, PhD, RN, FNP-C, FAHA, FAAN¹ ,
Sharon Leslie, MSLS, AHIP² , and
Nicole Carlson, CNM, PhD, RN, FACNM¹

Abstract

Metabolomics, one of the newest omics, allows for investigation of holistic responses of living systems to myriad biological, behavioral, and environmental factors. Researchers use metabolomics to examine the underlying mechanisms of clinically observed phenotypes. However, these methods are complex, potentially impeding their uptake by scientists. In this scoping review, we summarize literature illustrating nurse scientists' use of metabolomics. Using electronic search methods, we identified metabolomics investigations conducted by nurse scientists and published in English-language journals between 1990 and November 2019. Of the studies included in the review ($N = 30$), 9 (30%) listed first and/or senior authors that were nurses. Studies were conducted predominantly in the United States and focused on a wide array of clinical conditions across the life span. The upward trend we note in the use of these methods by nurse scientists over the past 2 decades mirrors a similar trend across scientists of all backgrounds. A broad range of study designs were represented in the literature we reviewed, with the majority involving untargeted metabolomics ($n = 16$, 53.3%) used to generate hypotheses ($n = 13$, 76.7%) of potential metabolites and/or metabolic pathways as mechanisms of clinical conditions. Metabolomics methods match well with the unique perspective of nurse researchers, who seek to integrate the experiences of individuals to develop a scientific basis for clinical practice that emphasizes personalized approaches. Although small in number, metabolomics investigations by nurse scientists can serve as the foundation for robust programs of research to answer essential questions for nursing.

Keywords

metabolomics, omics research, nursing, scoping review, lipidomics

Systems biology and omics approaches have emerged as key methods for elucidating biological mechanisms across multiple health conditions. In addition, these methods support advancement of precision health, which involves use of multiple types of biomedical data to tailor care to the individual patient (Collins & Varmus, 2015). Systems biology is a scientific discipline that uses advanced computational methods and high-throughput technology to explore complex biological systems at multiple levels including cellular, tissue, organ, and complete organism (Tavassoly et al., 2018). Research methods used in systems biology include omics approaches. These approaches involve using cellular molecules such as genes, epigenetic markers, transcripts, proteins, and/or metabolites within biological systems, collectively called the omics cascade, to understand the complex interactions of biological systems (Aizat et al., 2018). Over the last decade, development of instruments with the sensitivity and range to measure multiple substances within biologic samples (Newgard, 2017), as well as advancements in computational biology and high-throughput

analytics, have made analysis of complex biologic systems feasible (Aizat et al., 2018).

Methodologically, omics approaches offer researchers flexibility in terms of both the biologic systems and types of specimens suitable for analysis. Omics approaches can be used to study molecular mechanisms within a single cell (Jones et al., 2012; Liu & Locasale, 2017), tissue (Bafor et al., 2017), or organ (Jones et al., 2012; Liu & Locasale, 2017). In addition, the types of biologic specimens used in omics investigations are widely variable and can include blood components, such as

¹ School of Nursing, Emory University, Atlanta, GA, USA

² Woodruff Health Sciences Center Library, Emory University, Atlanta, GA, USA

Corresponding Author:

Laura P. Kimble, PhD, RN, FNP-C, FAHA, FAAN, School of Nursing, Emory University, 1520 Clifton Rd., NE, Atlanta, GA 30322, USA.

Email: lkimble@emory.edu

serum or plasma, as well as skin, hair, urine, saliva, and other specimens. Nurse scientists engage in investigations across the omics cascade and are thus increasingly making important contributions in the field of systems biology.

Among omics methods, metabolomics is one of the newest and offers nurse scientists the capacity to comprehensively investigate the holistic response of living systems to myriad biological, behavioral, and environmental factors by revealing the interactions of metabolites and metabolic pathways. Thus, metabolomics matches well with the unique perspective of nursing researchers, who seek to integrate the experiences of individuals to develop a scientific basis for clinical practice that emphasizes personalized approaches (National Institute of Nursing Research, 2016). The purpose of the present scoping review is to examine and summarize metabolomics investigations conducted by nurse scientists to gain insight into how nursing science is progressing in the field of metabolomics and to provide guidance for future nursing research.

Introduction to Metabolomics

Metabolomics involves the measurement of low-molecular-weight molecules within a particular tissue or cell (Liu & Locasale, 2017) to help identify the specific molecule and its role in cellular metabolism. Cellular metabolism is the totality of biochemical processes within a living system involving major molecules such as carbohydrates, fatty acids, and amino acids. Biochemical processes to create and break down molecules and eliminate cellular waste can be mapped into interrelated pathways and their associated metabolites (DeBerardinis & Thompson, 2012). Disruptions in metabolic pathways occur when certain metabolites are more or less biochemically active than normal. These disruptions, called perturbations, reflect the multifaceted response of an organism to disease states (DeBerardinis & Thompson, 2012). Thus, metabolomics offers researchers the capacity to examine the response of the biochemical system to disease or environmental exposures, revealing mechanisms of physiologic adaptation at a single point in time or longitudinally, depending on the study design. The exposome, a more recent concept within metabolomics, is focused on measuring metabolites associated with environmental factors, such as dietary intake or exposure to toxic chemicals (Jones, 2016).

There is growing interest in the field of metabolomics because it represents the multifaceted responses of biologic systems to internal or external stimuli and is thus closest to the clinical phenotype in human and animal models (Loscalzo et al., 2007). Unlike clinical laboratory tests and other biomarker assays, metabolomics can be used to measure thousands of different metabolites within a single sample (Johnson et al., 2016). In addition, metabolomic measures can be run using biofluids that are easier to collect from participants than blood such as expelled breath (Maniscalco et al., 2019) or saliva (Huan et al., 2018). Measured metabolites can be endogenous or exogenous to an organism, thus making metabolomics a useful methodology for understanding everything from environmental exposures (Shih et al., 2019) to cellular physiology (Bafar et al., 2017).

Lipidomics, a subset of metabolomics, involves the quantification of individual lipid molecular species through the use of advanced mass spectrometry (Zhao et al., 2014). Alterations in lipid metabolism are associated with multiple disease states (Wenk, 2005) including atherosclerosis, obesity, and diabetes. Lipid profiling, a type of focused lipidomics (Zhao et al., 2014), is a key component of cardiovascular care familiar to many clinicians and involves the measurement of low-density lipoproteins (LDL) and apolipoprotein-B (ApoB)-containing lipoproteins. Clinicians and researchers currently use targeted lipid profiling to evaluate cardiovascular risk and help guide interventions (FERENCE et al., 2018).

There are two principal metabolomic approaches: untargeted and targeted analyses (Liu & Locasale, 2017). Untargeted metabolomics is a more global approach; investigators often use this approach to generate hypotheses after examining associations between metabolites and/or metabolic pathways and a particular disease state (Jones et al., 2012; Liu & Locasale, 2017). A key aspect of untargeted metabolomics is that there is no *a priori* “target,” meaning the researcher is not focused on understanding how a specific list or class of metabolites associates with the disease state of interest. Instead, untargeted metabolomics measures all known and unknown metabolites within a sample, allowing investigators to identify previously unknown mechanisms of disease or environmental exposure (Gertsman & Barshop, 2018). Thousands of individual metabolites (Liu & Locasale, 2017) can be detected in a single untargeted metabolomics analyses, thus providing researchers with a wide view of the metabolic response to any particular clinical condition or intervention. However, this technique provides little information on the precise structural identity of differentiating metabolites, thus requiring follow-up experiments to confirm the identity of metabolites that are important to the outcome of interest.

