NARRATIVE REVIEW AND EVIDENCE MAPPING

Proteomics for Cancer and Cardiovascular Disease
Narrative Review and Evidence Mapping
Proteomics for Cancer and Cardiovascular Disease

Patricia Stapleton, Sameer Siddiqi, Eric Apaydin, Olamigoke Akinniranye, Alejandro Becerra, Grace Gahlon, Lea Xenakis, Max Griswold, Jody Larkin

RAND Corporation

January 2021

All statements, findings, and conclusions in this publication are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI) or its Board of Governors. This publication was developed through a contract to support PCORI’s work. Questions or comments may be sent to PCORI at info@pcori.org or by mail to Suite 900, 1828 L Street, NW, Washington, DC 20036.

©2021 Patient-Centered Outcomes Research Institute. For more information see www.pcori.org
Table of Contents

Abbreviations .................................................................................................................. 5
Executive Summary .......................................................................................................... 6
Introduction ...................................................................................................................... 9
Examples of Clinical Proteomics .................................................................................... 9
Aim of the Report ........................................................................................................... 10
Methodology Overview .................................................................................................. 11
Key Informant Interviews .............................................................................................. 11
Narrative Review ............................................................................................................ 12
  Search .......................................................................................................................... 12
  Screening ..................................................................................................................... 12
  Abstraction .................................................................................................................. 12
  Figure 1. Application of Fryback and Thornbury Framework to Genomics and Proteomics-Based Testinga ......................................................................................................... 13
  Synthesis ..................................................................................................................... 13
  Visualization ............................................................................................................... 14
Data Sources ................................................................................................................... 14
  Table 1. Landscape Review: Data Sources and Report Contenta ................................... 14
Organization of the Report .............................................................................................. 15
  Description of Proteomic Testing Applications .......................................................... 15
  Evidence for Proteomic Testing .................................................................................. 15
  Potential Near-Term Proteomic Testing Applications .............................................. 15
  Facilitators and Barriers to Testing Uptake .............................................................. 15
  Efficacy of Proteomic Testing .................................................................................... 15
  Evidence Gaps and Future Research ......................................................................... 15
Results ................................................................................................................................ 17
Description of Proteomic Tests and Applications .......................................................... 17
  Table 2. Strengths and Weaknesses of Proteomic Testing Applications ..................... 18
  Table 3. Characteristics of Proteomic Technology Applications in Cancer and Cardiology .................................................................................................................. 19
Proteomic Testing for Cancer ......................................................................................... 20
Proteomic Testing for Cardiovascular Diseases ............................................................... 20
Evidence ........................................................................................................................... 21
  Table 4. Characteristics of Evidence of Proteomic Testing Applications in Literature .......................................................................................................................... 21
  Table 5. Outcome Efficacy Type by Diseasea ............................................................. 22
Proteomic Testing for Cancer ......................................................................................... 23
  Table 6. Proteomic Tests by Cancer Disease Subtype and Cancer Stage ....................... 23
  Figure 2. Evidence Map for Proteomic Testing Related to Cancer (n = 128)a ................... 24
Proteomic Testing for Cardiovascular Diseases ............................................................... 25
  Table 7. Proteomic Tests by Cardiovascular Disease Subtype and Recurrence Status ....... 25
  Figure 3. Evidence Map for Proteomic Testing Related to Cardiovascular Disease (n = 26)a .................................................................................................................. 26
Potential Near-Term Applications ................................................................................... 27
Table 8. FDA-Cleared/-Approved and Commercially Available Proteomic Testing Applications\textsuperscript{a,b} ........................................ 28

Synthesis of Key Informant Observations............................................................................................................. 29

Facilitators and Barriers to Testing Uptake............................................................................................................. 30

Efficacy of Proteomic Testing ................................................................................................................................. 32

Figure 4. Application of Fryback and Thornbury Framework to Genomics and Proteomics-Based Testing With Article Counts\textsuperscript{a} .................................................. 32

Proteomic Testing for Cancer ................................................................................................................................. 33

Proteomic Testing for Cardiovascular Diseases .................................................................................................... 33

Evidence Gaps and Future Research ....................................................................................................................... 34

Table 9. Overview of Evidence Gaps and Future Research in Proteomic Testing for Cancer and Cardiovascular Disease\textsuperscript{a} ......................................................................... 35

Future Research on Clinical Utility and Uptake .................................................................................................... 36

Future Research Infrastructure Investments to Accelerate Progress .................................................................. 36

Conclusion .............................................................................................................................................................. 38

References .............................................................................................................................................................. 39

Appendix A. Stakeholder and Key Informant Interviews ...................................................................................... 44

Interviews ............................................................................................................................................................... 44

Recruitment .......................................................................................................................................................... 44

Procedure ............................................................................................................................................................... 44

Interview Data Collection and Analysis Strategy ................................................................................................ 48

Appendix B. Search Strategies ................................................................................................................................. 50

Published Literature ............................................................................................................................................... 50

Gray Literature—Industry Trade Publications ...................................................................................................... 52

Appendix C: Narrative Review Methodology ......................................................................................................... 53

Literature Searches ................................................................................................................................................ 53

Table 1. Literature Search Results ........................................................................................................................ 53

Literature Review Procedure ................................................................................................................................ 53

Inclusion Criteria ...................................................................................................................................................... 54

Data Extraction ..................................................................................................................................................... 55

Evidence Map ......................................................................................................................................................... 60

Evidence Table ....................................................................................................................................................... 60

Appendix D. Literature Review Flow Diagram\textsuperscript{a} ..................................................................................... 61

Appendix E. Evidence Table and References for Reviewed Publications ............................................................. 62

Evidence Table for Original Peer-Reviewed Research Articles (n = 154) ............................................................. 62

Peer-reviewed reviews and commentaries (n = 93) ............................................................................................. 84
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCT</td>
<td>Controlled clinical trial</td>
</tr>
<tr>
<td>CLIA</td>
<td>Clinical Laboratory Improvement Amendment</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal growth factor receptor</td>
</tr>
<tr>
<td>Embase</td>
<td>Excerpta Medica dataBASE</td>
</tr>
<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
</tr>
<tr>
<td>IGNITE</td>
<td>Implementing GeNomics In pracTicE</td>
</tr>
<tr>
<td>IVDMIA</td>
<td>In vitro diagnostic multivariate index assay</td>
</tr>
<tr>
<td>MRM</td>
<td>Multiple reaction monitoring</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non–small cell lung cancer</td>
</tr>
<tr>
<td>PCORI</td>
<td>Patient-Centered Outcomes Research Institute</td>
</tr>
<tr>
<td>PMID</td>
<td>PubMed ID</td>
</tr>
<tr>
<td>PRIDE</td>
<td>Proteomics Identification Database</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate-specific antigen</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>TKI</td>
<td>Tyrosine kinase inhibitor</td>
</tr>
</tbody>
</table>
Executive Summary

Key Points

- Proteomic testing applications for cancer and cardiovascular disease currently in clinical use vary in their approach to identifying and quantifying proteins and to matching them to a particular diagnosis, treatment, or prognosis. Global proteomic testing, in vitro diagnostic multivariate index assays, and several protein tests are the predominant approaches, with most leveraging innovation in mass spectrometry. More than half of proteomic research studies in these fields use a form of algorithmic processing to interpret protein biomarkers.

- There is broad expert consensus on the potential for proteomic testing to be effectively used in the diagnosis and treatment of cancer and cardiovascular disease. Although many studies focus on the diagnostic accuracy and patient outcome efficacy of proteomic testing for cancer and cardiovascular disease, there is limited evidence of proteomic testing applications that are likely to be widely adopted in the near future.

- Researchers face methodological limitations of study designs, disease heterogeneity, and inconsistent standards across testing platforms, which constrain the effectiveness of proteomic tests in terms of sensitivity and specificity and engender practical challenges for test development and deployment. Health care organizations face additional potential challenges related to the technical infrastructure and expertise needed to scale and integrate proteomic tests into existing clinical workflows.

- Only a limited number of proteomic testing studies in these fields focus on racial and ethnic minorities and the uninsured, validating earlier studies on the underrepresentation of racial and ethnic minorities in research on personalized or precision medicine.

Proteomics involves the identification and quantification of all or specific proteins in a biological sample, with the purpose of explaining the structure and function of those proteins in an organism. Clinical proteomics offers the promise of more precise risk assessment, diagnosis, and prognosis of disease. As such, proteomic testing has been proposed for a wide variety of applications, including for determining risk of conditions, diagnosing conditions, helping select optimal therapies, and determining response to therapies. Because of increased attention to the potential of proteomic testing, the Patient-Centered Outcomes Research Institute (PCORI) commissioned a narrative review and the development of evidence maps regarding these procedures. Evidence maps provide a visual overview of large research areas by indicating the research focus and the quantity of existing research as well as gaps in knowledge. This report presents, in an evidence map format, the evidence currently supporting approved proteomic tests in the United States for cancer and cardiovascular disease, as well as proteomic tests in these medical fields that may be available in the near term.

As part of our process of defining the review search and abstraction protocol, we conducted semistructured interviews with a diverse set of participants from key stakeholder groups, as identified by PCORI. We invited key informants to represent a range of perspectives (ie, patients and patient advocates, clinicians, payers and insurers, and public policymaker representatives) and to provide context for the use of proteomic testing in oncology and cardiology.
Between July and September 2020, we reviewed scientific journals and trade industry publications (ie, trade industry news articles) that assess innovations and technical advances to document the current state of proteomic testing in cardiology and oncology and to identify evidence of how proteomic testing impacts patient outcomes. We screened more than 6200 publications and abstracted 154 peer-reviewed original research articles, 93 peer-reviewed reviews and commentaries, and 99 trade industry publications that described clinical outcomes related to proteomic testing for oncology and cardiology. We abstracted study and proteomic test characteristics from the peer-reviewed original research articles and a broad range of facilitators, barriers, forecasts, and emerging applications from the peer-reviewed reviews and commentaries and the trade industry publications. We used Peng’s adaptation of the Fryback and Thornbury framework as our diagnostic evaluation framework. This framework provided an important, hierarchical model with which to classify efficacy data reported in each article included in the review. The results of the narrative review are documented in a comprehensive evidence table and other visualizations, such as the evidence maps, in this report.

Our search of the peer-reviewed literature identified 72 studies that used global proteomic testing, 37 studies that examined in vitro diagnostic multivariate index assays, and 41 studies that sought to identify several proteins in a patient sample to be used collectively as a biomarker for a diagnosis, treatment course, or prognosis. In addition, we found 2 studies that employed multiple approaches among the described testing applications, as well as 2 additional studies that used some other type of approach. Among the articles reviewed, we found that more than half (87 articles) used some form of algorithmic processing to interpret protein biomarkers, 8 used regression analysis or other analytic methods, and 59 did not specify their analytic approach.

Once we established the types of proteomic testing applications currently in clinical use in the areas of cancer and cardiovascular disease, we sought any available evidence evaluating benefits and/or harms related to the use of these applications, with specific attention to the types of efficacy. Of the 154 eligible peer-reviewed articles related to proteomic testing for cancer and cardiology, 63 were studies that compared proteins between patients with disease and without disease (ie, healthy). We classified articles in terms of overlapping efficacy outcome categories; most articles (73) focused on diagnostic accuracy efficacy, with fewer studies focusing on patient outcome (45 articles), therapeutic (16 articles), technical (14 articles), diagnostic thinking (9 articles), and societal (1 article) efficacy. Our review identified 128 articles that examined proteomic tests related to cancer, with approximately half (61) focusing on diagnostic accuracy. In comparison, we identified only 26 articles that examined proteomic tests related to cardiovascular disease, with about half (12) of those also focusing on diagnostic accuracy.

In addition to determining the evidence on existing proteomic testing applications, we also attempted to determine which applications are currently being evaluated with new research, or are otherwise being developed, that we expect may be adopted into clinical care in the next 5 years. With few exceptions, our review found limited evidence of proteomic testing applications that are likely to be widely adopted in the near future.

Our analysis of reviews and commentaries identified several important barriers that may limit the uptake of proteomic tests in clinical settings. For one, study designs and platforms have methodological limitations, such as lack of reporting of important demographic information or patient clinical indexes, that may have significant implications for protein and disease signatures. Moreover, there is variability in the sensitivity and specificity of competing proteomic testing
platforms, as well as a lack of standardization in terms of techniques, workflows, and sample collection, storage, handling, and profiling among laboratories. These technical issues further constrain the effectiveness of proteomic tests in terms of sensitivity and specificity and engender practical challenges such as skepticism from clinicians and significant costs associated with test development and deployment. As such, proteomic testing may be out of reach for health care organizations with limited resources.

Based on the current state of the evidence base for proteomic testing, we present several recommendations for future research. Our review suggests that future research on applications for cardiology and oncology could focus on specific levels of Fryback and Thornbury’s framework, namely diagnostic thinking, patient outcome, therapeutic, and societal efficacy. The review also validates earlier studies on the underrepresentation of racial and ethnic minorities and the uninsured in research on personalized or precision medicine. To address this critical gap, researchers and their funders should consider prioritizing racial and ethnic minorities in trial recruitment, biobanks, and databanks; ensuring controls are appropriately matched in terms of race, ethnicity, or ancestry; reporting relevant geographic, cultural, social, environmental, or epidemiological risk factors in analyses; and exploring the economic impact and patient acceptability of proteomic testing on diverse health care organizations and populations.

