Public Policy Considerations of Novel Cardiovascular Disease and Stroke Blood-based Biomarkers

March 2024

Summary of the Position of the American Heart Association

The American Heart Association supports extensive research, which includes funding for studies that enroll diverse patient populations in the validation and clinical utility of novel blood-based biomarkers, as well as standardized biomarker testing and validation protocols. Furthermore, the Association supports policies that ensure equitable access to those novel blood-based biomarkers that meet the standards for use in clinical practice, including addressing coverage by health insurance providers, reducing disparities in healthcare access, and making novel biomarkers available to all who would benefit as a standard of care. The use of novel biomarkers in clinical practice can be equity-enhancing if they are available by providing early diagnoses, allowing for preventive as well as early curative treatment. The American Heart Association supports public policies that fund robust research for validation and cost-effectiveness, equitable access to these novel cardiovascular disease and stroke blood-based biomarkers in the context of clinical care, patient and professional education, and data security to optimize the benefits of novel biomarker use in patient care and clinical research.

Introduction

Cardiovascular disease (CVD) and stroke are leading causes of mortality and morbidity worldwide. Early detection and risk stratification are crucial in preventing and managing these conditions effectively. The use of biomarkers has transformed cardiovascular medicine and stroke care. Though blood-based biomarkers are widely used in CVD care, despite the significant burden of stroke, blood-based biomarkers are not generally used for diagnosis or prognosis in stroke clinical practice.[1] The reason for this is there is no blood-based biomarker with high enough specificity to provide accurate diagnosis of ischemic stroke.[2,3] Because CVD remains a leading cause of death and stroke is a leading cause of disability, there continues to be an effort to develop novel blood-based biomarkers that are more accurate.[4] This continued effort has led to a large number of potential biomarkers that have extended beyond research and medical practice to areas of product development, nutrition, and even environmental policy.[5] Novel blood-based biomarkers have shown promise in improving risk assessment, diagnosis, and treatment outcomes in CVD and stroke care, as well as increased equity in the care and management of CVD and stroke. With the growing number of CVD and stroke biomarkers, it is critically important to ensure novel blood-based biomarkers have a strong evidence-base and are meeting scientific and clinical needs[5] as the American Heart Association develops a public policy position for any potential engagement in this space.

A biomarker is a measurable indicator of biological processes, pathogenic processes, or responses to interventions, obtained through various methods like molecular, histologic, radiographic, or physiologic characteristics.[5,6] While encompassing a wide range of indices, including imaging techniques, biomarkers are commonly associated with measurements of substances in peripheral blood, such as proteins, peptides, and

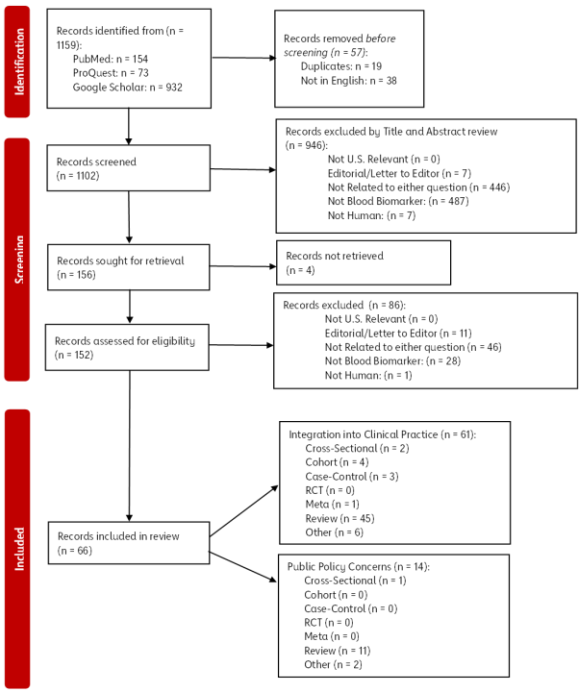
hormones.[7] A biomarker is considered 'novel' when it is a new discovery or identification, that offers the potential to improve diagnostic accuracy, prognosis, or monitoring capabilities over established biomarkers. In the biomarker field, the term 'novel' is commonly associated with technological advancements that allow genomic, transcriptomic, and metabolomic analysis.[8,9] 'Novelty' can also be related to previously unknown molecules and advancements in detecting and measuring biomarkers.[8] Another potential way biomarkers can be novel, is when they are combined into biomarker panels. A biomarker panel is a group of markers that reflect different pathophysiological processes of a disease and can be particularly important when the disease or disease process is complex and/or heterogenic.[10] For some biomarker panels, the results could be used to create a 'score' that then risk-stratifies the individual,[11] or a machine learning classifier/algorithm that can be applied for classification or prediction.[12] Policy considerations for novel CVD and stroke biomarkers involve interactions between science, ethics, economic, regulatory, and healthcare delivery factors.[5,13] Some important policy considerations for integration into clinical practice include, robust scientific validity and clinical utility, addressing ethical and privacy concerns, regulatory approval by the U.S. Food and Drug Administration and continued oversight, integration into clinical guidelines, insurance coverage and cost-effectiveness, and equitable access for all patients.[5,6,14] As the definition implies, there are a number of types of biomarkers, with imaging biomarkers increasing in number. However, for this review the focus will be on those biomarkers that can be derived/measured from blood samples (blood-based biomarkers) in adult populations. In addition, a direction that is still relatively unexplored, involves a combination of different types of biomarkers. For example, combining imaging and molecular blood biomarkers, or different types of molecular biomarkers (e.g. genomic and transcriptomic biomarkers).[12,15,16]