Targeted metabolomics analyses are narrower in scope and involve measurement of a pre-identified set of metabolites relative to a disease or condition (Jones et al., 2012; Liu & Locasale, 2017). This approach reduces the number of separate assays researchers have to perform and allows several metabolites to be precisely quantified at once to better understand a specific metabolic pathway or process. Unlike untargeted metabolomics analyses, which can only be used to describe the relative abundance of metabolites across samples, targeted metabolomics analysis can be used to quantify the exact amount of a particular metabolite in each sample across multiple experiments. Targeted analysis can be hypothesis driven (true targeted approach) or hypothesis generating (semi-targeted approach; Jones et al., 2012; Klepacki et al., 2016; Liu & Locasale, 2017).

Whether a researcher is considering an untargeted or targeted approach, metabolomics methods also vary by type of method and sample. The typical metabolomics workflow involves sample preparation, sample analysis, data extraction, bioinformatics and statistics, and interpretation (Jones et al., 2012). Figure 1 depicts this workflow. Depending on the type of metabolomics analysis, either mass spectrometry (MS) or nuclear magnetic resonance (NMR) is used to analyze samples. Prior to analysis of metabolites, researchers often use liquid (LC) or gas

Figure 1. Metabolomics workflow. Stages of the metabolomics workflow, from sample preparation to interpretation. apLCMS = adaptive processing of LC/MS metabolomics data (R package); GC-MS = gas chromatography-mass spectrometry; LC-MS = liquid chromatography-mass spectrometry; NMR = nuclear magnetic resonance; OPLS-DA = orthogonal partial least squares-discriminant analysis; PCA = principal component analysis.

chromatography (GC) to help separate densely packed metabolites for better resolution (Soltow et al., 2013). LC and GC approaches can also preferentially reveal different classes of metabolites, depending on the researcher's needs.

Data Sources and Search Strategy

We used a scoping review design (Peters et al., 2015) to characterize the published metabolomics research conducted by nurse scientists. We started by undertaking a comprehensive literature search to identify relevant articles that met the following inclusion criteria: 1) investigators report original preclinical and/or clinical research involving metabolomics analysis and 2) at least one of the authors was a nurse. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Selcuk, 2019) to guide our review process. An experienced medical librarian (SL) developed and conducted the search strategies with input from team members (LK, NC). We searched six bibliographic databases: CINAHL, EBSCO Health Source: Nursing/Academic Edition, Embase.com, PubMed, Web of Science Core Collection, and Scopus.

Our search strategy involved searching controlled vocabulary supplemented with keywords related to the concept of metabolomics (e.g., metabolom* OR lipidomic* OR exposome*). To help identify nurse authors, we developed searches to identify articles with the additional concepts of 1) written by an author with a

professional nursing degree or certification (RN, CNE, CNM, CM, CRNA, CNS, or NP), 2) written by an author with affiliation at an academic nursing school, or 3) published in a nursing journal. Two databases, PubMed and CINAHL, had the option to search a nursing journal subset, which we searched using the same criteria. CINAHL also has an "Any Author Is a Nurse" filter, which we used. The databases Embase and Web of Science had field codes for organizational affiliation, which we used for variations on the term *nurse*. Search dates ranged between January 1, 1990, and November 18, 2019. We chose to start the search period in 1990 to help assure that all relevant studies would be included, as this date precedes the earliest mention of metabolomics as a scientific field in 1998 (Oliver et al., 1998).

We uploaded all articles identified through the searches into EndNote and excluded duplicates. Using EndNote, the medical librarian searched these citations for evidence of "nurs*" in the abstract, article title, author address or journal title fields. These articles were marked for title and abstract review and uploaded to Covidence (www.covidence.org), a web-based program to facilitate systematic review. Two reviewers (NC, LK) independently assessed the titles/abstracts for inclusion (NC, LK). We resolved disagreements by consensus.

We reviewed the remaining studies, including published abstracts and full-text reports, to confirm nurse authorship and metabolomics analysis. To confirm nurse authorship, we conducted an internet search to identify the professional affiliation

Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow diagram for article inclusion in scoping review of literature on metabolomics research conducted by nurse scientists.

of the authors of the papers. A student research assistant completed the initial nurse-author review. Two of the authors (NC, LK) confirmed nurse authorship by locating documentation of the author being a nurse via organizational profiles, curriculum vitae, or other documents available online. We included only articles for which we could verify nurse authorship in the review. During the full-text review, we examined articles and abstracts a final time to ensure that the researchers had performed metabolomics analyses. This step resulted in the final group of published papers that served as the focus of the review.

Results

Search Results

We identified 712 papers in our initial search. After excluding duplicates across databases ($n = 437$), we entered the remaining 275 papers into Endnote, identifying one additional duplicate,

leaving 274 papers. The nurse librarian identified 173 of these papers as having “nurs*” in the abstract, article title, author address or journal title fields, and we included those in our full-text review. We then searched the 101 papers without “nurs*” in the abstract, article title, author address or journal title field to see if “nurs*” was included in keywords. This step yielded an additional 71 papers, resulting in a total of 244 papers for review. Two reviewers (NC, LK) independently assessed these 244 titles/abstracts for inclusion criteria and resolved disagreements by consensus. We excluded a total of 109 papers because they did not report original research with metabolomics analyses and an additional 105 because they did not include nurse authors. The final sample included 30 studies. Although an article by Menzies and colleagues (2020) was published in 2020 and is thus outside the time period of this review, this work was initially published online in 2019 and was therefore included. Figure 2 shows the PRISMA flow diagram illustrating the search process.

Study Characteristics

The 30 reviewed papers included six research abstracts and 24 full-text articles. We have summarized the key characteristics of the studies in Table 1. Of these studies, nine (30%) listed nurses as first authors (Cybulska et al., 2019; Downs et al., 2018; Ferranti et al., 2017; Gregory et al., 2013; Heitkemper et al., 2016; Lyon et al., 2018; Menzies et al., 2020; Starkweather et al., 2017; Thompson et al., 2019). Additionally, one research abstract (3.3%) listed nurse authors as both first and senior author (Faucher et al., 2019), and one study (3.3%) included a nurse as senior, but not first, author (Chen et al., 2019). Thus, in 36.6% ($n = 11$) of the reviewed papers, nurses led authorship and/or research teams reporting metabolomics investigations. The remaining 19 papers (63.4%) listed nurses as coauthors; these individuals appeared to provide supporting roles within their research teams.

Publication dates of the reviewed papers spanned the years 2010–2019. Following an initial metabolomics study by Shah et al. (2010) with a nurse scientist collaborator, there was a 2-year gap during which nurse authors did not publish metabolomics studies. Gregory and colleagues (2013) published the first metabolomics research paper with a nurse scientist as the primary author. From 2013 to the present, there was a gradual increase in nurse scientists' involvement in authoring metabolomics research papers, mirroring the overall increase in published metabolomics investigations during the same period (Figure 3).

The reviewed studies used metabolomic methods to investigate a wide array of clinical conditions, including cystic fibrosis (Alvarez et al., 2017; Alvarez, Frediani, et al., 2014; Alvarez, Smith, et al., 2014), heart failure (Cheng et al., 2015; Wang et al., 2016, 2017, 2018a, 2018b, 2019), coronary artery disease (Shah et al., 2010), postmenopause with hormone replacement therapy (Cybulska et al., 2019; Oh et al., 2017), obese pregnant women (Faucher et al., 2019), hypertension in pregnancy (Ferranti et al., 2017), premature neonates (Gregory et al., 2013), irritable bowel syndrome (Heitkemper et al., 2016; Hollister et al., 2019), Type II diabetes mellitus (Irving et al., 2015), breast cancer (Lyon et al., 2018; Sun et al., 2018), pancreatic ductal adenocarcinoma (Mayers et al., 2014), fibromyalgia (Menzies et al., 2020), acute low-back pain (Starkweather et al., 2017), cognitive impairment (Mapstone et al., 2017), and mild traumatic brain injury (Thompson et al., 2019). Among the 11 studies (36.6%) with nurse scientists as first and/or senior authors, four focused on women's health including pregnancy and pregnancy outcomes (Faucher et al., 2019; Ferranti et al., 2017), hormone replacement therapy in menopause (Cybulska et al., 2019), and breast cancer (Lyon et al., 2018). None of the reviewed studies focused solely on the exposome; for example, none used metabolomics to identify chemical toxins in specimens.