In addition to potential uses of proteomic testing, research should address barriers to clinical uptake. Future research could compare patient outcomes between interventions using proteomic tests against interventions using current gold standards and explore strategies to integrate novel assays into existing clinical workflows. To achieve gains in clinical utility, researchers and funders should consider strategic investments in research and bioinformatic infrastructure and tools. Future analyses should also combine proteomic data with genomic, epigenomic, histopathologic, and transcriptomic data, as well as data from other sources that characterize demographic and lifestyle risk factors. Researchers could design studies differently to address methodological limitations and develop novel collaborative approaches. For example, researchers could leverage larger sets of samples and include geographically and demographically diverse patients who may be at risk for disease as study controls rather than include healthy controls. Finally, to improve the quality of proteomic research for clinical utility, researchers, funders, and laboratories should consider adopting novel collaborative approaches and testing standards. To accelerate progress, future proteomic research stakeholders could invest in cutting-edge discovery and clinical validation research, develop proteomic research infrastructure, train and assemble interdisciplinary research teams, and/or adopt standard operating and reporting procedures.
Introduction

Clinical proteomics offers the promise of more precise risk assessment, diagnosis, and prognosis of disease. Like its cognate genomics, which seeks to characterize genetic material, proteomics involves the identification and quantification of all or specific proteins in a biological sample. The scientific discipline of proteomics seeks to explain both the structure and function of proteins in an organism. Proteomic tests identify proteins in a patient, which can then be matched to a particular diagnosis, treatment plan, or prognosis. Clinically, this can help health care providers understand the current or potential disease state of a patient, and it can assist providers in making more informed decisions regarding diagnosis and treatment. These clinical applications of proteomics are possible due to the methods and tools of bioinformatics. Test manufacturers, for example, can now employ laboratory techniques like mass spectrometry or immunoassays to characterize proteins in conjunction with large amounts of protein and disease data to predict which protein or set of proteins is related to a disease state. A small number of proteomic tests for cancers are currently on the market, and discovery and early-stage clinical research is underway to develop testing for cardiovascular conditions.

Examples of Clinical Proteomics

Several examples of proteomic testing illustrate current clinical uses. The VeriStrat test, manufactured by Biosdesix, Inc, is a Clinical Laboratory Improvement Amendment (CLIA) licensed proteomic treatment management tool for non–small cell lung cancer (NSCLC). NSCLC is often treated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), like gefitinib or erlotinib, though not all patients respond to treatment. Multiple studies and a systematic review have demonstrated VeriStrat’s predictivity of survival in response to EGFR TKIs for NSCLC. Another example, the OVA1 test manufactured by Vermillion, Inc, is a 510(k)-approved proteomic diagnostic tool to help gynecologists determine if patients need oncology referrals for diagnostic surgery for a potential ovarian adnexal mass. Several studies have demonstrated how the test has high sensitivity when compared with clinical assessment—the imaging or the measurement of the single protein CA125. However, the test has exhibited low specificity (ie, the ability to detect a true lack of malignancy) when compared with alternatives, which led the US Food and Drug Administration (FDA) to issue a black box warning informing providers that they should use the test only in conjunction with imaging and clinical judgment to avoid unnecessary diagnostic surgery.

Proteomic testing is also currently being developed for cardiovascular conditions such as obesity, heart disease, and type 2 diabetes. For example, Chacko et al used an innovative mass spectrometry–based approach (ie, surface-enhanced laser desorption/ionization time-of-flight mass spectrometry) to describe differences in protein expression among individuals who received dietary supplements, and Ganz et al used an aptamer-based proteomic profiling approach to derive and validate a 9-protein risk score for cardiovascular disease outcomes among high-risk individuals. Much of this research is still preliminary in nature in that it focuses on biomarker discovery, and more work needs to be done to test the predictivity of proteomic activity on cardiovascular risk or outcomes in individual medical interventions.

---

1 High sensitivity in this context means the ability to detect true malignancy.
Algorithmic testing\(^2\) of protein groups clearly holds promise to personalize medicine to a patient’s risk, diagnostic, prognostic, and treatment profile. At least 2 proteomic tests are on the market with FDA approval/clearance to aid in diagnosis, as with OVA1 and the Risk of Ovarian Malignancy Algorithm (ROMA\(^\circledR\)) test. Proteomic testing can be a powerful tool to tailor medicine to each patient but only if the testing proves accurate; sensitivity (detection of true positives) and specificity (detection of true negatives) are important attributes of the tests.

**Aim of the Report**

Given that proteomic testing has been proposed for a wide variety of applications, we sought to review the evidence base regarding current proteomic tests. To maintain a feasible literature scope for this review, we specifically examined proteomic testing for cardiology and oncology in the United States, as research in these 2 fields is more developed than in others. More specifically, this report presents the proteomic applications currently in use or potentially available over the next 1 to 5 years in cardiology and oncology, summarizes the underlying evidence base and identifies evidence gaps, and provides information about potential benefits or harms of these technologies for patients and consumers, payers and insurers, purchasers and employers, and public policymakers.

\(^2\) An algorithm is “the mathematical process by which various variables are combined into an actionable score. It is part of the assay, determines the cutoff, and should be locked down prior to validation.” Once an algorithm is “locked,” it should “provide the same result each time the same input is provided.”\(^\text{18}\)
Methodology Overview

Key Informant Interviews

As part of our process in defining the review search and abstraction protocol, we conducted interviews with key informants from 4 stakeholder groups as selected by PCORI: patients and patient advocates, clinicians, payers and insurers, and public policymaker representatives. We sought to interview a total of 6 to 8 representatives from across the identified stakeholder groups who have experience and/or expertise related to proteomic testing for cardiovascular disease or cancer. The research team worked with PCORI to identify and refine the list of potential participants and to establish the distribution of representation across the stakeholder groups. Due to the report’s emphasis on proteomic testing in cardiology and oncology and our effort to identify potential barriers to uptake in clinical settings, we aimed to have half of the interviewees be from the clinician stakeholder group. We also consulted with 3 external subject matter experts in proteomics and used their input to refine our methodological approach:

- Masanori Aikawa, MD, PhD, associate chair and founding director of the Center for Interdisciplinary Cardiovascular Sciences at Brigham and Women’s Hospital
- Karin Rodland, PhD, director of the Precision Medicine Innovation CoLaboratory at Pacific Northwest National Laboratory
- Hanno Steen, PhD, director of the Proteomics Center at Boston Children’s Hospital

In addition to suggestions from PCORI and the external subject matter experts, the research team identified points of contact from relevant professional organizations (eg, American Cancer Society, American Heart Association, The Heart Foundation) to ensure a robust list of potential participants.

We interviewed 6 key informants from the identified stakeholder groups. In addition to one participant each from the clinician and public policymaker stakeholder categories, we interviewed the following individuals:

**Patient Advocates**
- Susan Strong, PCORI ambassador, PCORI Ambassador Program

**Clinicians**
- Salim Hayek, MD, medical director, Michigan Medicine Frankel Cardiovascular Center Clinics
- Alex Kentsis, MD, PhD, cancer biologist and pediatric oncologist, Memorial Sloan Kettering Cancer Center

**Insurers**
- Eugean Jiwanmall, senior research analyst, Independence Blue Cross

---

3 Dr Steen worked with the team during the development of the work plan to ensure technical accuracy, and identified researchers and clinicians in cardiology and oncology who could serve as technical advisors or participate in interviews. He also made suggestions for interview participants from the public policymaker stakeholder category. Dr Aikawa and Dr Rodland reviewed the project work plan, provided guidance on the development of the narrative review and interview protocols, and evaluated the draft report.
Through semistructured interviews, these informants contributed detailed information about proteomic testing, its current use, and its potential applications in treating cancer and cardiovascular disease. We also sought their perspectives on important issues that might be raised by proteomic testing, particularly in regulatory, clinical, and systems contexts. Additionally, the interviewees provided critical input that helped us refine our search strategies and identify proteomic tests in development.  

**Narrative Review**

**Search**

We completed a narrative review of peer-reviewed and industry trade publications by searching multiple data sources to identify and examine proteomic applications currently in use or potentially available over the next 1 to 5 years in cardiology and oncology. We focused our search on peer-reviewed original research articles, reviews, and commentaries and on gray literature (ie, trade industry news articles) that assess innovations and technical advances to establish the evidence of the current state of proteomic testing in cardiology and oncology, as well as the evidence of the impacts of proteomic testing on patient outcomes and on other stakeholders. We performed searches in the Excerpta Medica database (Embase), PubMed, and Nexis Uni.  

**Screening**

The project team screened each abstract against the study inclusion and exclusion criteria. All citations that were deemed potentially relevant by at least one reviewer were obtained as full-text files and screened against the eligibility criteria.  

**Abstraction**

We created a standardized form with explicit and pilot-tested categorization rules to extract the data. For each peer-reviewed research article, we extracted the author and publication year (if applicable), inclusion criteria, study setting, disease, characteristics, population, proteomic analysis characteristics, and outcome characteristics. For each commentary or review, we extracted the author and publication year (if applicable), inclusion criteria, indication, barriers/challenges, benefits/opportunities, and future research.  

We used Peng’s adaptation of the Fryback and Thornbury framework as our diagnostic evaluation framework. This framework provided an important, hierarchical model with which to classify efficacy data reported in each article included in the review. While Fryback and Thornbury’s original application was for determining the efficacy of diagnostic imaging, Peng adapted the framework to genomics- and proteomics-based testing, providing us with a foundation for our own application (Figure 1). As with Fryback and Thornbury’s original application, efficacy at the lower levels of the hierarchy contribute to efficacy at the higher levels.

---

4 We provide further details on the key informant interviews in Appendix A.  
5 We detail our search strategies in Appendices B and C.  
6 We describe the methods for our review procedure and inclusion and exclusion criteria in Appendix C. Appendix D presents a visualization of our process for identifying and screening the literature, then assessing its eligibility for inclusion in the review.  
7 We describe more details of the data extraction process in Appendix C.
Synthesis
We selected this diagnostic evaluation framework for use because it provides a way to engage with the medical literature in the context of patient preferences and needs as represented in the higher levels, in addition to providing a way to evaluate the value of proteomic diagnostic testing to clinicians as represented in the lower levels. As such, this framework allows us to acknowledge that patients may have different expectations for outcomes than do health care providers. The lower levels capture provider preferences, such as the reliability and accuracy of proteomic testing, as well as whether proteomic testing facilitates the delivery of effective care, optimizes resource use, and/or minimizes long-term costs. Assuming that patients prefer symptom relief, prompt and effective treatment, and improvement in their quality of life, by including Level 5 (patient outcome efficacy) in our categorization, we were able to identify if the literature discusses the benefits of proteomic testing for the patient and determine costs associated with proteomic testing. Attention to societal efficacy, as represented in Level 6 of the framework, also helped us move beyond identifying individual risks and benefits in the literature to larger public health questions that policymakers consider as they determine resource allocation and implications for health systems. This adaptation of the Fryback and Thornbury framework thus facilitates understanding of how outcomes from proteomic testing are the result of many synergistic decisions, and it assists in identifying “the key constraints to delivering the desired patient outcomes while highlighting the value of the diagnostic test.” We hypothesized that research on the use of proteomic testing diagnosis, monitoring, and prognosis, which map to Levels 2, 4, and 5 in the Fryback and Thornbury framework, would be the most useful in identifying evidence related to test efficacy and patient outcomes.
Overall, our aims were to summarize the underlying evidence base, to identify gaps in that evidence base, and to provide critical information about potential benefits or harms of these technologies for patients and consumers, payers and insurers, purchasers and employers, and public policymakers.

**Visualization**

After completing abstraction, we documented the results of our narrative review in 2 evidence maps using the statistical computing software R—one for each area of study (cardiology and oncology)—and in a comprehensive evidence table. Evidence maps\(^8\) provide a visual overview of large research areas by indicating the research focus and the quantity of existing research, as well as gaps in knowledge.\(^22\)

**Data Sources**

The report is based on peer-reviewed academic literature, gray literature, and key informant interviews. (Table 1) indicates how our data sources align with the report’s content by noting from which sources we gathered information on a general topic. For example, we used information from our discussions with key informants to provide context on how proteomic testing is used for cancer and cardiovascular disease and to inform the content related to potential issues associated with proteomic testing.\(^9\)

**Table 1. Landscape Review: Data Sources and Report Content**

<table>
<thead>
<tr>
<th>Technology</th>
<th>Context</th>
<th>Ongoing studies</th>
<th>Current evidence</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peer-reviewed research articles</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Peer-reviewed trials</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Peer-reviewed reviews/commentaries</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Industry publications</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Informant interviews</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

\(^a\) Column titles note the type of content that we found in the indicated data source. “Technology” refers to the types of technologies relevant to proteomic testing that are mentioned in the reviewed literature. “Context” refers to contextualizing information on how proteomic testing is currently used for cancer and cardiovascular disease and future applications. If ongoing studies on and current evidence for proteomic testing were mentioned in a publication or interview, “Ongoing studies” and “Current evidence” are respectively marked. “Issues” refers to any issues raised by proteomic testing, particularly in regulatory, clinical, and systems contexts, that were noted in a source.

\(^8\) Additional description of the creation of the evidence maps and an evidence table is included in Appendix C.

\(^9\) For more details on the informant interview and narrative review methodologies, see Appendices A through D.
Organization of the Report

Our review of proteomic testing with a focus on cancer and cardiovascular disease returned a substantial number of studies (n = 6262). After screening out the ineligible studies, we organized the large amount of data by framing and organizing the key questions for the report.

Description of Proteomic Testing Applications

1. What proteomic testing applications are currently in clinical use in the areas of cancer and cardiovascular disease?

Evidence for Proteomic Testing

2. What evidence evaluating benefits and/or harms is available on the use of these applications?

Potential Near-Term Proteomic Testing Applications

3. What applications are currently being evaluated with new research, or are otherwise being developed, that may be adopted into clinical care in the next 5 years?

Facilitators and Barriers to Testing Uptake

4a. What health conditions, health care interventions, or other characteristics of patients, care, and systems are being addressed by current and future applications?

4b. How might these applications positively or negatively influence patients/consumers, payers/insurers, purchasers/employers, and policymakers?

4c. What are the perceived technical and other challenges to a broader adoption of proteomic technologies in clinical applications?

4d. What are the perceived challenges related to the availability, affordability, and uptake of cutting-edge technology for health care stakeholders?

4e. Do health care institutions have sufficient analytic expertise and technical capabilities to adopt proteomic testing?

Efficacy of Proteomic Testing

5. Where does the evidence for current and future applications fit within Fryback and Thornbury’s hierarchical model of efficacy? Specifically, what evidence exists for the technical efficacy, diagnostic accuracy efficacy, diagnostic thinking efficacy, therapeutic efficacy, patient outcome efficacy, and societal/stakeholder efficacy of proteomic testing?