The purpose of this review is to inform a policy statement of the American Heart Association regarding the public policy considerations of novel CVD and stroke blood biomarkers for adults. The scope of this review is to explore the literature surrounding the public policy issues of novel cardiovascular and stroke blood biomarkers. Particularly, this review focuses on the key factors that have been proposed that make novel biomarkers appropriate for integration into adult clinical practice and the associated public policy issues, including equity considerations, reimbursement, and affordability.

Methods

For this review there are two specific questions that were addressed: (1) What are the key factors that make novel biomarkers appropriate for integration into clinical practice? (2) What are the public policy issues related to cardiovascular disease and stroke biomarkers? To answer these questions Pubmed, ProQuest, and GoogleScholar databases were searched using keywords and MeSH terms (Pubmed only) including novel cardiovascular biomarkers, novel stroke biomarkers, validation, clinical practice, insurance, healthcare reimbursement, policy, regulation, and legislation. For Pubmed and ProQuest, the search was limited to 5 years and English language. For GoogleScholar, where exclusion for language was not an option, the search was limited to 5 years and records not available in English were manually confirmed and excluded (n=38, see **Figure 1**).

Figure 1. Results of literature search and screening process.



Adapted From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

See **Figure 1** for the results of the screening process. Once the search of each database was completed, duplicates were removed. Titles and abstracts were screened for inclusion/exclusion, then full papers were sought and screened for inclusion/exclusion on the remaining records. The inclusion criteria included records that were written in English, published or published-ahead-of-print between January 2018 and November 2023. Criteria for exclusion included those that were not generalizable to US health policy or practice, not related to one of the two primary questions, or were editorials, letter-to-editors, or commentaries. There were 66 articles included in the review.

Key Findings

What are the key factors that make novel biomarkers appropriate for integration into clinical practice?

There were 61 articles that were identified and included in this review that described key factors that are needed for novel biomarkers to be integrated into clinical practice (see **Appendix A** for a summary of the conclusions and recommendations from each of the articles). There were five primary categories of factors that were identified through this review (summarized in **Table 1**): (1) accessibility, (2) informational value, (3) validation aspects, (4) performance characteristics, and (5) decision-making support. The accessibility of a biomarker characterizes the cost-effectiveness, ease of use (easy to collect, analyze, and interpret), time involved collecting, analyzing, and receiving results, and would also include the ability to be performed at bedside if needed. Informational value relates to the ability of the biomarker to provide information not otherwise available. Validation aspects relate to how the biomarker was validated and considers other factors such as reliability. Performance characteristics relate to how well the biomarker discriminates between those with the disease versus those who do not have it, those who are at higher risk from those at lower risk or to distinguish prognostic categories. Lastly, decision-making support addresses the need for the biomarker to provide objective information that supports clinical decision-making, and provides clear clinical utility (risk stratification, diagnosis, prognosis, disease management, etc.) with demonstrated effective clinical outcome.