Authors of the reviewed articles were primarily based in the United States ($n = 20$, 66.6%), with the remaining studies conducted in Taiwan ($n = 5$, 16.7%) and China ($n = 4$, 13.3%) and one European team from Poland that included

investigators from Switzerland ($n = 1$, 3.3%). Among the 20 published studies conducted in the United States, 18 were completed within R1 academic institutions according to the Carnegie Classifications of Higher Education Institutions (Indiana University Center for Postsecondary Research, n.d.), one was completed at the National Institutes of Health (Oh et al., 2017) and the remaining study at the Mayo Clinic (Irving et al., 2015).

We examined funding sources for the metabolomics investigators for the 24 full-text articles (these data were not available for the six abstracts). Among the 17 U.S.-based full-text studies, 16 were supported completely or in part by the National Institutes of Health (NIH). The study by Shah (Shah et al., 2010) was funded by the American Heart Association and Medtronic. Funding sources for studies outside of the U.S. showed similar patterns of governmental support, with Chinese investigators primarily supported through the National Natural Science Foundation, and Taiwanese investigators supported by the National Science Council of Taiwan and the Ministry of Education. The European investigator, Cybulska (Cybulska et al., 2019), received support from the Pomeranian Medical University in Szczecin, Poland.

Metabolomics studies identified for this review were published in a wide array of biology/biochemistry, clinical, specialty, and nursing journals. Seven papers (23.3%) were published in biology/biochemistry journals (Alvarez et al., 2017; Chen et al., 2018, 2019; Downs et al., 2018; Gregory et al., 2013; Irving et al., 2015; Wang et al., 2018b). Eight papers (26.7%) were published in clinical journals (Cybulska et al., 2019; Hollister et al., 2019; Lu et al., 2016; Mapstone et al., 2017; Mayers et al., 2014; Menzies et al., 2020; Wang et al., 2018a, 2019). With respect to clinical specialties, four (13.3%) papers were published in cardiology journals (Cheng et al., 2015; Shah et al., 2010; Wang et al., 2016, 2017). Two papers (6.7%) were published in oncology journals (Oh et al., 2017; Sun et al., 2018). Only three papers (10%) were published in nursing journals, two in *Biological Research for Nursing* (Heitkemper et al., 2016; Lyon et al., 2018) and one in *Nursing Research* (Starkweather et al., 2017). Of note, all of the publications in nursing journals included first authored nurse scientist publications.

Sample sizes in the reviewed studies ranged from $n = 1$ (Bird et al., 2013) to $n = 1835$ (Oh et al., 2017). The mean sample size for the human subjects studies was 344.7 (SD 514.1, interquartile range 522), with a median of 59.5 individuals. The largest sample size for a study with a nurse as first or senior author was 156 (Cybulska et al., 2019).

The majority of the studies ($n = 25$, 83.3%) involved only human subjects, with the remainder involving mouse (Chen et al., 2018, 2019) and rat models (Downs et al., 2018; Lu et al., 2016) or both human and mouse data (Mayers et al., 2014). In studies involving human subjects ($n = 26$, including Mayers et al.), metabolomics analyses were predominantly performed on whole blood or blood components. Among these, over half ($n = 16$, 53%) used human plasma (Alvarez et al., 2017; Alvarez, Frediani, et al., 2014; Alvarez, Smith, et al., 2014; Cheng et al., 2015; Irving et al., 2015; Mapstone et al.,

Table 1. Summary of Key Features of Reviewed Studies (N = 30).

Authors (Year), Country	Nurse Author (First, Senior, Other)	Model & Design	Clinical Condition	Sample	Type of Specimen	Type of Analysis	Targeted/Untargeted Metabolomics	Single/Multi Omics	Pathway Analysis
Alvarez, Frediani, et al. (2014), U.S.	Other	Human; case-comparison	CFRD	N = 47. n = 30 adult CF patients (15 with CFRD), n = 17 healthy controls.	Plasma	Metabolomics	Untargeted	Single	No
Alvarez, Smith et al. (2014), U.S.	Other	Human; experimental	CF	N = 25 adult CF patients randomized to high-dose vitamin D	Plasma	Metabolomics	Untargeted	Single	No
Alvarez, Chong et al. (2017), U.S.	Other	Human; experimental	CF	N = 52. n = 24 adult CF patients, n = 28 age-matched controls	Plasma	Metabolomics	Untargeted	Single	Yes
Bird et al. (2013), U.S.	Other	Human; single sample	None	N = 1	Fecal	Lipidomics	Untargeted	Single	No
Chen et al. (2018), China	Other	Mouse; experimental	Metabolic syndrome	N not specified. three groups: normal, high-fat diet, and high-fat diet + resveratrol 10mg/kg/day.	Abdominal muscle tissue	Metabolomics	Untargeted	Single	Yes
Chen et al. (2019), China	Senior	Mouse; experimental	Ischemic stroke	N = 42. Three groups: control (n = 14), focal cerebral ischemia (n = 14), and hydrogen intervention (n = 14).	Right cerebral cortex tissue	Metabolomics	Untargeted	Single	Yes
Cheng et al. (2015), China	Other	Human; case-comparison, prospective	HF	N = 547. Discovery phase: n = 183 HF patients, n = 51 normal controls. Validation study: n = 218 HF patients, n = 63 healthy controls. Independent validation: n = 32 HF patients.	Plasma	Metabolomics	Untargeted & targeted	Single	No
Cybulska et al. (2019), Poland	First	Human; case-comparison	Postmenopausal metabolic diseases	N = 156. n = 107 women not using HRT, n = 49 women taking oral estrogen-progestrone HRT	Whole blood	Metabolomics	Targeted	Single	No
Downs et al. (2018), U.S.	First	Rat; in vitro	Exosome modulation of rat alveolar lung cells in response to oxidative stress	N = n/a. Rat alveolar epithelial cells exposed to exosomes then treated with either hydrogen peroxide or control solution.	Alveolar cell	Lipidomics	Targeted	Lipidomics & proteomics	No
Faucher et al. (2019), U.S.	First, senior	Human; case-comparison	Obesity in pregnancy	N = 25 healthy pregnant women with different levels of obesity	Urine	Metabolomics	Targeted	Metabolomics & microbiomics	No
Ferranti et al. (2017), U.S.	First	Human; case-comparison	Hypertensive complications in pregnancy	N = 104 pregnant women. n = 9 with preeclampsia, n = 9 with gestational HTN, n = 86 healthy controls.	Serum	Metabolomics	Untargeted	Single	Yes
Gregory et al. (2013), U.S.	First	Human; single pooled sample	Prematurity	N = 5 premature neonates, 1 pooled fecal sample	Fecal	Lipidomics	Untargeted	Single	Yes
Heitkemper et al. (2016), U.S.	First	Human; case-comparison	IBS	N = 59. n = 38 women with IBS, n = 21 healthy controls.	Serum	Metabolomics	Targeted	Single	No
Hollister et al. (2019), U.S.	Other	Human; case-comparison	IBS	N = 45. n = 23 children with IBS, n = 22 healthy controls.	Fecal	Metabolomics	Untargeted	Metabolomics & microbiomics	Yes
Irving et al. (2015), U.S.	Other	Human; experimental	Type 2 DM	N = 25 overweight/obese adults with impaired fasting glucose or untreated DM, n = 12 randomized to 3 months pioglitazone + metformin, n = 13 randomized to placebo.	Plasma	Metabolomics	Targeted	Single	No
Lu et al. (2016), China	Other	Rat; experimental	Postoperative fatigue syndrome	N = 24. 3 groups: n = 8 with 30% partial hepatectomy, n = 8 with 70% partial hepatectomy, n = 8 controls.	Serum	Metabolomics	Untargeted	Single	Yes
Lyon et al. (2018), U.S.	First	Human; pre-post	Breast cancer	N = 19 women with early-stage breast cancer	Serum	Metabolomics	Untargeted & targeted	Single	Yes