Evidence Gaps and Future Research

6a. What evidence gaps could be solved by future research?

6b. What types of future research could mitigate the perceived challenges to a broader adoption of proteomic technologies?
In addition to presenting our results (n = 154) in the context of these questions, we have organized the available evidence in a comprehensive evidence table (Appendix E) that lists key characteristics for all included original, peer-reviewed research studies. We stratify the evidence related to clinical utility by cancer and cardiovascular disease. Additional articles that describe candidate biomarkers and therapeutic targets are provided in Appendix E. We also provide 2 evidence maps (Figure 2 and Figure 3) to represent the state of proteomic testing for cancer and cardiovascular disease, respectively. Clinicians, researchers, policymakers, and funding agencies should find these maps useful for understanding the current state of and near-term evidence base for proteomic testing in these medical fields. Each evidence map also provides a broad overview of proteomic testing in the specified field, which could be useful for many different stakeholders with interest in this area.
Results

Description of Proteomic Tests and Applications

Proteomic testing applications vary widely in their approach to identifying proteins in a patient and then matching that protein “fingerprint” to a particular diagnosis, treatment plan, or prognosis. The ability to rapidly identify, quantify, and validate protein biomarkers has been made possible by recent advances in high-throughput mass spectrometry and algorithmic processing. Our review sought to identify the types of proteomic testing applications currently in clinical use in the areas of cancer and cardiovascular disease and their strengths and weaknesses. Whereas other reviews have focused on the association of clinical outcomes with single protein biomarkers that have broad clinical utility and acceptance, our review focuses on 3 types of multivariate proteomic tests: global proteomic testing, in vitro diagnostic multivariate index assays (IVDMIAs), and several protein tests.

**Global proteomic testing** involves identifying most proteins in a particular sample and matching that protein fingerprint to a reference fingerprint derived from a patient known to have a particular diagnosis, treatment course, or prognosis. This process entails separating (eg, via chromatography), quantifying, and identifying all proteins within a sample (eg, via a high-throughput mass spectrometry approach, like multiple reaction monitoring or matrix-assisted laser desorption/ionization imaging mass spectrometry) and subsequently assessing and validating differences between samples. Relative to targeted proteomic approaches, global proteomic testing is a bottom-up approach that is relatively unbiased and systematic (ie, it considers a broader range of proteins, as opposed to specific proteins that may be associated with particular types of disease or patients). This approach has particular utility for biomarker discovery or for exploring changes in protein expression related to a particular treatment or pathological state. Global proteomic testing is not used to target specific proteins related to disease processes, as the testing application relies on characterizing the global proteome of a diseased sample (Table 2). In our review, we found 72 studies (47% of studies included in our review) that used this testing strategy (Table 3).

Targeted proteomic approaches, like IVDMIAs, and several protein tests rely on a top-down approach using identified proteins or signals. Relative to global proteomic tests, these approaches are potentially more sensitive and selective. That is, some targeted proteomic technologies are able to detect low abundant proteins, which may be more difficult to quantify via global or discovery-based approaches, and they are able to focus on specific proteins that are hypothesized to be associated with particular types of disease or patient outcomes.

**IVDMIAs** involve algorithmically processing data from multiple proteins from a particular patient and creating a score to represent the likelihood that the patient has a particular diagnosis, treatment course, or prognosis. IVDMIAs are distinct from global proteomic testing in that they target specific protein profiles associated with disease risk or outcomes. IVDMIAs also characterize a wide range of proteins, but they generate algorithmically derived indexes or scores to help a clinician make a decision. These types of tests are susceptible to biases present in data used to train and develop algorithms. These applications are created to directly help clinical decision making but do not provide clinicians direct information about disease processes. IVDMIA applications operate as “black boxes,” wherein proprietary algorithms translate
proteins into manufacturer-specific indexes or scores that lead clinicians along companion decision trees. Their proprietary nature can tie clinicians to specific manufacturers and prevent the collection of generalizable knowledge about a patient’s proteome (Table 2). In our review, we found 37 studies (24% of studies included in our review) that examined IVDMIAs (Table 3).

Finally, several protein tests quantify multiple specific proteins in a patient sample, which are then used collectively to inform diagnosis, treatment course, or prognosis. Several protein testing is a simpler approach relative to IVDMIAs but builds on single protein tests (eg, prostate-specific antigen [PSA]) by combining protein quantities based on an understanding of the underlying biomedical processes of disease. However, it requires very specific protein targeting and can miss proteins in a sample if they are low in concentration or not evenly distributed within the sample (Table 2). We found 41 studies (27% of studies included in our review) that used this approach (Table 3). Two studies used multiple approaches among the testing applications described above, and 2 additional studies used some other type of approach (Table 3).

Table 2. Strengths and Weaknesses of Proteomic Testing Applications

<table>
<thead>
<tr>
<th>Application</th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global proteomic testing</td>
<td>• Covers most proteins in a sample&lt;br&gt;• Simple; no need to target specific proteins</td>
<td>• Imprecise&lt;br&gt;• Cannot target specific proteins involved in disease</td>
</tr>
<tr>
<td>IVDMIAs</td>
<td>• Creates an index or score that can sort patients into different diagnostic, treatment, or prognostic categories&lt;br&gt;• Directly contributes to decision making</td>
<td>• Tests are a black box; scores do not mean anything apart from the tests&lt;br&gt;• Algorithms are often proprietary; tests are not easily translated to a generic product</td>
</tr>
<tr>
<td>Several protein testing</td>
<td>• Relies on multiple proteins&lt;br&gt;• Easy to understand; only a few proteins are targeted&lt;br&gt;• New tests can be more quickly developed with new biomedical knowledge</td>
<td>• Requires very specific protein targeting; discovery more tightly linked to disease processes&lt;br&gt;• Easy to miss proteins if they are not evenly distributed in tissue</td>
</tr>
</tbody>
</table>

Abbreviation: IVDMIAs, in vitro diagnostic multivariate index assays.
Table 3. Characteristics of Proteomic Technology Applications in Cancer and Cardiology

<table>
<thead>
<tr>
<th>Proteomic technologies</th>
<th>Cancer (n = 128)</th>
<th>Cardiovascular disease (n = 26)</th>
<th>Total (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global proteomics</td>
<td>61 (48%)</td>
<td>11 (42%)</td>
<td>72 (47%)</td>
</tr>
<tr>
<td>IVDMIAs</td>
<td>33 (26%)</td>
<td>4 (15%)</td>
<td>37 (24%)</td>
</tr>
<tr>
<td>Several protein proteomics</td>
<td>31 (24%)</td>
<td>10 (38%)</td>
<td>41 (27%)</td>
</tr>
<tr>
<td>Other or multiple approaches</td>
<td>3 (2%)</td>
<td>1 (4%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td><strong>Processing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Algorithmic</td>
<td>77 (60%)</td>
<td>10 (38%)</td>
<td>87 (57%)</td>
</tr>
<tr>
<td>Other (eg, statistical regression)</td>
<td>8 (6%)</td>
<td>0 (4%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient clinic</td>
<td>19 (15%)</td>
<td>5 (19%)</td>
<td>24 (16%)</td>
</tr>
<tr>
<td>Offsite lab</td>
<td>7 (6%)</td>
<td>1 (4%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Onsite lab</td>
<td>17 (13%)</td>
<td>1 (4%)</td>
<td>18 (12%)</td>
</tr>
<tr>
<td>Outpatient clinic</td>
<td>1 (1%)</td>
<td>1 (4%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Other or unclear</td>
<td>84 (66%)</td>
<td>18 (69%)</td>
<td>102 (66%)</td>
</tr>
</tbody>
</table>

Abbreviation: IVDMIAs, in vitro diagnostic multivariate index assays.

In addition to the proteomic testing applications currently in clinical use, we noted when algorithmic processing was used by research teams to interpret protein biomarkers. **Algorithmic processing and machine learning** are critical platform components of next-generation proteomic testing applications, as they allow for analyses involving a large number of proteins and, potentially, other -omics and clinical information. Approximately half (n = 87; 57%) of the articles used some form of algorithmic processing to interpret protein biomarkers (Table 3).

We also sought to identify the settings in which proteomic testing applications are used. Our review found relatively few studies that analyzed protein samples within onsite laboratories (n = 18; 12%) or clinical settings (n = 24; 16%), although proteomic testing applications have broad potential for clinical uptake (Table 3). This finding has important implications given the specialized spectrometry equipment and personnel expertise needed to process next-generation proteomic testing applications.

We found 72 articles that reported the number of proteins identified by research teams as candidate biomarkers; the median number of proteins per test was 5 (range 1-85). We found 20 articles that reported only the number of spectrometry signals or peaks identified by research teams; the median number of peaks was 8 (range 1-404).
Proteomic Testing for Cancer

Our review found broad expert consensus about the potential for proteomic testing to be used to rapidly characterize an individual patient’s tumor profile and disease risk, thereby allowing for personalized treatment, improved clinical decision making, reduced toxicity, and avoidance of unnecessary care and associated costs and harms. Proteomic technology may shift care toward a temporal model in which a patient’s own baseline is used to detect changes in disease biomarkers, thereby facilitating early disease diagnosis, routine disease monitoring and management, and population-based screening via noninvasive proteomic testing (eg, salivary diagnostics). Regarding potential treatment benefits, proteomic testing may help identify new drug targets, formulate combinations of therapeutics based on an individual’s tumor profile, predict responses to therapy or radiation, and inform prognosis related to disease severity and relapse.

Proteomic Testing for Cardiovascular Diseases

Our review identified similar consensus about the potential for proteomic testing to prevent, stratify, manage, monitor, and treat cardiovascular disease. For example, tests based on proteins within plasma, atherosclerotic plaques, circulating cells and metabolites, and plasma extracellular vesicles may be used to monitor and characterize the severity of local and systemic issues following a cardiovascular disease event or be used to differentiate between types of heart failure (eg, proteomic testing has been used to distinguish between heart failure with preserved ejection fraction versus heart failure with reduced ejection fraction).
Evidence

We reviewed available evidence of the benefits and harms of proteomic applications. More specifically, we reviewed the literature to determine what evidence exists on the technical efficacy, diagnostic accuracy efficacy, diagnostic thinking efficacy, therapeutic efficacy, patient outcome efficacy, and societal/stakeholder efficacy of these applications. Our review found 154 articles examining clinical outcomes related to proteomic testing for cancer and cardiology (Table 4). We found that most studies were conducted in Europe (n = 44), followed closely by Asia (n = 51) and North America (n = 37). Most studies (n = 63) compared proteins in patients with disease against proteins in healthy patients, which suggests studies focused on identifying protein biomarkers that can be used to diagnose new cases of disease. Studies comparing patients with distinct stages of disease (n = 47) may be particularly useful in identifying protein biomarkers associated with disease severity or response to therapy. We found that the median study sample size was 87.

Table 4. Characteristics of Evidence of Proteomic Testing Applications in Literature

<table>
<thead>
<tr>
<th>Comparator arm</th>
<th>Cancer (n = 128)</th>
<th>Cardiovascular disease (n = 26)</th>
<th>Total (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients or samples with disease</td>
<td>40 (31%)</td>
<td>7 (27%)</td>
<td>47 (31%)</td>
</tr>
<tr>
<td>Healthy patients or samples</td>
<td>53 (41%)</td>
<td>10 (38%)</td>
<td>63 (41%)</td>
</tr>
<tr>
<td>No comparator</td>
<td>20 (16%)</td>
<td>4 (15%)</td>
<td>24 (16%)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (12%)</td>
<td>5 (19%)</td>
<td>20 (13%)</td>
</tr>
<tr>
<td><strong>Country or region of study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>35 (27%)</td>
<td>14 (54%)</td>
<td>44 (29%)</td>
</tr>
<tr>
<td>Australia</td>
<td>4 (3%)</td>
<td>0</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Brazil</td>
<td>2 (2%)</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Asia</td>
<td>47 (37%)</td>
<td>4 (15%)</td>
<td>51 (33%)</td>
</tr>
<tr>
<td>Africa</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Not specified or unclear</td>
<td>7 (5%)</td>
<td>0</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Middle East</td>
<td>3 (2%)</td>
<td>0</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>North America</td>
<td>29 (22%)</td>
<td>8 (31%)</td>
<td>37 (24%)</td>
</tr>
<tr>
<td><strong>Special populations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focus on women</td>
<td>33 (26%)</td>
<td>0</td>
<td>33 (22%)</td>
</tr>
<tr>
<td>Focus on racial and ethnic minorities</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Focus on uninsured individuals</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Our review found that most studies focused on diagnostic accuracy efficacy or diagnostic thinking efficacy (n = 82, with fewer studies focusing on patient (n = 45 and therapeutic (n = 16) outcome efficacy (Table 5).

These findings are consistent with prior reviews, which suggest proteomic testing is still largely focused on emerging protein biomarkers for diagnostic or prognostic purposes.\textsuperscript{36,37} Once next-generation proteomic testing gains broader clinical acceptance, we may expect to see studies examining clinical outcomes associated with proteomic testing–assisted diagnoses or treatment.

Table 5. Outcome Efficacy Type by Disease\textsuperscript{a}

<table>
<thead>
<tr>
<th>Outcome efficacy type</th>
<th>Cancer (n = 128)</th>
<th>Cardiovascular disease (n = 26)</th>
<th>Total (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical efficacy</td>
<td>12 (9%)</td>
<td>2 (8%)</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>Diagnostic accuracy efficacy</td>
<td>61 (48%)</td>
<td>12 (46%)</td>
<td>73 (47%)</td>
</tr>
<tr>
<td>Diagnostic thinking efficacy</td>
<td>8 (6%)</td>
<td>1 (4%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Therapeutic efficacy</td>
<td>16 (13%)</td>
<td>0</td>
<td>16 (10%)</td>
</tr>
<tr>
<td>Patient outcome efficacy</td>
<td>35 (28%)</td>
<td>10 (38%)</td>
<td>45 (29%)</td>
</tr>
<tr>
<td>Societal efficacy</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Other efficacy</td>
<td>0</td>
<td>2 (8%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Several articles examined multiple types of outcome efficacy. Accordingly, outcome efficacy types are not mutually exclusive.
Proteomic Testing for Cancer

Our review identified 128 articles that examined proteomic tests related to cancer (Table 6). The largest share of tests focused on digestive (n = 39), reproductive (n = 38), respiratory (n = 26), and endocrine (n = 9) cancer, and tests were spread equally between metastatic (n = 42) and nonmetastatic (n = 23) cancer.