These characteristics appear to be of key concern for integrating novel biomarkers into clinical practice. Though how much importance each of these factors have in influencing integration into clinical practice might be influenced by the intended use of the biomarker (risk factor, diagnosis, prognosis, disease management, etc.), analysis of the findings did not yield differences in this regard. This may be due to many of the articles having interest in defining characteristics for multiple intended uses and considering several novel biomarkers, both limiting the ability to make this discernment. However, there may be some prioritization of factors (based on frequency of mentions) whether cardiovascular disease (all forms) or stroke was the disease in question. In both disease categories, accessibility had the most mentions and decision-making support had the fewest. Performance characteristics were more dominant in stroke-related papers (second-most mentions) than in the CVD-related papers (third-most mentions). For stroke-related papers, following performance characteristics, were validation aspects, informational value, and decision-making support. For the CVD-related papers, the order was accessibility, informational value, performance characteristics, validation aspects, and decision-making support.

1) Accessibility: 46 articles identified cost, ease, and/or timeliness of results as important factors for novel biomarkers to be integrated into clinical practice. Firstly, cost and cost-effectiveness are crucial factors as these biomarkers must offer added value compared to existing markers and be affordable for routine use.[1,3,7,12,15-39] Assessing the cost-effectiveness of novel biomarkers is crucial. There is a need for robust research of the cost-effectiveness of novel biomarkers to understand and quantify the affordability of implementing into clinical practice.[18] Secondly, ease of use and patient acceptance are vital for widespread adoption, meaning biomarkers should be simple to measure, interpret, (relatively) non-invasive, and convenient for patients.[1,2,7,12,15,16,18-20,24,26,27,30,32,33,36,38,40-50] Lastly, rapid test results are essential for timely decision-making in clinical practice. Biomarkers providing quick and accurate results can greatly impact patient management, especially in acute or time-sensitive situations.[2,7,12,17,21,26,27,31,32,34,36,43,48,51-55] Therefore, considering these characteristics, it is important to choose novel biomarkers that demonstrate favorable cost-effectiveness, user-friendliness, and rapid testing capabilities to ensure successful integration into clinical practice.

2) Informational Value: 37 articles identified informational value gained from the biomarker as important for integration into clinical practice. Novel biomarkers play a crucial role in clinical practice when they can provide independent new information about a disease or its prognosis that is not available through traditional risk factors or existing biomarkers.[7,12,16-22,24,25,27,31-36,40,42,47-49,51,52,55-61] This unique characteristic allows for a more comprehensive understanding of disease pathophysiology and risk assessment.[31-33,39,46,51,55,56,59] These biomarkers need to be objectively measured and should ideally predict important clinical outcomes or provide information about the response to therapeutic interventions.[18,31,32,34,37,39,49,62] Furthermore, novel biomarkers should add valuable information not captured by traditional risk scores, thus enhancing risk stratification and guiding clinical decision-making in cardiovascular medicine.[7,32,51] In summary, the ability of novel biomarkers to provide independent new information about a disease or its prognosis, which is not available through traditional risk factors or existing biomarkers, is a fundamental characteristic necessary for their successful integration into clinical practice.

3) Validation Aspects: 35 articles identified validation aspects as important factors for uptake into clinical practice. It's indeed crucial to rigorously validate novel biomarkers before their adoption into clinical practice. Evidence for a many of the novel biomarkers is based on retrospective, observational cohorts