(continued)

Table 1. (continued)

Authors (Year), Country	Nurse Author (First, Senior, Other)	Model & Design	Clinical Condition	Sample	Type of Specimen	Type of Analysis	Targeted/Untargeted Metabolomics	Single/Multi Omics	Pathway Analysis
Mapstone et al. (2017), U.S.	Other	Human; case-comparison	Cognitive impairment	N = 224 older adults. n = 41 w/superior memory, n = 109 w/normal memory, n = 74 w/mild cognitive impairment or Alzheimer's.	Plasma	Metabolomics & lipidomics	Targeted	Single	No
Mayers et al. (2014), U.S.	Other	Human; case-comparison. Mouse; experimental	PDAC	N = 1351 adults. n = 453 w/PDAC, n = 898 matched controls. N = 20 mice. n = 14 male mice w/ specific genetic modification to show oncogenic expression, n = 16 matched controls.	Plasma	Metabolomics	Targeted	Single	No
Menzies et al. (2020), U.S.	First	Human; case-comparison	FM	N = 40 women. n = 20 w/FM, n = 20 age-matched controls.	Plasma	Metabolomics & lipidomics	Untargeted	Single	No
Oh et al. (2017), U.S.	Other	Human; cohort	Postmenopausal hormone-therapy use	N = 1835 postmenopausal women. n = 957 never/former MHT users; n = 878 MHT users.	Serum	Metabolomics	Targeted	Single	No
Shah et al. (2010), U.S.	Other	Human; case-comparison	CAD	N = 628 adults. Initial sample: n = 174 CAD cases, n = 174 age/gender-matched controls. Validation sample: n = 140 CAD cases, n = 140 controls.	Plasma	Metabolomics	Targeted	Single	No
Starkweather et al. (2017), U.S.	First	Human; case-comparison	Low-back pain	N = 30 adults with acute low-back pain; n = 22 with central/thermal pain sensitization, n = 8 without sensitization.	Plasma	Lipidomics	Untargeted	Single	No
Sun et al. (2018), U.S.	Other	Human; experimental	Breast cancer	N = 60 women w/breast cancer receiving Paclitaxel	Whole blood	Metabolomics	Untargeted	Single	No
Thompson et al. (2019), U.S.	First	Human; case-comparison	Mild TBI	N = 24 adults. n = 14 w/mild TBI, n = 10 controls.	Plasma	Metabolomics	Untargeted	Single	No
Wang et al. (2016), Taiwan	Other	Human; case-comparison	HF	N = 187. n = 136 HF patients, n = 31 controls.	Plasma	Metabolomics	Targeted	Single	No
Wang et al. (2017), Taiwan	Other	Human; cross-sectional	HF	N = 212 HF patients with range of cardiac fibrosis scores	Plasma	Metabolomics	Targeted	Single	No
Wang et al. (2018b), Taiwan	Other	Human; case-comparison	HF	N = 1,084. Initial cohort: n = 599 HF patients, n = 94 normal controls. Validation cohort: n = 391 HF patients.	Plasma	Lipidomics	Targeted	Single	No
Wang et al. (2018a), Taiwan	Other	Human; case-comparison	HF	N = 1,288. Initial cohort: n = 712 HF patients, n = 129 controls. Validation cohort: n = 447 HF patients.	Plasma	Metabolomics	Targeted	Single	No
Wang et al. (2019), Taiwan	Other	Human; cohort	HF	N = 890 HF patients with different ranges of functional heart ability	Plasma	Metabolomics	Targeted	Single	No

Note. Study types were categorized according to the Metabolomics Standards Institute categories. CAD = coronary artery disease; CF = cystic fibrosis; CFRD = cystic fibrosis-related diabetes; DM = diabetes mellitus; FM = fibromyalgia; HF = heart failure; HRT = hormone-replacement therapy; HTN = hypertension; IBS = irritable bowel syndrome; MHT = menopausal hormone therapy; PDAC = pancreatic ductal adenocarcinoma; TBI = traumatic brain injury.

Figure 3. Comparison of total metabolomics and nurse scientist metabolomics publications, 1990–2019.

2017; Mayers et al., 2014; Menzies et al., 2020; Shah et al., 2010; Starkweather et al., 2017; Thompson et al., 2019; Wang et al., 2016, 2017, 2018a, 2018b, 2019). An additional seven (25.9%) of the studies involving human subjects used serum (Ferranti et al., 2017; Heitkemper et al., 2016; Lu et al., 2016; Lyon et al., 2018; Oh et al., 2017) or whole blood (Cybulska et al., 2019; Sun et al., 2018). The remainder of the studies with human studies used fecal (Bird et al., 2013; Gregory et al., 2013; Hollister et al., 2019) or urine (Faucher et al., 2019) samples for their metabolomics analyses. Additional tissues utilized in studies involving animal models included mouse abdominal tissue (Chen et al., 2018), mouse cerebral cortex tissue (Chen et al., 2019), and rat alveolar cells (Downs et al., 2018).

Study Designs

We also classified studies included in this review according to their research design. Among the four studies (13.3%) involving animal tissues, one was an *in vitro* investigation of cellular response to oxidants (Downs et al., 2018), while in the others researchers used metabolomics to identify predictive (Chen et al., 2018) or prognostic biomarkers (Chen et al., 2019; Lu et al., 2016) for various conditions. In arguably the most rigorous of the studies in the present review, Mayers and colleagues (2014) validated their findings regarding metabolic

predictors of pancreatic cancer in humans by repeating analyses in mice with early-stage pancreatic cancer.

Among the studies using only human samples, three were conducted within the context of randomized clinical trials (Alvarez et al., 2017; Alvarez, Frediani, et al., 2014; Irving et al., 2015) wherein researchers used metabolomics to identify prognostic biomarkers of disease progression and/or predictive biomarkers of treatment response. An additional six utilized samples from prospective cohorts (Cheng et al., 2015; Faucher et al., 2019; Lyon et al., 2018; Mapstone et al., 2017; Oh et al., 2017; Sun et al., 2018) to identify biomarkers of disease or treatment. Half of the studies (50%, $n = 15$) involving samples from humans had case–comparison designs, and these investigators largely used metabolomics or lipidomics to preliminarily identify biomarkers of various disease states (Table 1). Finally, investigators in two human studies (Bird et al., 2013; Gregory et al., 2013), reported single or pooled-sample case studies to describe the development of lipidomics methods for discovery using fecal samples.

Using available data from the articles and abstracts, we characterized studies as being either hypothesis generating (i.e., exploratory, discovery) or hypothesis testing. All were hypothesis generating except for seven studies (23.3%; Irving et al., 2015; Mayers et al., 2014; Wang et al., 2016, 2017, 2018a, 2018b, 2019).