**Table 6. Proteomic Tests by Cancer Disease Subtype and Cancer Stage**

<table>
<thead>
<tr>
<th>Cancer subtype</th>
<th>Count (n = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive</td>
<td>39 (30%)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>9 (7%)</td>
</tr>
<tr>
<td>Integumentary</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Nervous</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Reproductive</td>
<td>38 (20%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>26 (20%)</td>
</tr>
<tr>
<td>Urinary</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer stage</th>
<th>Count (n = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced/metastatic</td>
<td>42 (33%)</td>
</tr>
<tr>
<td>Both early-stage and advanced</td>
<td>31 (24%)</td>
</tr>
<tr>
<td>Early-stage/nonmetastatic</td>
<td>23 (18%)</td>
</tr>
<tr>
<td>Unclear</td>
<td>32 (25%)</td>
</tr>
</tbody>
</table>

The vast majority of published studies were related to cancer, most of which focused on diagnostic accuracy (n = 61; Figure 2). These studies demonstrated positive benefit in terms of their utility in discerning disease status or severity. In many cases, proteomic tests were shown to demonstrate greater sensitivity and specificity than did conventional diagnostic approaches. However, there appeared to be limited evidence on how these tests ultimately influence clinical practice or patient outcomes.
Figure 2. Evidence Map for Proteomic Testing Related to Cancer (n = 128)\textsuperscript{a}

\textsuperscript{a} Shapes with crosses indicate the study was missing information on the sample size. Markers are randomly positioned within each cell.
Proteomic Testing for Cardiovascular Diseases

Our review identified 26 articles examining proteomic tests related to cardiovascular disease. The largest shares of these tests focused on heart failure (n = 6) and general cardiovascular disease (n = 5), and tests were spread equally between new (n = 9) and recurring (n = 10) cardiovascular disease (Table 7).

Table 7. Proteomic Tests by Cardiovascular Disease Subtype and Recurrence Status

<table>
<thead>
<tr>
<th>Cardiovascular disease subtype</th>
<th>Count (%; n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General cardiovascular disease</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6 (23%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Multiple</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (38%)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular disease recurrence</th>
<th>Count (%; n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New disease</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>Recurring disease</td>
<td>10 (38%)</td>
</tr>
<tr>
<td>Unclear</td>
<td>7 (27%)</td>
</tr>
</tbody>
</table>

As with cancer, our findings suggest the vast majority of published studies related to cardiovascular disease demonstrate benefits in terms of their utility in discerning disease status or severity, particularly for diagnostic accuracy (n = 12; Figure 3). In many cases, proteomic tests were shown to demonstrate greater sensitivity and specificity than did conventional diagnostic approaches.
Figure 3. Evidence Map for Proteomic Testing Related to Cardiovascular Disease (n = 26)\textsuperscript{a}

\textsuperscript{a} Markers are randomly positioned within each cell. Regarding cardiovascular disease type, “Other” refers to studies that addressed another subindication within cardiovascular disease, and “Multiple” refers to studies that addressed more than one subindication within cardiovascular disease.
Potential Near-Term Applications

In addition to assessing the evidence on existing proteomic testing applications, we also attempted to determine which applications, if any, are currently being evaluated with new research or are otherwise being developed that may be adopted into clinical care in the next 5 years. Our review suggests that, in addition to the 154 studies included in our review that demonstrate clinical utility, an additional 1200 studies propose novel protein biomarkers and promising candidate biomarkers with adequate sensitivity and specificity. However, our review found only 17 studies that evaluated commercially available proteomic tests in terms of improved disease diagnosis, prognosis, and prediction relative to existing standards of clinical practice (eg, conventional immunoassays or diagnostic imaging). Of those, 14 studies focused on VeriStrat, a proteomic test for non–small cell lung cancer. The remaining 3 focused on Biodesix’s BDX008, Integrated Diagnostic’s Xpresys Lung 2 (acquired in 2018 by Biodesix), and Provista’s Videssa Breast. Accordingly, our review found limited evidence of proteomic testing applications that are likely to be widely adopted in the near future. Although a variety of single protein markers have received FDA approval, relatively few can be classified as next-generation proteomic testing applications. Examples of FDA-cleared/approved and promising commercially available proteomic testing application are provided in Table 8. In addition, clinical coverage policies from major insurers, like Aetna, Cigna, and Blue Cross Blue Shield affiliates, indicate that proteomic testing applications are still largely considered experimental or investigational, with 2 exceptions (ie, for some insurers, VeriStrat meets the standard for medical necessity for advanced non–small cell lung cancer and OVA1 meets the standard for medical necessity for ovarian cancer).38-40

---

10 See Appendix E for additional details on the list of novel protein biomarkers and promising candidate biomarkers.
11 We identified relatively few tests with FDA approval during the review; however, we do note that FDA approval is not required to employ proteomic testing, though laboratories performing any protein testing are required to have a CLIA Certificate of Waiver to ensure testing standards.38
Table 8. FDA-Cleared/-Approved and Commercially Available Proteomic Testing Applications\(^a_b\)

<table>
<thead>
<tr>
<th>FDA-cleared/approved proteomic testing applications</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA1(^b); IVDMIA</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Ovarian Malignancy Risk (ROMA(^®); IVDMIA)</td>
<td>Ovarian cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Commercially available proteomic testing applications, not yet FDA-cleared/-approved</th>
<th>Potential Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>VeriStrat</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>Xpresys Lung 2</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>IMMray™ PanCan-d</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>BDX-XL2</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Nodify XL2</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>ProMark Proteomic Prognostic Test</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>4Kscore</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>OvaCheck</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Olink Proteomics CVD II and CVD III</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Prevencio HART</td>
<td>Peripheral artery disease</td>
</tr>
<tr>
<td>GPS Cancer</td>
<td>Non-small cell lung cancer</td>
</tr>
</tbody>
</table>

\(^a\) The table lists examples of FDA-cleared/approved and commercially available proteomic testing applications that are not yet FDA-cleared/-approved, but are conducted in a CLIA-certified laboratory, and the indication for which the test would be used. As noted, major insurers largely consider these applications to be experimental or investigational in their clinical coverage policies with few exceptions. Although payers may label applications that are not yet FDA-cleared/-approved as investigational, they are still available commercially.

\(^b\) In 2011, the FDA issued a black box safety warning regarding OVA1: “The OVA1™ Test should not be used without an independent clinical/radiological evaluation and is not intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of the OVA1™ Test carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.”\(^14\)

A review of industry trade articles supports our findings in the peer-reviewed literature—although there are at least 13 potentially promising commercial tests (Table 8), there is limited evidence of the near-term broad adoption of new proteomic testing applications. We identified 99 industry trade articles published within the past 24 months (June 1, 2018, to June 1, 2020) related to proteomic testing in cardiology and oncology. Of these, 68 articles focused on market forecasts. Although projections vary, recent forecasts suggest the global proteomic market is expected to grow significantly in coming years to $24 billion by 2024 and $27 billion by 2026.\(^41,42\) These projections are attributed to recent technological advances in mass spectrometry and the potential for proteomic testing to respond to growing health care needs, including chronic disease management, early-stage disease monitoring and prognosis, detection of infectious disease outbreaks, and personalized medicine.\(^41,42\) Of the 28 trade industry articles
related to specific tests or platforms, several were related to existing proteomic testing applications, like Biodesix’s VeriStrat, or emerging tests and platforms from MRM Proteomics (eg, an article describing a tool for predicting therapeutic response based on patient tumor registry information), Prevencio, Inc (eg, an article about an artificial intelligence-based tool for diagnosing peripheral artery disease), and Seer (eg, an article about a novel liquid biopsy platform that includes algorithmic processing).43-45

Synthesis of Key Informant Observations

Our interviews with key informants provided context for the near future of proteomic testing in cardiology and oncology and the lack of evidence in the literature for forthcoming tests. In line with what we found in the industry trade publications, one informant anticipated significantly more mass spectrometry markers will be deployed in the next 5 years for proteomic testing in general, of which most will be protein markers. In this informant’s view, the expectation within the field of proteomics is that single protein markers will dominate development efforts because they are directly connected to the disease. With that type of connection, clinicians should be able to use tests to identify patients who are most at risk of disease progression and negative disease outcomes. Another informant shared that cardiology could use more early detection markers to facilitate a better selection of therapies, as existing capabilities do not provide adequate risk assessments for myocardial infarction and stroke. Yet another informant discussed the possibility of advancements in blood plasma analysis, urine and spinal fluid analysis, and tissue analysis over the next 5 years. However, these advancements are expected to occur within research studies, which might have long-term impacts on testing deployment but are unlikely to lead to approved and available testing within the next 5 years. Another key informant noted that a substantial amount of preclinical research on proteomic biomarkers is occurring, but that research has not yet moved into clinical practice. Moreover, clinical trials are not reporting efficacy for these tests. When considering the 2 fields, informants asserted that near-term developments were much more likely in oncology than cardiology due to the heterogeneity of cardiovascular diseases. Nevertheless, this heterogeneity does not deter scientists from pursuing discoveries in proteomic testing for cardiology; one informant detailed research on tests that would differentiate thrombotic versus nonthrombotic myocardial infarction and on health surveillance markers that would allow monitoring a patient after heart failure or after heart transplantation. The general sense from informants was that proteomics was on the precipice of significant developments, as found in our review of the gray literature, though widespread clinical use of proteomic tests was further out than 5 years.
Facilitators and Barriers to Testing Uptake

Our review identified several important technical, methodological, and practical barriers that may limit the uptake of proteomic tests in clinical settings. First, many proteomic studies have important technical limitations related to disease heterogeneity that constrain the efficacy of proteomic tests in terms of sensitivity and specificity. The magnitude of the challenge posed by these barriers is significant but may be addressed through continued technological improvements in sample preparation, mass spectrometry, and validation technologies. For example, abundant proteins may mask or make it difficult to detect rare proteins associated with disease, particularly early-stage disease. Protemic testing is also vulnerable to biological variability in terms of blood biomarker concentration and tumor heterogeneity, and digested protein fragments may match multiple proteins, which may trigger false positives. Other technical challenges may be addressed through more robust study designs. For example, proteins may be surrogates for risk factors, not diagnostic of a particular disease, and may therefore have limited utility in populations at low risk for a particular disease.

In addition to technical issues, there are a variety of methodological challenges. For example, given the focus on biomarker discovery, many studies tend to lack a narrowly focused clinically motivated research question, and studies are typically conducted in small cross-sectional samples. Many studies do not report important demographic information or patient clinical indexes, which may have significant implications for protein and disease signatures. In particular, the dearth of demographic data makes it difficult to determine if the results are generalizable to less-represented populations. Many challenges are related to proteomic testing platforms themselves—that is, there is variation in the sensitivity and specificity of competing platforms, and there is a lack of standardization in terms of techniques, workflows, and sample collection, storage, handling, and profiling between laboratories, all of which are important given the uniquely sensitive nature of proteins. These challenges were also cited by our key informants in discussions about barriers to development and uptake. Some of these issues could be addressed through improved coordination between research funders, laboratories, and researchers and reporting standards for journals and trials.

Finally, there are several practical challenges related to the acceptability and cost of proteomic testing applications. Our review suggests clinical proteomics may be perceived skeptically among clinicians given high expectations and the limited number of biomarker candidates that have been successful, particularly in fields outside oncology. Proteomic testing may be out of reach for health care organizations with limited resources—that is, it requires expertise, specialized staff, and technology related to bioinformatics, computational biology, next-generation mass spectrometry, testing platforms, and complex bioinformatic algorithms. For example, studies may require robotic systems to standardize sample preparation and multiple mass spectrometry instruments, which may be out of reach for most institutions. The significant costs associated with both the development and adoption of proteomic testing in clinical settings were also raised during informant interviews. In particular, one informant noted how the intersection of the funding landscape and the length of development time has posed challenges for getting the necessary support for development and trials. However, mass spectrometry–based multiple reaction monitoring (MRM) tests are already used in clinical settings and multiple
CLIA-approved tests are used for diagnostic purposes. Although our review identified few studies examining the cost or acceptability of proteomic tests, these issues were frequently highlighted as potential challenges in reviews and expert commentaries.

These types of technical and practical barriers to clinical adoption are similar to those that are experienced in multiomic testing (eg, genomics, epigenomics, transcriptomics). Clinicians often lack the knowledge, access to data, and resources to use multiomic data in regular clinical care. Further, multiomic testing is often not easily integrated into clinical practice, as changes in clinical decisions from a particular test or result are not obvious. Surveys of physicians indicate a range of experiences and confidence in the adoption of genetic medicine into clinical practice. In a survey of 285 physicians who work at institutions funded by IGNITE (Implementing GeNomics In pracTicE), most participants stated that genetic testing was useful, but that it would not change their ability to care for patients. Physicians at sites focused on disease risk genetics also did not feel the information would change their care. In contrast, most physicians involved in pharmacogenetic programs reported that genetic testing would change their ability to care for patients. And, like proteomic testing, cost acts as a barrier to physician uptake, as there is often a lack of reimbursement for testing by payers.

---

12 IGNITE is the genomic medicine implementation initiative developed by the National Institutes of Health.
Efficacy of Proteomic Testing

Our review found that most articles related to proteomic testing applications in cancer and cardiovascular disease focused on diagnosing accuracy efficacy (n = 73), or level 2 on Peng’s adaptation of Fryback and Thornbury’s framework for genomics- and proteomics-based testing (Figure 4). Based on our review, clinical proteomic research in cardiology and oncology focuses on the reliability and accuracy of proteomic testing, which has important implications for its ability to facilitate appropriate diagnosis, prognosis, and delivery of effective care. A sizable share of articles addressed patient outcome efficacy (ie, level 5 of the framework), including studies examining the utility of proteomic tests in predicting survival or disease recurrence. Of the 45 articles that addressed patient outcome efficacy, 10 were trials with clinical end points related to cancer (eg, disease-free survival, recurrence) and 1 was a trial with clinical end points related to cardiovascular disease (eg, cardiovascular events, heart failure, mortality). Only one article addressed societal efficacy, as represented in level 6 of the framework; it found that use of a proteomic test (VeriStrat) for treatment selection increased survival and decreased drug acquisition, surveillance, and administrative costs. These findings suggest that studies of proteomic testing applications in cardiology and oncology are still relatively nascent.