and prospective validation is still needed.[7] Additionally, a systematic approach in biomarker discovery and validation is essential for the successful integration of novel biomarkers into routine clinical practice,[19,34] and the validation for novel biomarkers requires the research to be representative of at-risk populations.[18,23,29,54] There is global, regional, and national burden of cardiovascular diseases, which highlights the vast diversity and complexity of these conditions.[3,18,39,47,54,58,63] It is essential to validate the clinical utility of these novel biomarkers through robust large-scale studies across diverse populations to ensure their reproducibility and generalizability.[1,3,18,22-24,27,39,41,43,56,64-66] Biomarker validation should involve validation in independent populations and different subsets of populations.[19,34,50] Furthermore, the U.S. Food and Drug Administration emphasizes the need for well-characterized study populations with a wide age range for biomarker validation. Also, there is a need for further larger collaborative studies for biomarker discovery and validation based on standardized protocols for sample collection and processing, and data analysis.[3,12,18,20,22,27,44,47-49,54-57,61,62] This ensures that the biomarker performs consistently across diverse demographic and clinical groups. Public policies should support research initiatives that establish the clinical utility and accuracy of these biomarkers across racial/ethnic diverse populations,[7,19,21,24,27,35,39,43,58] and for research for sex-specific, race/ethnicity-specific, and clinical subgroup-specific biomarkers if needed for higher performance.

Standardization of methods, assays, and analysis plays a crucial role in validating novel biomarkers by ensuring the accuracy and reproducibility of results. Standardization is critical to address sources of variability in the pre-analytical and analytical stages of biomarker assessment.[3,32] Standardization helps mitigate influences from factors like sample storage conditions, type of biological sample, and assay design, thereby enhancing the reliability of biomarker measurements.[3,32] Additionally, the adoption of standard methodologies in data acquisition, such as those related to sample processing, RNA extraction, and miRNA measurement platforms, contributes to the robustness and reliability of biomarker analysis.[62] Moreover, the public disclosure of crucial details, including reagent catalog and batch numbers, computational codes and programs, and data processing parameters, promotes transparency and reproducibility in biomarker research.[21,61] By adhering to standardized methods and assays, researchers can foster consistency in biomarker measurements and enhance the comparability of results across different studies and laboratories. This not only facilitates the validation of novel biomarkers but also reinforces their potential for clinical applicability and translational relevance. Therefore, standardization serves as a cornerstone in establishing the validity and utility of novel biomarkers, laying the foundation for their successful implementation in clinical practice.

4) Performance Characteristics: 44 articles identified various performance characteristics that should be considered when integrating novel biomarkers into clinical practice. The performance of a biomarker can be defined based on its ability to discriminate and classify disease risk or prognosis, diagnose disease, and identify the etiology of disease.[1,2,7,31-34,39,42,46,48,54,56,61,62,64,67,68] Discriminating and classifying disease risk or prognosis involves assessing the biomarker's ability to predict the likelihood of developing a disease or the likely course of an existing condition.[1,7,31,34,37,39,51-53,62] The diagnostic performance assesses the biomarker's capability to differentiate between individuals with and without a specific disease.[31,32,34,38,53,59] Finally, identifying the etiology of disease evaluates how well the biomarker can provide information about the underlying cause or origin of the disease.[18,22,29,33,36,39,44,55] Whether for risk, prognosis, or diagnosis biomarkers need to have clearly defined cut-off and/or reference values in order to be effectively utilized in clinical practice.[20,21,28,43,48,50,53,54,69] Key statistical tools such as sensitivity,

specificity, and area under the curve analysis are important performance elements are important elements that are needed to demonstrate a biomarker's performance.[1,3,12,18,27,28,41,42,45,47,51-54,56,57,62-64,67]

5) Decision-Making Support: 40 articles identified the need for novel biomarkers to aid and/or improve decision-making for implementation into clinical practice. Novel biomarkers should play a crucial role in supporting clinical decision-making,[3,7,15-17,19-21,24-26,30-36,38,39,43,46-48,50,53,55,57-60,62,64,66,69,70] especially in the context of personalized medicine.[22,37,40,52] They provide valuable information that can guide healthcare clinicians in making more informed treatment decisions for their patients.[22,32,52] The use of biomarkers as predictive, prognostic, and therapeutic tools can help in identifying individuals who are more likely to respond to a specific therapy, thus improving personalized treatment approaches.[7,43,52] Furthermore, the accurate and reliable measurement of biomarkers is essential for their clinical and public health utility.[7,21,32,33,35,36,39,47] An area of research focus should be to assess strategies for implementing novel biomarkers into clinical practice and public health to determine whether they help to optimize decision-making and disease management.[39]

   Clinicians must be educated about the significance of these biomarkers and their potential impact on patient management, which requires ongoing training and updates on the latest advancements in biomarker research.[34] Patient awareness of these novel biomarkers is equally important, as it can contribute to shared decision-making between patients and clinicians.[21] Enhancing patients' understanding of biomarkers can lead to improved adherence to treatment plans and better engagement in their healthcare journey.