Methodological Approaches

We also examined studies to determine what type of metabolomics analysis investigators performed. Almost half ($n = 14$; 46.7%) of the studies included solely targeted metabolomics investigations (Cybulska et al., 2019; Downs et al., 2018; Faucher et al., 2019; Heitkemper et al., 2016; Irving et al., 2015; Mapstone et al., 2017; Mayers et al., 2014; Oh et al., 2017; Shah et al., 2010; Wang et al., 2016, 2017, 2018a, 2018b, 2019), two studies (6.6%) used both untargeted and targeted methods (Cheng et al., 2015; Lyon et al., 2018), and the remaining 14 (46.7%) involving untargeted metabolomics (Alvarez et al., 2017; Alvarez, Frediani, et al., 2014; Alvarez, Smith, et al., 2014; Bird et al., 2013; Chen et al., 2018, 2019; Ferranti et al., 2017; Gregory et al., 2013; Hollister et al., 2019; Lu et al., 2016; Menzies et al., 2020; Starkweather et al., 2017; Sun et al., 2018; Thompson et al., 2019). In seven studies (23.3%), investigators used lipidomics methods to target the amount and identity of lipids within samples (Bird et al., 2013; Downs et al., 2018; Gregory et al., 2013; Mapstone et al., 2017; Menzies et al., 2020; Starkweather et al., 2017; Wang et al., 2018b). In 27% of the studies ($n = 8$) researchers additionally performed pathway analysis whereby, not only the individual metabolites, but also the larger biologic networks are measured within samples (Alvarez et al., 2017; Chen et al., 2018, 2019; Ferranti et al., 2017; Gregory et al., 2013; Hollister et al., 2019; Lu et al., 2016; Lyon et al., 2018).

We also identified whether studies were solely metabolomics investigations or included additional omics analyses, finding that three (10%) included two types of omics analyses (Downs

et al., 2018; Faucher et al., 2019; Hollister et al., 2019). Downs and colleagues (2018) used proteomics to identify proteins expressed in rat alveolar epithelial cell exosomes exposed to oxidative stress. Faucher and colleagues (2019) examined whether vaginal microbiomes and urinary metabolites differed in pregnant African American women by pre-pregnancy body mass index and other variables. Hollister and colleagues (2019) studied the intestinal microbiome and fecal metabolites as they relate to recurrent abdominal pain in children with irritable bowel syndrome.

Discussion

In this scoping review of literature published over the past 3 decades, we have described the breadth of metabolomics studies conducted by or with nurse scientists. While some of the nurse authors led the investigations, others likely played critical roles in research teams. Our findings about the scope of this research are consistent with broader trends in metabolomics research (Guo et al., 2018), with most of the studies we reviewed having been conducted within the United States and published across a broad array of biological journals. The number of nurse scientists publishing research involving metabolomics methods increased over the study period, although nurse scientists still constituted only a small portion of the scientific community that was using metabolomics (Figure 3). Metabolomics methods offer considerable promise in the investigation of mechanisms contributing to a variety of clinical conditions, supporting a spectrum of study objectives, from hypothesis development to hypothesis testing. Due to the current and likely future impacts of metabolomics on discovery around patient outcomes, it is important for nurse scientists to be part of the community of scholars using these cutting-edge methods. In the present review, we found that nurse scientists were not just involved in metabolomics research; in 40% of the identified papers, they led the research teams. With their focus on patient-centered research, nurse scientists are ideally situated to enhance the potential of metabolomics by leading research teams in studies that deliver clinically relevant findings useful for designing high-quality, precision interventions.

The review also revealed that there is currently more breadth than depth in nurse scientists' use of metabolomics. This finding is not surprising because the field of metabolomics is only a few decades old (Oliver et al., 1998), with nursing's incorporation of metabolomics methods starting only 10 years ago (Shah et al., 2010). The nurse scientists' program of metabolomics-oriented research with the most depth appears to be Wang and colleagues' studies of heart failure patients (Wang et al., 2016, 2017, 2018a, 2018b, 2019). However, these investigations were not led by nurse scientists. Greater emphasis on omics science in nursing doctoral programs would increase the likelihood that nurse scientists would incorporate metabolomics methods earlier in their scholarly and research trajectories so that, within the next 5–10 years, there would be more nurse scientists with cohesive and mature programs of research in metabolomics (Conley et al., 2015).

Most of the studies in the present review were hypothesis generating rather than hypothesis testing and performed metabolomic investigations using samples originally collected to measure other biomarkers. Therefore, these samples may not have been collected or stored according to the strict specimen protocols recommended for robust metabolomics analyses (NIH, 2020; Saigusa et al., 2016). Use of existing specimens for secondary analyses is efficient; however, science driven by available data is not as robust as science built on prospective specimen collection to test plausible hypotheses. We are hopeful that, in the coming decade, nurse scientists will make a concerted effort to logically build their programs of research toward hypothesis-testing studies involving prospective collection of metabolomics data that includes comparison groups of healthy controls and validation samples to confirm findings (Trivedi et al., 2017).

Limitations

The present scoping review had several limitations. First, we focused on literature retrieved in standard databases and thus did not include gray literature. Although there may have been additional nurse scientist metabolomics studies in the gray literature, we made this decision in order to focus on the work of nurse scientists who successfully published their metabolomics analyses in the peer-reviewed literature. In addition, it is possible that this review did not include all published metabolomics studies by nurse scientists. Although we made a concerted effort to capture nurse authors using both database and hand searches, most databases of peer-reviewed literature do not support queries for authors' professional background. Specifically, because our major search strategy focused on nurse scientists affiliated with nursing schools, we may have missed nurse scientists with appointments in other disciplines. Finally, this review is limited by a lack of a comprehensive analysis of the quality of included studies. Assessment of the methodological quality of studies is generally not a requirement of scoping reviews (Peters et al., 2015). Although it would have been preferable to assess study quality, the field of metabolomics has not established a recognized framework for evaluating study rigor (Spicer et al., 2017). Thus, there is substantial heterogeneity in metabolomics methods (Clish, 2015) both within and outside nursing science.

Implications for Nursing

Metabolomics is one of a growing number of methods that makes it possible for researchers to comprehensively describe physiologic mechanisms underlying human disease. As such, it is important that nurse scientists incorporate metabolomics methods as they seek to improve care for people experiencing a range of health challenges. The National Institutes of Health, including the National Institute of Nursing Research, has a history of funding metabolomics and other omics investigations. Metabolomics is inherently a multidisciplinary area of inquiry that requires participation by clinical scientists as well as experts in molecular chemistry and bioinformatics. It is at the

Table 2. Pros and Cons of Incorporating Metabolomics Methods into Nursing Research.**Pros**

- Provides insights into biological mechanisms underlying phenomena important to nursing such as disease risk, symptoms, and health outcomes
- Results have strong potential to be translated into personalized interventions for patients
- Can be conducted on multiple types of biological specimens (blood, urine, feces, exhaled breath, etc.) using small sample volumes
- Can be combined with other omics or complex clinical data into multi-omic analyses to better reveal potential mechanisms underlying disease or symptoms
- Has wide applicability across the spectrum of nursing science

Cons

- Requires sufficient research infrastructure to support the storage and processing of biological specimens
- The cost for specimen processing and high-throughput data analysis can be high
- Requires strict control measures to assure accuracy of results, including efforts to minimize batch effects, ensure consistency in type of laboratory supplies, and use protocol-driven specimen collection/handling
- Interpretation of the findings often requires expertise of biostatistician and additional collaborators

intersection among disparate and traditionally siloed disciplines where innovation happens and science rapidly advances (Hockfield, 2009). Along with the need for training in omics research approaches, one of the most significant challenges nurse scientists will face in incorporating metabolomics research into their programs of research will be data analysis (Gertsman & Barshop, 2018). Specifically, nurse scientists need preparation in advanced statistical programming languages like R or Python, experience in data management, and training in statistical analysis methods, including basic statistical inference, study design, and machine-learning methods. Even though most omics projects involve multidisciplinary teams, in order to become integral leaders or collaborators of these types of projects, nurse scientists will be well served by undergoing training in modern analytical methods (Dinov, 2020). In addition, educational programs preparing nursing students to conduct this type of research should consider including programs of study on the biochemical mechanisms of disease so that the students will be equipped to help interpret how specific metabolites or metabolic pathways are important in a particular disease state. Student nurse scientists should also understand how to align their research problems with the basic science and laboratory resources within their institutions, including how to mobilize critical resources to facilitate the collection, processing, and storage of biological samples according to gold-standard metabolomics protocols (NIH, 2020). High-throughput analysis of samples and data interpretation are commercially available from bioinformatics companies (for example, www.metabolon.com), which can help nurse scientists who do not have access to bioinformatics services within their institutions. Table 2 provides additional considerations around the pros and cons of conducting metabolomics research.