*Figure 4. Application of Fryback and Thornbury Framework to Genomics and Proteomics-Based Testing With Article Counts*

| Level 6: Societal efficacy — Cost-effectiveness of test as measured from societal perspective | n = 1 (1%) |
| Level 5: Patient outcome efficacy — Number of deaths prevented or change in quality of life | n = 45 (29%) |
| Level 4: Therapeutic efficacy — Percentage of time that therapy planned before diagnostic is altered by results | n = 16 (10%) |
| Level 3: Diagnostic thinking efficacy — Estimated probability of diagnostic before versus after results | n = 9 (6%) |
| Level 2: Diagnostic accuracy efficacy — Sensitivity, specificity, and other measures | n = 73 (47%) |
| Level 1: Technical efficacy — Reliability of proteomics technology | n = 14 (9%) |

*a Several articles examined multiple types of outcome efficacy. Accordingly, outcome efficacy types are not mutually exclusive. Due to this overlap, percentages may not add up to 100%.*
Proteomic Testing for Cancer

Of the 128 articles related to cancer, 111 demonstrated positive clinical utility (ie, the test had greater sensitivity or specificity compared with alternative approaches or was able to predict disease diagnosis, prognosis, patient outcomes, or response to therapy). Although the degree of utility varied, particularly when compared with conventional diagnostic or prognostic approaches, these findings highlight the clinical potential of proteomic testing in cancer. Most articles included in our review focused on diagnostic accuracy, followed closely by articles examining the utility of proteomic testing applications in terms of patient outcomes. Only one article related to cancer addressed societal, population-level, or health care system benefits.

Proteomic Testing for Cardiovascular Diseases

Similarly, of the 26 articles related to cardiology, 18 demonstrated positive clinical utility. As with cancer, the degree of utility varied, particularly when compared with conventional diagnostic or prognostic approaches. Most articles related to cardiology focused on diagnostic accuracy (n = 12) or patient outcome efficacy (n = 10). No articles related to cardiology addressed societal, population-level, or health care system benefits.
Evidence Gaps and Future Research

Our review suggests that there are several gaps in the evidence base for proteomic testing for cancer and cardiovascular disease (Table 9). To address those gaps, future research on proteomic testing applications for cardiology and oncology may benefit from focusing on higher levels of the Fryback and Thornbury framework, such as diagnostic thinking, patient outcome, therapeutic, and societal efficacy, in addition to existing cutting-edge research on biomarker discovery. Accordingly, proteomic researchers and funders might consider shifting toward research on clinical utility and validation, particularly for innovative clinical uses, and investments in critical research infrastructure, like comprehensive biobanking and bioinformatic infrastructure (Table 9).
Table 9. Overview of Evidence Gaps and Future Research in Proteomic Testing for Cancer and Cardiovascular Disease

<table>
<thead>
<tr>
<th>Evidence gaps</th>
<th>Future research</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical utility and uptake</strong></td>
<td>• Compare patient outcomes between interventions using proteomic tests against interventions using existing gold standards.</td>
</tr>
<tr>
<td>• Validate proteomic tests in clinical contexts.</td>
<td>• Evaluate the cost-effectiveness of novel assays.</td>
</tr>
<tr>
<td>• Establish the accuracy of commercially available platforms.</td>
<td>• Explore strategies to integrate novel assays into existing clinical workflows.</td>
</tr>
<tr>
<td>• Focus on racial and ethnic minorities and the uninsured.</td>
<td>• Examine the utility of noninvasive sampling techniques to avoid unnecessary treatments.</td>
</tr>
<tr>
<td>• Compare patient outcomes between interventions using proteomic tests against interventions using existing gold standards.</td>
<td>• Prioritize racial and ethnic minorities in trial recruitment, biobanks, and databanks.</td>
</tr>
<tr>
<td>• Evaluate the cost-effectiveness of novel assays.</td>
<td>• Ensure controls are appropriately matched in terms of race, ethnicity, or ancestry.</td>
</tr>
<tr>
<td>• Explore strategies to integrate novel assays into existing clinical workflows.</td>
<td>• Report relevant geographic, cultural, social, environmental, or epidemiological risk factors in analyses.</td>
</tr>
<tr>
<td>• Examine the utility of noninvasive sampling techniques to avoid unnecessary treatments.</td>
<td>• Explore economic impact and patient acceptability of proteomic testing in diverse health care organizations and populations.</td>
</tr>
<tr>
<td><strong>Infrastructure investments</strong></td>
<td>• Develop and validate risk stratification software that integrates imaging, -omics data, and pulmonary function tests.</td>
</tr>
<tr>
<td>• Invest strategically in research, bioinformatic, and -omics infrastructure and tools.</td>
<td>• Combine proteomic data with genomic, epigenomic, histopathologic, and transcriptomic data, as well as other data sources.</td>
</tr>
<tr>
<td>• Adopt novel collaborative approaches and testing standards.</td>
<td>• Leverage larger samples, prospective cohorts and therapeutic trials, and longitudinal designs, and include geographically and demographically diverse patients.</td>
</tr>
<tr>
<td>• Train and assemble interdisciplinary research teams that collaborate with diagnostic and pharmaceutical companies.</td>
<td>• Train and assemble interdisciplinary research teams that collaborate with diagnostic and pharmaceutical companies.</td>
</tr>
<tr>
<td>• Encourage standard operating procedures, quality assurance and control, and test validation methods.</td>
<td>• Encourage standard operating procedures, quality assurance and control, and test validation methods.</td>
</tr>
<tr>
<td>• Standardize reporting of candidate biomarkers, methods, quality control, and workflow procedures.</td>
<td>• Standardize reporting of candidate biomarkers, methods, quality control, and workflow procedures.</td>
</tr>
</tbody>
</table>

*a The table lists perceived needs for research on proteomic testing for cancer and cardiovascular disease based on evidence gaps in the literature. It also offers potential research topics that could help address the identified gaps.*
Future Research on Clinical Utility and Uptake

We evaluated clinical utility and efficacy in terms of potential benefits for patients, clinicians, health care organizations, and other stakeholders regarding disease detection, diagnosis, prognosis, and treatment. Per Peng’s adaptation of Fryback and Thornbury’s framework, we sought to understand whether novel proteomic tests were perceived by researchers as being beneficial or superior to conventional diagnostic and therapeutic tests in terms of technical, diagnostic accuracy, diagnostic thinking, patient outcome, therapeutic, and societal efficacy. Although our review found evidence that supports the utility of proteomic testing in improving the accuracy of disease diagnosis, there remain important evidence gaps about the direct link between proteomic testing and improvements in patient outcomes and broader issues, like the potential for proteomics to be incorporated into routine clinical practice.

The limited number of studies focused on racial and ethnic minorities and the uninsured are consistent with earlier studies on the underrepresentation of racial and ethnic minorities in research on -omics and personalized medicine. To address this critical gap in proteomics and -omics more broadly, researchers and their funders might consider prioritizing racial and ethnic minorities in trial recruitment, biobanks, and databanks; ensuring controls are appropriately matched in terms of race, ethnicity, or ancestry; reporting relevant geographic, cultural, social, environmental, or epidemiological risk factors in analyses; and exploring the economic impact and patient acceptability of proteomic testing in diverse health care organizations and populations.

Based on our analysis of reviews and expert commentaries, there is particular interest among researchers in validating proteomic tests in clinical contexts and establishing the accuracy of commercially available platforms for the purpose of distinguishing between disease subtypes, determining disease aggressiveness and severity, and predicting patient response to treatment, particularly in cases of drug or radiation resistance. Research should also address barriers to clinical uptake and explore strategies to integrate novel assays into existing clinical workflows. For example, future research might assess whether novel proteomic tests improve patient outcomes when compared to existing diagnostic and therapeutic tests. Research funders interested in population health outcomes may be particularly interested in studies that examine the utility of noninvasive sampling techniques that could be used for preventive screening and prognostic biomarkers to avoid unnecessary treatment for patients with low-risk tumors or to appropriately stratify/classify patients.

Future Research Infrastructure Investments to Accelerate Progress

To achieve these gains in clinical utility, researchers and funders might consider strategic investments in research, bioinformatic, and -omics infrastructure and tools. For example, future research could develop and validate risk stratification software that integrates imaging, -omics data, and pulmonary function tests to provide more comprehensive information about early diagnosis, disease susceptibility, staging, disease monitoring, and personalized treatment. Future analyses might also combine proteomic data with genomic, epigenomic, histopathologic, and transcriptomic data, as well as data from clinical imaging, electronic health records, smartphones and personal monitors, and other data sources that characterize demographic and lifestyle risk factors. For example, a recent funding opportunity announcement from the...
National Institutes of Health (PAR-19-377: Omics-Guided Biobehavioral Interventions for Improved Health Outcomes: A Step Forward in Translation) encourages studies that integrate -omics data to inform biobehavioral interventions. Algorithmic and machine learning approaches will be key to processing these distinct and large volumes of data.29,30,68 Researchers could design studies differently to address methodological limitations and develop novel collaborative approaches. For example, researchers could leverage larger sets of samples and include geographically and demographically diverse patients who may be at risk for disease as study controls rather than include healthy controls.28,29,48,49,56

Finally, to improve the quality of proteomic research for clinical utility, researchers, funders, and laboratories might consider adopting novel collaborative approaches and testing standards. To accelerate progress, future -omics research endeavors could train and assemble research teams that include bioinformatic specialists, clinicians, data science researchers, and researchers with expertise in proteomics, as well as collaboration between diagnostic and pharmaceutical companies.49,69,71 Funders, regulators, and laboratories might consider encouraging standard operating procedures and quality assurance and control, and focus on test validation methods with appropriate study governance.37,56,72 Similarly, investigators could be encouraged to report candidate biomarkers, methods, quality control, and workflow procedures in a more standardized manner.46,47,73,74
Conclusion

The promise of more precise risk assessment, diagnosis, and prognosis of disease has created significant interest in clinical proteomics and its current and future capabilities. To address that interest, this report has provided a comprehensive overview of the existing evidence base, as well as knowledge gaps, for current and near-term proteomic testing applications for cancer and cardiovascular disease.

Our review found that most studies related to proteomic testing applications in cancer and cardiovascular disease focused on diagnostic accuracy efficacy and patient outcome efficacy. Our findings suggest proteomic testing shows promise for improving disease diagnosis and prognosis, and the delivery of effective care. Regarding innovative use cases, proteomic testing may be particularly useful for early disease diagnosis, routine disease monitoring and management, population-based screening via noninvasive proteomic testing, identification of new drug targets, identification of therapeutics based on an individual’s tumor profile, prediction of patient responses to therapy or radiation, and prediction of patient prognosis related to disease severity and relapse.

Our analysis identified several barriers that may limit the uptake of proteomic tests in clinical settings. For one, study designs and platforms have methodological limitations, such as lack of reporting of important demographic information or patient clinical indexes that may have significant implications for protein and disease signatures. Moreover, there is variability in the sensitivity and specificity of competing proteomic testing platforms, as well as a lack of standardization in terms of techniques, workflows, and sample collection, storage, handling, and profiling between laboratories. These technical issues further constrain the effectiveness of proteomic tests in terms of sensitivity and specificity, and they engender practical challenges such as the significant costs associated with test development and deployment and skepticism from clinicians. Consequently, proteomic testing may be out of reach for health care organizations with limited resources. Our analysis also validates earlier work on the underrepresentation of racial and ethnic minorities in research on personalized or precision medicine.

Based on the evidence presented, we have offered several suggestions for future research topics on proteomic testing applications for cardiology and oncology that could focus on diagnostic thinking, patient outcome, therapeutic, and societal efficacy, as defined in Peng’s adaptation of the Fryback and Thornbury framework. For example, proteomic research stakeholders could invest in cutting-edge discovery and clinical validation research, develop proteomic research infrastructure, train and assemble interdisciplinary research teams, and/or adopt standard operating and reporting procedures to accelerate progress in development and clinical uptake. Researchers and their funders might also consider a range of efforts to prioritize racial and ethnic minorities in study design, execution, and reporting. Finally, to improve the quality of proteomic research for clinical utility, researchers, funders, and laboratories might consider adopting novel collaborative approaches and testing standards. In addition to framing research on proteomic testing, this analysis can serve as a foundation for pursuing specific research questions about the state of proteomic testing that could be addressed in more targeted future syntheses.
References

Where possible, we have included direct links to the full text articles or have included the PubMed ID (PMID) for further information. The PMID is the record number in the free search engine PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) that contains more information on the publication.


Appendix A. Stakeholder and Key Informant Interviews

Interviews

We conducted key informant interviews to gather detailed information about proteomics in general and current proteomic tests in cardiology and oncology from a variety of perspectives. The purpose of the interviews was to collect perspectives from patients and patient advocates, clinicians, payers and insurers, and public policymaker representatives. The goal was to ensure that perspectives of different stakeholders had been considered and were reflected in the research approach. Our application to RAND’s Human Subjects Protection Committee (HSPC: 2020-0461) was initially approved for exempt status on June 3, 2020, and reapproved with amendment (HSPC: 2020-0461-AM01) to allow for the possibility of audio recording on July 1, 2020.