Table 1: Key Standards for Novel Biomarker Development and Integration into Public Policy

Standard	Description
Accessibility	Must offer added value compared to existing markers and be affordable for routine use; should be simple to measure, interpret, (relatively) non-invasive, and convenient for patients; and provide quick and accurate results. Point-of-care testing enhances accessibility.
Informational Value	Provide independent new information about a disease or its prognosis that is not available through traditional risk factors or existing biomarkers.
Validation Aspects	Essential to validate the clinical utility of these novel biomarkers through robust large-scale studies across diverse populations to ensure their reproducibility and generalizability
Performance Characteristics	A biomarker's ability to discriminate and classify disease risk or prognosis, diagnose disease, and/or identify the etiology of disease.
Decision-Making Support	Provide valuable information that can guide clinicians in making more informed treatment decisions for their patients.

It is very difficult for biomarkers to reach these standards. Even very well-established biomarkers sometimes do not meet all these criteria.[51] Several of the articles also promoted the use of multi-marker or biomarker panel approaches to address these factors.[7,15,21,23,26,27,31,32,34,39,44,47,49,50,53,57,65,66] A multi-biomarker approach might grant broader information across different pathophysiologic pathways, which in turn might be

helpful for the daily clinical management of clinical conditions.[15] Nevertheless, novel biomarker panels, as a whole panel, should meet the key standards described in this section.

What are the public policy concerns for cardiovascular disease and stroke biomarkers?

There were 14 articles reviewed that were identified as highlighting the potential public policy concerns for cardiovascular and stroke biomarkers (see **Appendix B** for a summary of the conclusions and recommendations from each of the articles). From this literature there were several public policy concerns that arose, including validity and reliability, regulatory and legal considerations, economic feasibility, equity, collaborative development pathways, and ethical considerations.

1) Validity and Reliability: Regulatory agencies should provide clear guidance for biomarker validation and approval processes.[47] Ensuring the clinical validity and reliability of novel blood biomarkers is crucial. Numerous novel biomarkers are not translated into clinical practice due to inadequate appreciation of the performance characteristics and the rigor required to identify, test, and validate biomarkers.[19] There is a need to emphasize more prospective studies to validate biomarkers for ischemic stroke.[71] Without robust validation, there is a risk of misdiagnosis or inappropriate treatment plans.[19,71] Regulatory agencies can provide crucial guidance for biomarker validation and approval through established processes and requirements.[19] Regulation can further mandate clinical performance data, scientific validity reports, and benefit/risk analysis for regulatory approval.[19] Regulatory guidance may include requirements to demonstrate the technical, preclinical, and clinical validation of the biomarker, stability of the biomarker, and clinical utility.[19,47] Moreover, the accuracy, reproducibility, and standardized measurement are essential factors that may be emphasized within these regulatory guidelines.[47] These processes are crucial in ensuring that novel biomarkers meet established standards for accuracy, validation, and clinical utility before approval and implementation.[19,52] To achieve successful navigation of these regulatory pathways, collaboration and communication among researchers, regulatory bodies, industry stakeholders, and clinicians are vital, as they play significant roles in driving standards and improvements in biomarker research and implementation.[19,52]