Conclusion

The findings of this scoping review show that nurse scientists have established a presence in the metabolomics landscape. Ultimately, to lead interdisciplinary teams in metabolomics research and spur the long-term growth of nursing-relevant metabolomics science, nurse scientists must develop the

advanced knowledge and skills necessary to design high-quality metabolomics investigations and build robust programs of research using omics methods. By strengthening training for nurse scientists, we can ensure that nurses are leaders, not “bystanders,” in these emerging areas of science (Conley et al., 2015, p. 408).

Acknowledgments

The authors would like to acknowledge Adam Bullock, accelerated baccalaureate of nursing student at Emory University School of Nursing for his contributions to this work. Additionally, we would like to thank Jennifer Frediani, PhD, Assistant Research Professor, Emory University School of Nursing, for her assistance with the construction of Figure 1 for this manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by a research re-entry supplement to L. Kimble (<https://orcid.org/0000-0003-4007-4824>) under the parent award 1P30NR018090-02S1 Center for the Study of Symptom Science, Metabolomics, and Multiple Chronic Conditions (Song, PI) funded by the National Institute of Nursing Research. N. Carlson (<https://orcid.org/0000-0003-2642-9174>) was supported by grant number K01NR016984 from the National Institute of Nursing Research during manuscript production.

ORCID iDs

Laura P. Kimble <https://orcid.org/0000-0003-4007-4824>
 Sharon Leslie <https://orcid.org/0000-0002-6597-977X>
 Nicole Carlson <https://orcid.org/0000-0003-2642-9174>

References

- Aizat, W. M., Ismail, I., & Noor, N. M. (2018). Recent development in omics studies. *Advances in Experimental Medicine and Biology*, 1102, 1–9. https://doi.org/10.1007/978-3-319-98758-3_1
- Alvarez, J. A., Chong, E. Y., Walker, D. I., Chandler, J. D., Michalski, E. S., Grossmann, R. E., Uppal, K., Li, S., Frediani, J. K., Tirouvanziam, R., Tran, V. T., Tangpricha, V., Jones, D. P., & Ziegler,

- T. R. (2017). Plasma metabolomics in adults with cystic fibrosis during a pulmonary exacerbation: A pilot randomized study of high-dose vitamin D3 administration. *Metabolism*, 70, 31–41. <https://doi.org/10.1016/j.metabol.2017.02.006>
- Alvarez, J. A., Frediani, J. K., Jones, D. P., Grossmann, R. E., Uppal, K., Tranpricha, V., & Ziegler, T. R. (2014). Plasma metabolomic profiling in adults with cystic fibrosis and cystic-fibrosis related diabetes. *Federation of American Societies for Experimental Biology Journal*, 28(Suppl. 1), Abstract 248.1.
- Alvarez, J. A., Smith, E. M., Jones, D. P., Grossmann, R. E., Frediana, J. K., Uppal, K., Tirouvanziam, R., Tangpricha, V., & Ziegler, T. R. (2014). Discovery-based, high-resolution plasma metabolomics following a vitamin D3 intervention in adult patients with cystic fibrosis. *Pediatric Pulmonology*, 49, 418–419.
- Bafor, E. E., Rowan, E. G., & Edrada-Ebel, R. (2017). Toward understanding myometrial regulation: Metabolomic investigation reveals new pathways of oxytocin and ritodrine activity on the myometrium. *Reproductive Sciences*, 24, 691–705. <https://doi.org/10.1177/1933719116667224>
- Bird, S. S., Gregory, K. E., Gross, V. S., Marur, V. R., Lazarev, A. V., Walker, W. A., & Kristal, B. S. (2013). Fecal lipidomics analysis using liquid chromatography-mass spectrometry. *Federation of American Societies for Experimental Biology*, 27(Suppl. 1), Abstract 815.3.
- Chen, G., Ye, G., Zhang, X., Liu, X., Tu, Y., Ye, Z., Liu, J., Guo, Q., Wang, Z., Wang, L., Dong, S., & Fan, Y. (2018). Metabolomics reveals protection of resveratrol in diet-induced metabolic risk factors in abdominal muscle. *Cell Physiology & Biochemistry*, 45, 1136–1148. <https://doi.org/10.1159/000487354>
- Chen, L., Chao, Y., Cheng, P., Li, N., Zheng, H., & Yang, Y. (2019). UPLC-QTOF/MS-based metabolomics reveals the protective mechanism of hydrogen on mice with ischemic stroke. *Neurochemical Research*, 44, 1950–1963. <https://doi.org/10.1007/s11064-019-02829-x>
- Cheng, M. L., Wang, C. H., Shiao, M. S., Liu, M. H., Huang, Y. Y., Huang, C. Y., Mao, C.-T., Lin, J.-F., Ho, H.-Y., & Yang, N. I. (2015). Metabolic disturbances identified in plasma are associated with outcomes in patients with heart failure: Diagnostic and prognostic value of metabolomics. *Journal of the American College of Cardiology*, 65, 1509–1520. <https://doi.org/10.1016/j.jacc.2015.02.018>
- Clish, C. B. (2015). Metabolomics: An emerging but powerful tool for precision medicine. *Cold Spring Harbor Molecular Case Studies*, 1(1), a000588. <https://doi.org/10.1101/mcs.a000588>
- Collins, F. S., & Varmus, H. (2015). A new initiative on precision medicine. *New England Journal of Medicine*, 372, 793–795. <https://doi.org/10.1056/NEJMp1500523>
- Conley, Y. P., Heitkemper, M., McCarthy, D., Anderson, C. M., Corwin, E. J., Daack-Hirsch, S., Dorsey, S. G., Gregory, K. E., Groer, M. W., Henly, S. J., Landers, T., Lyon, D. E., Taylor, J. Y., & Voss, J. (2015). Educating future nursing scientists: Recommendations for integrating omics content in PhD programs. *Nursing Outlook*, 63, 417–427. <https://doi.org/10.1016/j.outlook.2015.06.006>
- Cybulska, A. M., Skonieczna-Zydecka, K., Drozd, A., Rachubinska, K., Pawlik, J., Stachowska, E., Jurczak, A., & Grochans, E. (2019). Fatty acid profile of postmenopausal women receiving, and not receiving, hormone replacement therapy. *International Journal of Environmental Research & Public Health*, 16, 4723. <https://doi.org/10.3390/ijerph16214273>
- DeBerardinis, R. J., & Thompson, C. B. (2012). Cellular metabolism and disease: What do metabolic outliers teach us? *Cell*, 148, 1132–1144. <https://doi.org/10.1016/j.cell.2012.02.032>
- Dinov, I. D. (2020). Modernizing the methods and analytics curricula for health science doctoral programs. *Frontiers in Public Health*, 8, 22. <https://doi.org/10.3389/fpubh.2020.00022>
- Downs, C. A., Dang, V. D., Johnson, N. M., Denslow, N. D., & Alli, A. A. (2018). Hydrogen peroxide stimulates exosomal cathepsin B regulation of the receptor for advanced glycation end-products (RAGE). *Journal of Cellular Biochemistry*, 119, 599–606. <https://doi.org/10.1002/jcb.26219>
- Faucher, M. A., Greathouse, K. L., & Hastings-Tolsma, M. (2019). Exploration of the vaginal and gut microbiome, dietary intake, and metabolomics in African American women by body mass index and gestational weight gain. *Journal of Midwifery & Women's Health*, 64, 674–675.
- Ference, B. A., Graham, I., Tokgozoglu, L., & Catapano, A. L. (2018). Impact of lipids on cardiovascular health: JACC health promotion series. *Journal of the American College of Cardiology*, 72, 1141–1156. <https://doi.org/10.1016/j.jacc.2018.06.046>
- Ferranti, E. P., Frediani, J. K., Corwin, E. J., & Dunlop, A. L. (2017). Amino acid pathways are altered in cardiovascular complications of pregnancy. *Circulation*, 136(Suppl. 1), Abstract 19031.
- Gertsman, I., & Barshop, B. A. (2018). Promises and pitfalls of untargeted metabolomics. *Journal of Inherited Metabolic Disease*, 41, 355–366. <https://doi.org/10.1007/s10545-017-0130-7>
- Gregory, K. E., Bird, S. S., Gross, V. S., Marur, V. R., Lazarev, A. V., Walker, W. A., & Kristal, B. S. (2013). Method development for fecal lipidomics profiling. *Analytical Chemistry*, 85, 1114–1123. <https://doi.org/10.1021/ac303011k>
- Guo, S., Tian, J., Zhu, B., Yang, S., Yu, K., & Zhao, Z. (2018). Trends in metabolomics research: A scientometric analysis (1992–2017). *Current Science*, 114, 2248–2254.
- Heitkemper, M. M., Han, C. J., Jarrett, M. E., Gu, H., Djukovic, D., Shulman, R. J., Raftery, D., Henderson, W. A., & Cain, K. C. (2016). Serum tryptophan metabolite levels during sleep in patients with and without irritable bowel syndrome (IBS). *Biological Research for Nursing*, 18, 193–198. <https://doi.org/10.1177/1099800415594251>
- Hockfield, S. (2009). The next innovation revolution. *Science*, 323, 1147. <https://doi.org/10.1126/science.1170834>
- Hollister, E. B., Oezguen, N., Chumpitazi, B. P., Luna, R. A., Weidler, E. M., Rubio-Gonzales, M., Dahdouli, M., Cope, J. L., Mistretta, T.-A., Raza, S., Metcalf, G. A., Muzny, D. M., Gibbs, R. A., Petrosino, J. F., Heitkemper, M., Savidge, T. C., Shulman, R. J., Versalovic, J., & Versalovic, J. (2019). Leveraging human microbiome features to diagnose and stratify children with irritable bowel syndrome. *Journal of Molecular Diagnostics*, 21, 449–461. <https://doi.org/10.1016/j.jmoldx.2019.01.006>
- Huan, T., Tran, T., Zheng, J., Sapkota, S., MacDonald, S. W., Camicioli, R., Dixon, R. A., & Li, L. (2018). Metabolomics analyses of saliva detect novel biomarkers of Alzheimer's disease. *Journal of*