Recruitment

We developed a list of key informants and organizations in consultation with PCORI and the expert advisors working with the research team, in addition to our own efforts to identify members of the selected stakeholder groups. Due to the scope of the project, we prioritized contacting a few potential informants in each stakeholder category in the initial phase. We emailed invitations to the identified individuals and organizations soliciting their participation in interviews. These emails included a 2-paragraph English-language lay description of the project. We informed individuals that we were inviting them to participate in the project because of their experience with and/or expertise in proteomic testing (as a patient or patient advocate, clinician, payer or insurer, or public policymaker representative, depending on the interviewee), and asked if they would be interested in participating. If they were unavailable, we asked them to recommend for participation other experts with relevant experience. When contacting organizations, we first emailed a listed point-of-contact to request assistance in identifying members of the organization who might be interested in participating based on their experience and expertise and the project description. If we could not reach a key informant or the informant declined to participate, we returned to our list to identify an alternate participant for the next phase of invitations.

We initially identified 29 potential interviewees, of whom we contacted 15: 7 clinicians, 1 patient and patient advocate, 2 payers/insurers, and 5 public policymaker representatives. Among those we contacted, 3 clinicians, 1 patient advocate, 1 payer/insurer, and 1 public policymaker representative participated.

Procedure

We conducted the semistructured interviews using Microsoft Teams software, allowing for participants to call in as needed. Interviews lasted approximately 1 hour. We relied on the interview protocol developed by the research team to guide the discussion over the course of the interview with each individual. The protocol provided a set of questions that had been shared with each interviewee in advance of the meeting, though participants had the opportunity to depart from the questions to expand on relevant topics. We designed the interview questions for a wide set of stakeholder perspectives; therefore, not all of the questions listed in the protocol were relevant to each participant. We encouraged interviewees to note if any question was not...
relevant to their experience or expertise. Direct and follow-up questions were adapted based on the participant’s relation to the identified stakeholder groups.

The intent of the informant interviews was to effectively gather current and detailed information about proteomic testing and its use in treating cancer and cardiovascular disease. We were particularly interested in stakeholders’ identification and discussion of important issues raised by proteomic testing. Our aim was to combine research from our narrative review with information shared in the key informant interviews from a range of stakeholders (patients/patient advocates, clinicians, payers/insurers, and public policymaker representatives), especially to identify any research gaps that must be addressed for advancements in proteomic testing. To that end, we asked interview questions that solicited information about the regulatory, clinical, and systems contextual issues related to the use of proteomic testing for cancer and cardiovascular disease and that helped us identify current applications and potential interventions under development and any barriers or facilitators to testing uptake.

_Informed Consent Protocol_
Interview participants read the below information in advance of the interview.

**Research Description**
Proteomics involves the applications of technologies for the identification and quantification of overall proteins present in a cell, tissue, or organism. Proteomics-based technologies are used in various capacities for different research settings, such as in the detection of diagnostic markers and in the interpretation of functional protein pathways in different diseases. Proteomics can provide significant biological information for many problems; for example, testing can be done to determine which proteins interact with a particular protein of interest in tumor suppression.

The goal of this study is to use an evidence map format and landscape review to describe the current evidence base for proteomic testing in cardiology and oncology. Evidence maps provide a visual overview of a research area by communicating the results along multiple dimensions. Each evidence map will include a central figure that visualizes the state of the research in this area. As part of the work of building the evidence maps, we are conducting key stakeholder interviews to gather detailed information about proteomic testing in cardiology and oncology from a variety of perspectives, as informative research questions need to consider a range of stakeholders. In particular, clinicians and policymakers should not be solely responsible for selecting patient-centered outcomes; patients should be engaged in the research process as well. Our key informant interviews include a range of participants, from patients or patient advocates to clinicians, payers/insurers, and public policymaker representatives. The goal is to ensure that our research approach considers and reflects the perspectives of different stakeholders. This project is supported by the Patient-Centered Outcomes Research Institute (PCORI) and facilitated by the RAND Corporation.

**Risks and Benefits**
There are no known risks related to participation in this study. Participants were selected based on our understanding of your experience and/or expertise related to this research area, and you will be asked questions within the scope of that experience and/or expertise. During the interview, if a question is not applicable to you or you feel uncomfortable answering, you may decline to answer. The project aims to improve our understanding of the use of proteomic testing in cardiology and oncology, as well as to help the research team identify new advancements or forthcoming developments in proteomic testing that may become available in the next 5 years.
As such, this report will be a critical means to spread knowledge that will benefit patients, researchers, and practitioners.

**Duration**
Your participation will last about an hour.

**Participation and Withdrawal**
Participation in this study is entirely voluntary. You have the right not to participate at all or to end the interview at any time. You may also decline to answer any questions that you do not want to answer and still remain in the study. Deciding not to participate or choosing to leave the study will not result in any negative consequences.

**Audio Recording**
This study involves the audio recording of your interview with the researcher(s). Neither your name nor any other identifying information will be associated with the audio recording or the transcript. Only the research team will be able to listen to the recording. The recording will be transcribed by the research team and erased once the transcriptions are checked for accuracy. Transcripts of your interview may be reproduced in whole or in part for use in presentations or written products that result from this study. Neither your name nor any other identifying information (such as your voice) will be used in presentations or in written products resulting from the study. Immediately following the interview, you will be given the opportunity to have the tape erased if you wish to withdraw your consent to taping or participation in this study.

**Confidentiality**
Your name will not be linked to your interview responses in any feedback of results to the group, and your name and your responses will not be stored together. Your interview responses will be kept confidential. Study results will be accessible only to the research team. Interview responses and discussion points will be documented in aggregate form across participants. You will be asked for consent to be acknowledged as a key stakeholder in future publications describing the results of the project.

**Contact Information**
If you have questions about this research, please email Dr Patricia Stapleton (pstatlet@rand.org) or Dr Sameer Siddiqi (ssiddiqi@rand.org). If you have questions about your rights as a research participant or need to report a research-related injury or concern, you can contact RAND’s Human Subjects Protection Committee toll-free at (866) 697-5620 or by emailing hspcinfo@rand.org. If possible, when you contact the Committee, please reference Study # 2020-0461.

**Consent**
Your consent to participate in this project will be implied by selecting the option, “Yes, I consent to participate in this study (proceed with the interview)” and by participating in the interview.
**Interview Guide**

**Introduction**

**Brief Project Overview**

**Review of Completed Consent Protocol**

**Questions for Discussion**

**Review Questions**

1. Please share a brief overview of your experience with proteomic testing related to [oncology/cardiology]. To what extent are members of your organization/community aware of proteomic testing?

2. Are there interventions (either FDA-approved or those with a CLIA waiver) missing from our preliminary search strategy?

3. Which clinical effectiveness outcomes should be assessed when evaluating the effects of proteomic testing?

4. Which adverse events should be assessed when evaluating the effects of proteomic testing?

5. In your opinion, are there other outcomes that should be assessed?

6. What is an appropriate follow-up time frame for the assessment?

**Proteomic Efficacy Questions**

7. How would you define the *efficacy* of proteomic testing?

   *Potential prompt:* Some common definitions of proteomic efficacy include:

   a. Technical efficacy: do tests from different manufacturers predict the same results for the same patients?

   b. Diagnostic accuracy efficacy: do tests measure what they intend to measure (e.g., sensitivity, specificity)?

   c. Diagnostic thinking efficacy: do clinicians change their diagnoses with tests results?

   d. Therapeutic efficacy: do test results alter therapeutic decisions?

   e. Patient outcome efficacy: do test results improve patient outcomes?

   f. Societal efficacy: do proteomic tests have positive impact on societal costs and outcomes?

8. Which of these types of efficacy are most important in determining the “overall” efficacy of proteomic testing? Why?

**Patient-Focused Questions**

9. What effect would increased uptake of proteomic testing have on your organization/community?

10. What information is important to patients that has perhaps not been the focus of expert discussions or in existing research?

11. What are the decisional dilemmas for patients?
Stakeholder-Focused Questions
12. What considerations will help key stakeholders to decide the value of a proteomics test?
   
   Potential prompts:
   
a. What practices or factors might facilitate the uptake of proteomic testing within your organization/community?

b. What practices or factors might hinder the uptake of proteomic testing within your organization/community?

13. Our evidence map can display only a limited number of dimensions to establish a picture of the existing evidence base. Using the draft example, which dimensions do you think are critical to display (e.g., number of patients, number of successful tests, study design distribution, replication by independent researchers, clinical effectiveness, severity of adverse events, costs, quality of evidence across studies)?

Advances in Proteomic Testing
14. How might proteomic testing be deployed within the next 5 years to advance patient care in oncology and cardiology?

15. Without revealing any proprietary information that you might know, please share which tests will be adopted into clinical care within the next 5 years.

16. What are the major facilitators and barriers for advancement in proteomic testing?
   
   Potential prompt: How might contextual issues related to regulation, clinical practice, or systems might affect how your organization/community thinks about proteomic testing?

Impacts of Proteomics
17. What, if any, ethical dilemmas should be discussed regarding proteomic testing?

The Future of Proteomics
18. What are the major hopes for proteomic applications?

19. What are the major gaps in understanding that need to be addressed to improve the development of FDA-approved or CLIA-waivered proteomic testing?

20. What suggestions do you have to bring more approved proteomic testing from bench to bedside?

21. Are any other important characteristics of patients, care, or systems addressed by proteomic testing that should be highlighted?

Interview Data Collection and Analysis Strategy
We conducted interviews using the Microsoft Teams application, which allowed external participants to call in to the interview by phone, if needed. At least 2 researchers participated in each interview: one served as the interview lead, while the other served as a note taker. Results of the interviews were documented in aggregated and deidentified format. We performed an initial review to evaluate the responses in the context of revising our narrative review protocol and to determine whether any unanticipated themes had emerged. We found that our interview questions provided 3 general categories for coding (methods review, stakeholder interests, and impacts and future of proteomic testing).

Because the goal of these informant interviews was to ensure that perspectives of different stakeholders were considered and reflected in the research approach, we grouped responses...
related to the review of our protocols and framework together for analysis (Questions 2-8 and 13 in the protocol). These questions explicitly asked participants to consider earlier drafts of our protocols and provide feedback on our search terms and strategies, as well as insight into defining efficacy, outcomes, and adverse events. The relevant information from the interview responses in this category were discussed among the project leads and with PCORI. The responses informed our search parameters, sources, and terms, allowing us to refine our methodological approach for the narrative review to ensure that it was comprehensive and representative of the literature.

We also analyzed the content of the interviews by coding responses according to other topics addressed. For this step, we grouped together questions on patients’ and other stakeholders’ interests (Questions 2 and 9-12 in the protocol). We separately considered responses to our questions on the impacts and future of proteomic testing (Questions 14-21 in the protocol). Both categories provided a broader context to the results from the narrative review, more detail on existing tests and the technologies, insight into how we should evaluate the evidence, and a better understanding of what efficacy would look like in practice for each of the categories in the adapted Fryback and Thornbury framework. Though the primary aim of the informant interviews was to shape the narrative review protocol, the additional context provided from these discussions for interpreting our findings is noted, where relevant, in the report.
Appendix B. Search Strategies

Published Literature

PubMed: Trials Search

Filters applied: English Language; Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Randomized Controlled Trial, English; 2000-present

Search run: July 22, 2020

AND
AND

Embase: Trials Search

Filters applied: English Language; Randomized Clinical Trial; Controlled Clinical Trial; Human

Search run: 22 July 2020

'proteome'/exp/mj OR 'proteomics'/exp/mj OR proteome:ti,ab OR proteomes:ti,ab OR proteomic:ti,ab OR proteomics:ti,ab OR proteogenomic*:ti,ab
AND
'neoplasm'/exp/mj OR neoplasm*:ti,ab OR oncology:ti,ab OR cancer*:ti,ab OR leukemia:ti,ab OR carcinoma:ti,ab OR sarcoma:ti,ab OR adenocarcinoma:ti,ab OR 'cardiovascular disease'/exp/mj OR "cardiovascular disease*":ti,ab OR "heart disease*":ti,ab OR "vascular disease*":ti,ab OR cardiomyopathy*:ti,ab OR "atrial fibrillation":ti,ab OR atherosclerosis:ti,ab OR myocarditis:ti,ab OR "myocardial infarction*":ti,ab OR arrhythmias:ti,ab OR "heart
failure":ti,ab OR aneurysm*:ti,ab OR stroke:ti,ab OR "coronary artery disease*":ti,ab OR "angina pectoris":ti,ab OR "acute coronary syndrome*":ti,ab OR "peripheral artery disease*":ti,ab OR "vein graft disease":ti,ab OR "arteriovenous fistula*":ti,ab OR "limb ischemia":ti,ab OR "intermittent claudication":ti,ab
AND
test*:ti,ab OR diagnos*:ti,ab OR measure*:ti,ab OR precis*:ti,ab OR sensitiv*:ti,ab OR specific*:ti,ab OR predict*:ti,ab OR accura*:ti,ab OR "next generation":ti,ab OR "new generation":ti,ab OR "high throughput":ti,ab OR algorithm*:ti,ab OR "artificial intelligence":ti,ab OR "machine learning":ti,ab OR "deep learning":ti,ab OR "precision medicine":ti,ab OR "personalized medicine":ti,ab OR "diagnostic multivariate index assay":ti,ab OR IVDIMA:ti,ab

PubMed: General Search

Filters applied: English Language; 2000-present
Search run: 22 July 2020

AND

Embase: General Search

Filters applied: English Language; Human
Search run: 22 July 2020

'proteome'/exp/mj OR 'proteomics'/exp/mj OR proteome:ti OR proteomes:ti OR proteomic:ti OR proteomics:ti OR proteogenomic*:ti AND
'neoplasm'/exp/mj OR neoplasm*:ti OR oncology:ti OR cancer*:ti OR leukemia:ti OR carcinoma:ti OR sarcoma:ti OR adenocarcinoma:ti OR 'cardiovascular disease'/exp/mj OR
"cardiovascular disease*":ti OR "heart disease*":ti OR "vascular disease*":ti OR cardiomyopath*:ti OR "atrial fibrillation":ti OR atherosclerosis:ti OR myocarditis:ti OR "myocardial infarction*":ti OR arrhythmias:ti OR "heart failure":ti OR aneurysm*:ti OR stroke:ti OR "coronary artery disease*":ti OR "angina pectoris":ti OR "acute coronary syndrome*":ti OR "peripheral artery disease*":ti OR vein graft disease":ti OR "arteriovenous fistula*":ti OR "limb ischemia":ti OR "intermittent claudication":ti AND test*:ti,ab OR diagnos*:ti,ab OR measure*:ti,ab OR precis*:ti,ab OR sensitiv*:ti,ab OR specific*:ti,ab OR predict*:ti,ab OR accura*:ti,ab OR "next generation":ti,ab OR "new generation":ti,ab OR "high throughput":ti,ab OR algorithm*:ti,ab OR "artificial intelligence":ti,ab OR "machine learning":ti,ab OR "deep learning":ti,ab OR "precision medicine":ti,ab OR "personalized medicine":ti,ab OR "diagnostic multivariate index assay*":ti,ab OR IVDMIA:ti,ab

**Gray Literature—Industry Trade Publications**
Database: Nexis Uni, limited to trade industry publications. Search terms: (proteomic or proteome or proteogenomic) and (test or diagnos*) and (cancer or cardiovascular). Narrowed to date range: June 1, 2018, to June 1, 2020.
Appendix C: Narrative Review Methodology

This project aimed to produce a narrative review of multiple data sources. Our narrative review included the creation of 2 evidence maps based on published studies evaluating the use of proteomic testing for cancer and cardiovascular disease.

Literature Searches
We searched multiple data sources to identify and examine proteomic applications currently in use or potentially available over the next 1 to 5 years in cardiology and oncology (Table 1). We also sought to summarize the underlying evidence base, to identify gaps in that evidence base, and to provide critical information about potential benefits or harms of these technologies for patients/consumers, payers and insurers, purchasers and employers, and public policymakers. Our search strategy focused on documenting the current state of proteomic testing in cardiology and oncology, as well as identifying evidence of how proteomic testing impacts patient outcomes, in peer-reviewed and gray literature that index innovations and technical advances.

Table 1. Literature Search Results

<table>
<thead>
<tr>
<th>Literature Type</th>
<th>General search</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade industry publications</td>
<td>467</td>
<td>N/A</td>
</tr>
<tr>
<td>PubMed</td>
<td>1820</td>
<td>156</td>
</tr>
<tr>
<td>Embase</td>
<td>2298</td>
<td>73</td>
</tr>
<tr>
<td>Separate Search Totals</td>
<td>4118</td>
<td>226</td>
</tr>
<tr>
<td>Peer-reviewed literature total</td>
<td>4344</td>
<td></td>
</tr>
</tbody>
</table>

Literature Review Procedure
To identify current applications of proteomic testing, the project team searched for peer-reviewed literature in PubMed and Embase. The literature searches were conducted by an evidence-based practice center librarian (Jody Larkin) experienced in transparent and comprehensive literature searches. Searches were limited to English-language studies of human subjects. Searches were designed to explicitly address ongoing premarket and postmarket studies, current evidence on the use of proteomic biomarkers and their safety, and other important issues, like current levels of adoption of proteomic testing as well as future diffusion. To focus on current and future applications, only articles published in English since 2010 were included and only reviews/commentaries published in English since 2015 were included. The search was supplemented through several additional databases. To identify gray literature on approved or developing proteomic technologies, the project team searched the Food and Drug Administration-National Cancer Institute Clinical Proteomics Program Databank, Global Proteome Machine, the Proteomics Identification Database online repository, and Proteomics Database. However, these databases included a large volume of candidate biomarkers that were not limited to those with clinical utility and many overlapped with articles included in our search of peer-reviewed literature; accordingly, these additional databases were excluded from our review. To identify additional relevant gray literature, the project team searched Nexis Uni, which provides access to publications that report on pharmaceutical regulatory affairs, federal activity, and upcoming technologies and products; these searches were limited to the past 24 months to identify near-term applications. Citations were managed using EndNote and Distiller SR.
At least one member of the project team screened each abstract on the basis of the study inclusion and exclusion criteria. Reviewers applied explicit inclusion and exclusion criteria designated a priori. Screening decisions were tracked in Distiller SR. All citations that were deemed potentially relevant by at least one reviewer were obtained as full text and screened against the eligibility criteria. Following completion of the search and screening activities, 6 members of the project team abstracted screened articles. An electronic standardized abstraction form in Distiller SR was used to support the collection of information on a variety of factors. We used Peng’s adaptation of the Fryback and Thornbury framework to classify efficacy data reported in each article included in the review. Following the data abstraction, the project team developed 2 evidence maps in R (ie, one for proteomic testing in cardiovascular research and one for proteomic testing in cancer research) to describe the current evidence base available for the use of proteomic biomarkers and their safety. Evidence maps present the results from “a systematic search of a broad field to identify gaps in knowledge and/or future research needs.”

The evidence maps included in this report provide an overview of the research in proteomic testing and indicate the research focus and the quantity of existing research.

**Inclusion Criteria**

We applied explicit inclusion and exclusion criteria for our searches in both the gray and peer-reviewed literature and in peer-reviewed trials.

**Inclusion criteria for gray literature (ie, trade industry articles)**
- Articles must be related to near-term applications of proteomic testing for clinical use.
- Articles were published between June 1, 2018, and June 1, 2020.

**Inclusion criteria for peer-reviewed research articles**
- Articles must focus on high-throughput proteomic tests used for targeted treatment or diagnostic purposes, specifically those that are currently in use or will potentially be available over the next 5 years.
- Articles must focus on oncology or cardiology.
- Articles must describe clinical outcomes or existing clinical use.
- Articles must include original findings related to current or future applications of proteomic testing, facilitators/barriers related to testing, or potential impacts of these technologies on different audiences, such as patients/consumers, payers/insurers, purchasers/employers, and public policymakers. The review intended to include both IVDMIs and global proteomic methods. For example, barriers to uptake include limited access to cutting-edge instruments required for large-scale sample preparation and highly sensitive analysis; high costs of such equipment; limited availability of data scientists who have expertise in artificial intelligence to analyze large volumes of clinical data; challenges related to electronic health records; variability and heterogeneity of clinical data; and data storage concerns.
- Articles were published since 2010.

**Inclusion criteria for peer-reviewed trials**
- **Population:** Participants undergoing a proteomic test for cardiovascular disease or cancer were eligible for inclusion. Studies may include people of all ages but must include human participants.
• **Intervention:** Eligible proteomic tests include high-throughput proteomic tests used for targeted treatment or diagnostic purposes in cardiology and oncology, specifically those that are currently in use or will potentially be available over the next 5 years. The review intended to include both IVDMIA and global proteomic methods.
  o Relevant uses include FDA-approved applications, as well as applications in practice but subject to approval (eg, those done through a CLIA certified laboratory).

• **Comparator:** Studies may compare interventions against no comparator or concurrent comparators used for the same purpose. Eligible studies may also include multiomic analyses, such as those integrating genomics, transcriptomics, and proteomics.

• **Outcome:** Outcomes of interest include disease-related effectiveness indicators such as remission, recurrence, disease progression, mortality, patient-centered outcomes including psychosocial outcomes such as anxiety and worry, and treatment-associated adverse events.

• **Study Design:** Primary clinical research studies are eligible. Publications may self-identify as either experimental or observational clinical research. We also included observational cohort studies where cohort assignment was not investigator assigned.

• **Year:** Articles published since 2000 (this time frame was intended to focus on current and emerging applications)

• **Other:** Studies that use proteomic testing to categorize cells/tissues/patients or describe treatment mechanisms, rather than predict or influence patient outcomes, should be marked as “proof-of-concept.”

**Exclusion criteria for peer-reviewed research articles and trials**

• Studies that focus on using proteomics outside the context of testing for diagnosis or patient care for cardiovascular disease or cancer (eg, the identification of a novel infectious agent or other uses)

• Studies that focus on conventional protein biomarkers (eg, PSA)

• Studies that analyze the proteomic composition of cells or tissue

• Studies that use proteomic testing to categorize cells/tissues/patients or describe treatment mechanisms, rather than predict or influence patient outcomes, should be marked as “proof-of-concept.” Although these studies were not included in the final analysis and evidence maps, they demonstrate the large volume of studies that have moved beyond basic research, are focused on biomarker discovery, and have the potential to inform clinical outcomes.

**Exclusion criteria for peer-reviewed reviews and commentaries**

• Studies older than 5 years

The literature flow diagram is shown in Appendix D.

**Data Extraction**

We created a standardized form with explicit and pilot-tested categorization rules to extract the data. For each peer-reviewed research article, we extracted the author and publication year (if applicable), inclusion criteria, study setting, disease, characteristics, population, proteomic analysis characteristics, and outcome characteristics. For each commentary or review, we
extracted the author and publication year (if applicable), inclusion criteria, indication, barriers/challenges, benefits/opportunities, and future research.

**Abstraction form for original peer-reviewed research articles**

1. Is this article freely available? If no, exclude.
   - o Yes
   - o No

**INCLUSION FOR ABSTRACTION**

2. Should the study be abstracted? If no, write the exclusion criteria. If unsure, list the reason for hesitation.
   As a reminder, studies must focus on (1) next-generation/high-throughput proteomic tests used for targeted therapeutic, prognostic, or diagnostic purposes; (2) focus on cancer or cardiovascular disease; and (3) include clinical outcomes. We are excluding studies that focus on basic science (eg, disease etiology or mechanisms, proteomic composition of cells or tissues) or conventional single protein biomarkers (eg, PSA).
   - o Yes
   - o No
   - o Unsure

3. Study ID. Please use the following example: Author, year

4. Related studies. If multiple publications, please indicate any related studies.

**STUDY SETTING, DISEASE CHARACTERISTICS, AND POPULATION**

5. Setting. Where are the proteomic tests processed?
   - o Inpatient clinic
   - o Outpatient clinic
   - o Onsite lab
   - o Offsite lab
   - o Other

6. Country. What country was this study conducted in?

7. Indication category
   - o Cancer
   - o Cardiovascular disease

8. Indication subcategory (cancer). Which organ system is affected by the cancer?
   - o Respiratory
   - o Digestive
   - o Cardiovascular
   - o Urinary
   - o Integumentary (skin, hair, nails, etc)
   - o Skeletal
   - o Muscular
9. What stage is the cancer?
   - Early-stage/nonmetastatic
   - Advanced-stage/metastatic
   - Both/mixed
   - Unsure

10. Indication subcategory (cardiovascular disease). Which cardiovascular indication is studied?
    - Cardiovascular disease
    - Myocardial infarction (heart attack)
    - Heart failure
    - Congenital heart defects
    - Cardiomyopathy
    - Peripheral artery disease
    - Stroke
    - Arrhythmia
    - Heart valve disorders
    - Multiple
    - Other

11. Is the cardiovascular disease new or recurring?
    - New
    - Recurring

12. Indication description. If necessary, please describe any additional information about the specific disease studied.

13. Patient inclusion/exclusion criteria (open ended). Focus on patient or disease characteristics (eg, pediatric population, adults older than age X, survivors, individuals with X risk factor, etc).

14. Comparator. To what population or samples are the tests being compared?
    - Healthy cells/tissue/patients
    - Other diseased cells/tissue/patients
    - None
    - Other
15. Special populations. Does this study exclusively examine patients who are part of a special population (check all that apply)?
   o Women
   o Racial or ethnic minorities
   o Uninsured individuals
   o Other
   o None

PROTEOMIC ANALYSIS CHARACTERISTICS

16. Proteomic technology application. If described, indicate the technology underlying the proteomic analysis approach.
   o Global = analysis of all proteins in a sample
   o IVDMIA = algorithmic creation of a score, index, or classification using data from analysis of multiple proteins
   o Several = analysis of several proteins in a sample
   o Single protein tests should result in the article being excluded.
   o Article location: Methods
   o Global proteomics
   o In vitro diagnostic multivariate index assays
   o Several protein proteomics
   o Multiple
   o Other

17. Proteomic test function. Indicate the function of the proteomic test.
   o Diagnostic = diagnose disease
   o Prognostic = predict the course of a disease
   o Medication dosage = predict the optimal dosage of a medication
   o Article location: Methods
   o Diagnostic
   o Prognostic
   o Medication dosage
   o Other therapeutic use
   o Multiple
   o Other

18. Algorithmic processing of proteomic data. Check if the article mentions algorithmic processing of proteomic data.
   o Yes
   o No
   o Other

19. Proteomic technology application description. If relevant details are provided in the article, describe the proteomic technology used to analyze the protein samples.
OUTCOME CHARACTERISTICS

20. Outcomes by efficacy type. Note the outcomes presented in the article by efficacy type.
   - Technical efficacy: Reliability of proteomics technology
   - Diagnostic accuracy efficacy: Sensitivity, specificity, and other measures
   - Diagnostic thinking efficacy: Estimated probability of diagnostic before versus after results
   - Therapeutic efficacy: Percentage of time that therapy planned before diagnostic is altered by results
   - Patient outcome efficacy (choose indication): Number of deaths prevented or change in quality of life; any change in other patient outcomes
   - Societal efficacy: Economic impact of test as measured from societal perspective
   - Article location: Results

21. Efficacy: Outcome description. List all relevant outcomes; note if primary (only one) or secondary (all others).

   - Survival
   - Recurrence
   - Quality of life
   - None
   - Multiple
   - Other
   - Death
   - Hospitalization
   - Myocardial infarction
   - Stroke/transient ischemic attack
   - Heart failure event
   - Stent or other intervention
   - Multiple
   - Other
   - Positive
   - Negative
   - No effect
   - Other

24. Serious adverse events/harms. If noted in the article, describe any serious adverse events or harms associated with proteomic testing.

25. Major findings/conclusions

Abstraction form for commentaries/reviews

1. Is this article freely available? If no, exclude.
   - Yes
   - No

2. Inclusion for abstraction. Should the study be abstracted? If no, write the exclusion criteria. If unsure, list the reason for hesitation.
   - Yes
   - No
   - Unsure

3. Study ID. Please use the following example: Author, year

4. Indication category
   - Cancer
   - Cardiovascular disease

5. Barriers/challenges. What are perceived barriers/challenges to clinical applications of proteomic testing (eg, issues with availability, affordability, uptake)?

6. Benefits/opportunities. What are perceived benefits/opportunities for clinical applications of proteomic testing (eg, issues with availability, affordability, uptake)?