- Alzheimer's Disease*, 65, 1401–1416. <https://doi.org/10.3233/JAD-180711>
- Indiana University Center for Postsecondary Research. (n.d.). *Carnegie classification of institutions of higher education, 2018 edition*. <https://carnegieclassifications.iu.edu/>
- Irving, B. A., Carter, R. E., Soop, M., Weymiller, A., Syed, H., Karakelides, H., Bhagra, S., Short, K. R., Tatpati, L., Barazzoni, R., Sreekumaran Nair, K., & Nair, K. S. (2015). Effect of insulin sensitizer therapy on amino acids and their metabolites. *Metabolism*, 64, 720–728. <https://doi.org/10.1016/j.metabol.2015.01.008>
- Johnson, C. H., Ivanisevic, J., & Siuzdak, G. (2016). Metabolomics: Beyond biomarkers and towards mechanisms. *Nature Reviews Molecular Cell Biology*, 17, 451–459. <https://doi.org/10.1038/nrm.2016.25>
- Jones, D. P. (2016). Sequencing the exposome: A call to action. *Toxicology Reports*, 3, 29–45. <https://doi.org/10.1016/j.toxrep.2015.11.009>
- Jones, D. P., Park, Y., & Ziegler, T. R. (2012). Nutritional metabolomics: Progress in addressing complexity in diet and health. *Annual Review of Nutrition*, 32, 183–202. <https://doi.org/10.1146/annurev-nutr-072610-145159>
- Klepacki, J., Klawitter, J., Klawitter, J., Karimpour-Fard, A., Thurman, J., Ingle, G., Patel, D., & Christians, U. (2016). Amino acids in a targeted versus a non-targeted metabolomics LC-MS/MS assay. Are the results consistent? *Clinical Biochemistry*, 49, 955–961. <https://doi.org/10.1016/j.clinbiochem.2016.06.002>
- Liu, X., & Locasale, J. W. (2017). Metabolomics: A primer. *Trends in Biochemical Sciences*, 42, 274–284. <https://doi.org/10.1016/j.tibs.2017.01.004>
- Loscalzo, J., Kohane, I., & Barabasi, A. L. (2007). Human disease classification in the postgenomic era: A complex systems approach to human pathobiology. *Molecular Systems Biology*, 3, 124. <https://doi.org/10.1038/msb4100163>
- Lu, Y., Yang, R., Jiang, X., Yang, Y., Peng, F., & Yuan, H. (2016). Serum metabolite profiles of postoperative fatigue syndrome in rat following partial hepatectomy. *Journal of Clinical Biochemistry and Nutrition*, 58, 210–215. <https://doi.org/10.3164/jcbtn.15-72>
- Lyon, D. E., Starkweather, A., Yao, Y., Garrett, T., Kelly, D. L., Menzies, V., Dereziński, P., Datta, S., Kumar, S., & Jackson-Cook, C. (2018). Pilot study of metabolomics and psychoneurological symptoms in women with early stage breast cancer. *Biological Research for Nursing*, 20(2), 227–236. <https://doi.org/10.1177/1099800417747411>
- Maniscalco, M., Fuschillo, S., Paris, D., Cutignano, A., Sanduzzi, A., & Motta, A. (2019). Clinical metabolomics of exhaled breath condensate in chronic respiratory diseases. *Advances in Clinical Chemistry*, 88, 121–149. <https://doi.org/10.1016/bs.acc.2018.10.002>
- Mapstone, M., Lin, F., Nalls, M. A., Cheema, A. K., Singleton, A. B., Fiandaca, M. S., & Federoff, H. J. (2017). What success can teach us about failure: The plasma metabolome of older adults with superior memory and lessons for Alzheimer's disease. *Neurobiology of Aging*, 51, 148–155. <https://doi.org/10.1016/j.neurobiolaging.2016.11.007>
- Mayers, J. R., Wu, C., Clish, C. B., Kraft, P., Torrence, M. E., Fiske, B. P., Yuan, C., Bao, Y., Townsend, M. K., Tworoger, S. S., Davidson, S. M., Papagiannakopoulos, T., Yang, A., Dayton, T. L., Ogino, S., Stampfer, M. J., Giovannucci, E. L., Qian, Z. R., Robinson, D. A., & Wolpin, B. M. (2014). Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development. *Nature Medicine*, 20, 1193–1198. <https://doi.org/10.1038/nm.3686>
- Menzies, V., Starkweather, A., Yao, Y., Thacker, L. R. 2nd, Garrett, T. J., Swift-Scanlan, T., Kelly, D. L., Patel, P., & Lyon, D. E. (2020). Metabolomic differentials in women with and without fibromyalgia. *Clinical and Translational Science*, 13, 67–77. <https://doi.org/10.1111/cts.12679>
- National Institute of Nursing Research. (2016). *NINR strategic plan: Advancing science, improving lives. A vision for nursing science*. National Institutes of Health. https://www.ninr.nih.gov/sites/files/docs/NINR_StratPlan2016_reduced.pdf
- National Institutes of Health. (2020). Metabolomics workbench: Study specific protocols. <https://www.metabolomicsworkbench.org/protocols/studyspecific.php>
- Newgard, C. B. (2017). Metabolomics and metabolic diseases: Where do we stand? *Cellular Metabolism*, 25, 43–56. <https://doi.org/10.1016/j.cmet.2016.09.018>
- Oh, H., Coburn, S. B., Matthews, C. E., Falk, R. T., LeBlanc, E. S., Wactawski-Wende, J., Sampson, J., Pfeiffer, R. M., Brinton, L. A., Wentzensen, N., Anderson, G. L., Manson, J. E., Chen, C., Zaslavsky, O., Xu, X., & Trabert, B. (2017). Anthropometric measures and serum estrogen metabolism in postmenopausal women: The Women's Health Initiative Observational Study. *Breast Cancer Research*, 19, 28. <https://doi.org/10.1186/s13058-017-0810-0>
- Oliver, S. G., Winson, M. K., Kell, D. B., & Bagan, F. (1998). Systematic functional analysis of the yeast genome. *Trends in Biotechnology*, 16, 373–378. [https://doi.org/10.1016/s0167-7799\(98\)01214-1](https://doi.org/10.1016/s0167-7799(98)01214-1)
- Peters, M. D., Godfrey, C. M., Khalil, H., McInerney, P., Parker, D., & Soares, C. B. (2015). Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare*, 13, 141–146. <https://doi.org/10.1097/XEB.0000000000000050>
- Saigusa, D., Okamura, Y., Motoike, I. N., Katoh, Y., Kurosawa, Y., Saijyo, R., Koshiba, S., Yasuda, J., Motohashi, H., Sugawara, J., Tanabe, O., Kinoshita, K., & Yamamoto, M. (2016). Establishment of protocols for global metabolomics by LC-MS for biomarker discovery. *PLoS One*, 11(8), e0160555. <https://doi.org/10.1371/journal.pone.0160555>
- Selcuk, A. A. (2019). A guide for systematic reviews: PRISMA. *Turkish Archives of Otorhinolaryngology*, 57, 57–58. <https://doi.org/10.5152/tao.2019.4058>
- Shah, S. H., Bain, J. R., Muehlbauer, M. J., Stevens, R. D., Crosslin, D. R., Haynes, C., Dungan, J., Newby, L. K., Hauser, E. R., Ginsburg, G. S., Newgard, C. B., & Kraus, W. E. (2010). Association of a peripheral blood metabolic profile with coronary artery disease and risk of subsequent cardiovascular events. *Circulation Cardiovascular Genetics*, 3, 207–214. <https://doi.org/10.1161/CIRCGENETICS.109.852814>
- Shih, C. L., Wu, H. Y., Liao, P. M., Hsu, J. Y., Tsao, C. Y., Zgoda, V. G., & Liao, P. C. (2019). Profiling and comparison of toxicant metabolites in hair and urine using a mass spectrometry-based metabolomic data processing method. *Analytica Chimica Acta*, 1052, 84–95. <https://doi.org/10.1016/j.jaca.2018.11.009>