7. Future research. What are areas for future proteomic research?

Evidence Map
The evidence maps on pages 22 and 24 are based on a bubble plot, where each “bubble” in the figure represents an identified study that has been reviewed. We created 2 evidence maps: one for proteomic testing related to cancer and one for proteomic testing related to cardiovascular disease. The shape of the bubbles on the map denote the type of proteomic application discussed in the study. The color of the bubbles represents the effect direction. The evidence maps show the presence as well as the absence of evidence for proteomic testing in the selected fields of medicine.

Evidence Table
We also created an evidence table to provide an overview of the peer-reviewed literature (original research articles and reviews/commentaries) and trade industry publications. In the evidence table, we have documented the indication and indication type, type of proteomic technology, test function, and efficacy type discussed in each article.

See Appendix E for the evidence table and reference lists of reviewed publications.
Appendix D. Literature Review Flow Diagram

Records identified through PubMed and EMBASE (n = 5795)

Additional records identified through Nexis Uni (n = 467)

Records screened (no duplicates detected) (n = 6262)

Articles excluded, with reasons (n = 4057) Excluded (n = 1184) Proof of concept (n = 21) Background/systematic review (n = 654) Background/narrative review/commentary

Studies included in qualitative synthesis (n = 154) Peer-reviewed original research studies (n = 93) Peer-reviewed reviews/commentaries (n = 99) Trade industry publications

---

*a Flow diagram created based on PRISMA 2009 Flow Diagram.*75
This appendix includes the evidence table for the peer-reviewed research articles, as well as reference lists for the articles reporting candidate biomarkers/therapeutic targets and trade industry publications, reviewed for the report.

## Evidence Table for Original Peer-Reviewed Research Articles (n = 154)

<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>Journal</th>
<th>Year</th>
<th>Indication category</th>
<th>Proteomic technology</th>
<th>Test function</th>
<th>Efficacy type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>-----------------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Lourenco AP, Benson KL, Henderson MC, et al</td>
<td>A noninvasive blood-based combinatorial proteomic biomarker assay to detect breast cancer in women under the age of 50 years</td>
<td>Clin Breast Cancer</td>
<td>2017</td>
<td>Cancer</td>
<td>Several protein test</td>
<td>Diagnostic</td>
<td>Diagnostic accuracy</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>---------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Fan NJ, Chen HM, Song W, et al</td>
<td>Macrophage mannose receptor 1 and S100A9 were identified as serum diagnostic biomarkers for colorectal cancer through a label-free quantitative proteomic analysis</td>
<td><em>Cancer Biomark</em></td>
<td>2016</td>
<td>Cancer</td>
<td>Global proteomic test</td>
<td>Diagnostic</td>
<td>Diagnostic accuracy</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>---------</td>
<td>------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Kakimoto Y, Ito S, Abiru H, et al</td>
<td>Sorbin and SH3 domain-containing protein 2 is released from infarcted heart in the very early phase: proteomic analysis of cardiac tissues from patients</td>
<td>J Am Heart Assoc</td>
<td>2013</td>
<td>Cardiovascular disease</td>
<td>Global proteomic test</td>
<td>Diagnostic</td>
<td>Diagnostic accuracy</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>-----------------------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Han CL, Chen JS, Chan EC, et al</td>
<td>An informatics-assisted label-free approach for personalized tissue membrane proteomics: case study on colorectal cancer</td>
<td><em>Mol Cell Proteomics</em></td>
<td>2011</td>
<td>Cancer</td>
<td>Global proteomic test</td>
<td>Diagnostic</td>
<td>Diagnostic accuracy</td>
</tr>
<tr>
<td>Wang Q, Shen J, Li ZF, et al</td>
<td>Limitations in SELDI-TOF MS whole serum proteomic profiling with IMAC surface to specifically detect colorectal cancer</td>
<td><em>BMC Cancer</em></td>
<td>2009</td>
<td>Cancer</td>
<td>In vitro diagnostic multivariate index assay (IVDMIA)</td>
<td>Diagnostic</td>
<td>Diagnostic accuracy</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Brozkova K, Budinska E, Bouchal P, et al</td>
<td>Surface-enhanced laser desorption/ionization time-of-flight proteomic profiling of breast carcinomas identifies clinicopathologically relevant groups of patients similar to previously defined clusters from cDNA expression</td>
<td><em>Breast Cancer Res</em></td>
<td>2008</td>
<td>Cancer</td>
<td>Global proteomic test</td>
<td>Diagnostic</td>
<td>Diagnostic accuracy</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------</td>
<td>------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Silvestri GA, Tanner NT, Kearney P, et al</td>
<td>Assessment of plasma proteomics biomarker’s ability to distinguish benign from malignant lung nodules: results of the PANOPTIC (pulmonary nodule plasma proteomic classifier) trial</td>
<td>Chest</td>
<td>2018</td>
<td>Cancer</td>
<td>Several protein test</td>
<td>Diagnostic</td>
<td>Diagnostic accuracy, diagnostic thinking</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>---------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Nayor M, Short MI, Rasheed H, et al</td>
<td>Aptamer-based proteomic platform identifies novel protein predictors of incident heart failure and echocardiographic traits</td>
<td><em>Circ Heart Fail</em></td>
<td>2020</td>
<td>Cardiovascular disease</td>
<td>Several protein test</td>
<td>Diagnostic</td>
<td>Other</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>---------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Hu X, Du S, Yu J, et al</td>
<td>Common housekeeping proteins are upregulated in colorectal adenocarcinoma and hepatocellular carcinoma, making the total protein a better “housekeeper”</td>
<td><em>Oncotarget</em></td>
<td>2016</td>
<td>Cancer</td>
<td>Several protein test</td>
<td>Diagnostic</td>
<td>Technical</td>
</tr>
<tr>
<td>Ahn YH, Shin PM, Oh NR, Park GW, Kim H, Yoo JS</td>
<td>A lectin-coupled, targeted proteomic mass spectrometry (MRM MS) platform for identification of multiple liver cancer biomarkers in human plasma</td>
<td><em>J Proteomics</em></td>
<td>2012</td>
<td>Cancer</td>
<td>Global proteomic test</td>
<td>Diagnostic</td>
<td>Technical</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>---------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Liu XP, Shen J, Li ZF, Yan L, Gu J</td>
<td>A serum proteomic pattern for the detection of colorectal adenocarcinoma using surface enhanced laser desorption and ionization mass spectrometry</td>
<td>Cancer Invest</td>
<td>2006</td>
<td>Cancer</td>
<td>Global proteomic test</td>
<td>Diagnostic</td>
<td>Technical, diagnostic accuracy</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>---------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Zhang ZY, Ravassa S, Nkuipou-Kenfack E, et al</td>
<td>Novel urinary peptidomic classifier predicts incident heart failure</td>
<td><em>J Am Heart Assoc</em></td>
<td>2017</td>
<td>Cardiovascular disease</td>
<td>Several protein test</td>
<td>Multiple functions</td>
<td>Diagnostic accuracy, patient outcome (cardiovascular disease)</td>
</tr>
<tr>
<td>Ferrannini G, Manca ML, Magnoni M, et al</td>
<td>Coronary artery disease and type 2 diabetes: a proteomic study</td>
<td><em>Diabetes Care</em></td>
<td>2020</td>
<td>Cardiovascular disease</td>
<td>Global proteomic test</td>
<td>Multiple functions</td>
<td>Other</td>
</tr>
<tr>
<td>Nowak C, Carlsson AC, Östgren CJ, et al</td>
<td>Multiplex proteomics for prediction of major cardiovascular events in type 2 diabetes</td>
<td><em>Diabetologia</em></td>
<td>2018</td>
<td>Cardiovascular disease</td>
<td>Several protein test</td>
<td>Other functions</td>
<td>Diagnostic accuracy</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>---------------</td>
<td>------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>-------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Cardin DB, Goff L, Li CI, et al</td>
<td>Phase II trial of sorafenib and erlotinib in advanced pancreatic cancer</td>
<td>Cancer Med</td>
<td>2014</td>
<td>Cancer</td>
<td>IVDMIA</td>
<td>Therapeutic</td>
<td>Therapeutic</td>
</tr>
<tr>
<td>Pishvaian MJ, Bender RJ, Halverson D, et al</td>
<td>Molecular profiling of patients with pancreatic cancer: initial results from the Know Your Tumor Initiative</td>
<td>Clin Cancer Res</td>
<td>2018</td>
<td>Cancer</td>
<td>Several protein test</td>
<td>Therapeutic</td>
<td>Therapeutic</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------</td>
<td>---------------------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>---------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Barderas R, Mendes M, Torres S, et al</td>
<td>In-depth characterization of the secretome of colorectal cancer metastatic cells identifies key proteins in cell adhesion, migration, and invasion</td>
<td><em>Mol Cell Proteomics</em></td>
<td>2013</td>
<td>Cancer</td>
<td>Global proteomic test</td>
<td>Prognostic</td>
<td>Diagnostic accuracy</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>---------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Kim SI, Jung M, Dan K, et al</td>
<td>Proteomic discovery of biomarkers to predict prognosis of high-grade serous ovarian carcinoma</td>
<td><em>Cancers</em></td>
<td>2020</td>
<td>Cancer</td>
<td>Several protein test</td>
<td>Prognostic</td>
<td>Diagnostic thinking</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>---------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Rader JS, Pan A, Corbin B, et al</td>
<td>Identification and validation of a prognostic proteomic signature for cervical cancer</td>
<td><em>Gynecol Oncol</em></td>
<td>2019</td>
<td>Cancer</td>
<td>Other</td>
<td>Prognostic</td>
<td>Patient outcome (cancer)</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Spigel DR, Burris HA, Greco FA, et al</td>
<td>Erlotinib plus either pazopanib or placebo in patients with previously treated advanced non–small cell lung cancer: a randomized, placebo-controlled phase 2 trial with correlated serum proteomic signatures</td>
<td><em>Cancer</em></td>
<td>2018</td>
<td>Cancer</td>
<td>IVDMIA</td>
<td>Prognostic</td>
<td>Patient outcome (cancer)</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------</td>
<td>------</td>
<td>---------------------</td>
<td>-----------------------</td>
<td>----------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>---------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Emmens JE, Jones DJL, Cao TH, et al</td>
<td>Proteomic diversity of high-density lipoprotein explains its association with clinical outcome in patients with heart failure</td>
<td>Eur J Heart Fail</td>
<td>2018</td>
<td>Cardiovascular disease</td>
<td>IVDMIA</td>
<td>Prognostic</td>
<td>Patient outcome (cardiovascular disease)</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>------------------------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Zhang ZY, Thijs L, Petit T, et al</td>
<td>Urinary proteome and systolic blood pressure as predictors of 5-year cardiovascular and cardiac outcomes in a general population</td>
<td><em>Hypertension</em></td>
<td>2015</td>
<td>Cardiovascular disease</td>
<td>IVDMIA</td>
<td>Prognostic</td>
<td>Patient outcome (cardiovascular disease)</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>---------</td>
<td>------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Kuiper JL, Lind JS, Groen HJ, et al</td>
<td>VeriStrat(®) has prognostic value in advanced stage NSCLC patients treated with erlotinib and sorafenib</td>
<td>Br J Cancer</td>
<td>2012</td>
<td>Cancer</td>
<td>IVDMIA</td>
<td>Prognostic</td>
<td>Therapeutic</td>
</tr>
<tr>
<td>Helgason HH, Engwegen JYMN, Zapatka M, et al</td>
<td>Identification of serum proteins as prognostic and predictive markers of colorectal cancer using surface enhanced laser desorption ionization-time of flight mass spectrometry</td>
<td>Oncol Rep</td>
<td>2010</td>
<td>Cancer</td>
<td>IVDMIA</td>
<td>Prognostic</td>
<td>Therapeutic</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Indication category</td>
<td>Proteomic technology</td>
<td>Test function</td>
<td>Efficacy type</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Mok TS, Geater SL, Su WC, et al</td>
<td>A Randomized phase 2 study comparing the combination of ficlatuzumab and gefitinib with gefitinib alone in Asian patients with advanced stage pulmonary adenocarcinoma</td>
<td><em>J Thorac Oncol</em></td>
<td>2016</td>
<td>Cancer</td>
<td>IVDMIA</td>
<td>Therapeutic</td>
<td>Patient outcome (cancer)</td>
</tr>
</tbody>
</table>
Peer-reviewed reviews and commentaries (n = 93)


20. Corbo C, Cevenini A, Salvatore F. Biomarker discovery by proteomics-based approaches for early


22. De Franciscis S, Metzinger L, Serra R. The discovery of novel genomic, transcriptomic, and proteomic
biomarkers in cardiovascular and peripheral vascular disease: the state of the art. *Biomed Res Int.*
2016;2016.

23. Di Meo A, Pasic MD, Yousef GM. Proteomics and peptidomics: moving toward precision medicine in


25. Faria SS, Morris CFM, Silva AR, et al. A timely shift from shotgun to targeted proteomics and how it
can be groundbreaking for cancer research. *Front Oncol.* 2017;7:13.


27. Fert-Bober J, Murray CI, Parker SJ, Van Eyk JE. Precision profiling of the cardiovascular post-
translationally modified proteome where there is a will, there is a way. *Circ Res.* 2018;122(9):1221-
1237.

28. Flores-Moraes A, Iglesias-Gato D. Quantitative mass spectrometry-based proteomic profiling for

29. Frantzi M, Latosinska A, Merseburger AS, Mischak H. Recent progress in urinary proteome analysis for


31. Gaudreau PO, Stagg J, Soulières D, Saad F. The present and future of biomarkers in prostate cancer:


35. Hanash S, Taguchi A, Wang H, Ostrin EJ. Deciphering the complexity of the cancer proteome for


38. Ho M, Bianchi G, Anderson KC. Proteomics-inspired precision medicine for treating and understanding

39. Huang Z, Ma L, Huang C, Li Q, Nice EC. Proteomic profiling of human plasma for cancer biomarker

40. Jin P, Wang K, Huang C, Nice EC. Mining the fecal proteome: from biomarkers to personalised


**Trade industry publications (n = 99)**