- Soltow, Q. A., Strobel, F. H., Mansfield, K. G., Wachtman, L., Park, Y., & Jones, D. P. (2013). High-performance metabolic profiling with dual chromatography-Fourier-transform mass spectrometry (DC-FTMS) for study of the exposome. *Metabolomics*, 9(Suppl. 1), S132–S143. <https://doi.org/10.1007/s11306-011-0332-1>
- Spicer, R. A., Salek, R., & Steinbeck, C. (2017). A decade after the metabolomics standards initiative it's time for a revision. *Scientific Data*, 4, 170138. <https://doi.org/10.1038/sdata.2017.138>
- Starkweather, A., Julian, T., Ramesh, D., Heineman, A., Sturgill, J., Dorsey, S. G., Lyon, D. E., & Wijesinghe, D. S. (2017). Circulating lipids and acute pain sensitization: An exploratory analysis. *Nursing Research*, 66, 454–461. <https://doi.org/10.1097/NNR.0000000000000248>
- Sun, Y., Kim, J. H., Vangipuram, K., Hayes, D. F., Smith, E. M. L., Yeomans, L., Henry, N. L., Stringer, K. A., & Hertz, D. L. (2018). Pharmacometabolomics reveals a role for histidine, phenylalanine, and threonine in the development of paclitaxel-induced peripheral neuropathy. *Breast Cancer Research and Treatment*, 171, 657–666. <https://doi.org/10.1007/s10549-018-4862-3>
- Tavassoly, I., Goldfarb, J., & Iyengar, R. (2018). Systems biology primer: The basic methods and approaches. *Essays in Biochemistry*, 62, 487–500. <https://doi.org/10.1042/EBC20180003>
- Thompson, H., Rivara, F., Temkin, N., Becker, K., & Maile, R. (2019). Relationship of metabolomic profile and functional trajectory following mild traumatic brain injury in older adults. *Journal of Neurotrauma*, 36, A29.
- Trivedi, D. K., Hollywood, K. A., & Goodacre, R. (2017). Metabolomics for the masses: The future of metabolomics in a personalized world. *New Horizons in Translational Medicine*, 3, 294–305. <https://doi.org/10.1016/j.jnhtml.2017.06.001>
- Wang, C. H., Cheng, M. L., & Liu, M. H. (2018a). Amino acid-based metabolic panel provides robust prognostic value additive to B-natriuretic peptide and traditional risk factors in heart failure. *Disease Markers*, 2018, 3784589. <https://doi.org/10.1155/2018/3784589>
- Wang, C. H., Cheng, M. L., & Liu, M. H. (2018b). Simplified plasma essential amino acid-based profiling provides metabolic information and prognostic value additive to traditional risk factors in heart failure. *Amino Acids*, 50, 1739–1748. <https://doi.org/10.1007/s00726-018-2649-9>
- Wang, C. H., Cheng, M. L., Liu, M. H., & Fu, T. C. (2019). Amino acid-based metabolic profile provides functional assessment and prognostic value for heart failure outpatients. *Disease Markers*, 2019, 8632726. <https://doi.org/10.1155/2019/8632726>
- Wang, C. H., Cheng, M. L., Liu, M. H., Kuo, L. T., & Shiao, M. S. (2017). Metabolic profile provides prognostic value better than galectin-3 in patients with heart failure. *Journal of Cardiology*, 70, 92–98. <https://doi.org/10.1016/j.jcc.2016.10.005>
- Wang, C. H., Cheng, M. L., Liu, M. H., Shiao, M. S., Hsu, K. H., Huang, Y. Y., Lin, C.-C., & Lin, J. F. (2016). Increased p-cresyl sulfate level is independently associated with poor outcomes in patients with heart failure. *Heart Vessels*, 31, 1100–1108. <https://doi.org/10.1007/s00380-015-0702-0>
- Wenk, M. R. (2005). The emerging field of lipidomics. *Nature Reviews Drug Discovery*, 4, 594–610. <https://doi.org/10.1038/nrd1776>
- Zhao, Y. Y., Cheng, X. L., & Lin, R. C. (2014). Lipidomics applications for discovering biomarkers of diseases in clinical chemistry. *International Review of Cellular and Molecular Biology*, 313, 1–26. <https://doi.org/10.1016/B978-0-12-800177-6.00001-3>