2) Regulatory and Legal Considerations: The legal framework surrounding biomarkers could be better defined to facilitate innovation through the establishment of clear guidelines for the qualification and utilization of new methodologies for specific uses. The evolving technologies in the fields of genomics, proteomics, and metabolomics pose unique challenges in the development, validation, and implementation of new cardiovascular biomarkers.[19,72] The legal framework, including the complexities of patent laws, surrounding biomarkers needs to be clearly defined to facilitate innovation while protecting intellectual property rights.[19,52] Frameworks for companion diagnostics, which are crucial for the use of medicinal products, are also a vital legal aspect that influences biomarker innovation.[24] The regulatory field of drug development relies on several factors such as proof of concept, dose finding, and characterization of safety, among others, which determine the requirements for accepting a biomarker in this context.[19] Moreover, legal considerations are integral in ensuring the standardization and traceability of biomarker measurements.[47] This includes the establishment of reference methods and materials for the standardization of measurements, contributing to the reliability and comparability of biomarker data.[72] There is a need to work toward establishing clear legal and regulatory frameworks for biomarker development and usage.[24,47] This involves navigating patent laws and ensuring ethical standards are maintained in biomarker research and application.

3) Economic Feasibility: To comprehensively describe the economic factors related to novel biomarker implementation, several aspects can be considered, such as cost-effectiveness, development costs, reimbursement, and insurance coverage.[19] Policies should support economic evaluations to determine the value of these biomarkers in improving patient outcomes.[39] The commercialization pathway is integral to ensuring the translation of biomarkers into clinical practice, encompassing the establishment of standard protocols for assays, defining the market, and providing the service.[52] Cost-effectiveness is a crucial element in the adoption of novel biomarkers, as their clinical utility and impact on patient outcomes need to justify the investment in their development and implementation.[39,47] Reimbursement and insurance coverage play a significant role in the accessibility and utilization of novel biomarkers. New and potentially expensive biomarkers may not be immediately covered under standard insurance plans, restricting access for a substantial segment of the population.[52] However, reimbursement policies should align with the clinical utility and cost-effectiveness data.[39] Policymaking should focus on promoting cost-effective alternatives to make these biomarkers widely accessible.[39,52] Collaboration with health insurance plans and policymakers to advocate for the inclusion of those novel biomarkers that meet the recommendations above for adoption into clinical practice in insurance coverage. Also, work toward making these biomarkers affordable, possibly through subsidies or regulatory measures.

4) Equity: A critical policy concern is ensuring equitable access to novel biomarkers for all populations. Disparities in healthcare access and outcomes based on race, ethnicity, socioeconomic status, and geographic location are well-documented. It is evident that implementing policies to promote affordable and widespread access to encourage diversity, including race/ethnicity, sex, socioeconomic status, and geographic region, during the development, validation, and implementation of novel biomarkers is crucial.[56,61,71-74] There is a risk that these biomarkers might not be uniformly effective across different demographic groups, potentially exacerbating health disparities.[71-75] Policies that could achieve this goal may include: encouraging diversity in clinical trials by ensuring representation of diverse populations based on race, ethnicity, sex, socioeconomic status, and geographic region to improve the generalizability of findings;[19,52,61,71] developing and implementing policies that emphasize ethical considerations and regulatory guidelines to promote equity and equal access to novel biomarkers across diverse populations;[19,61,72] implementing policies aimed at ensuring affordable access to novel biomarkers for diverse populations, including considerations for reimbursement, insurance coverage, and cost-effectiveness;[19] and policies focused on education and awareness campaigns aimed at healthcare clinicians and patients regarding the importance of diversity in biomarker development and utilization.[52] These are some high-level policy considerations that could be implemented to promote affordable and widespread access to encourage diversity during the development, validation, and implementation of novel cardiovascular and stroke biomarkers. In this way, novel biomarkers become equity-enhancing, allowing for early diagnosis and treatment.

5) Collaborative Development Pathways: Biomarker development and implementation depend on collaborative efforts and must be founded on actionable, quantifiable clinical information.[19,47] Developing a clear pipeline linking scientific and industrial sectors is essential to ensure that these biomarkers are effectively incorporated into healthcare practices.[20,52] The proposed collaborations required to effectively incorporate biomarkers into healthcare practice involve a multidisciplinary approach. In the context of cardiovascular medicine, the involvement of various interested parties is essential, and should include researchers, clinicians, industry partners, regulatory bodies,

community/patients, and clinicians.[19,20,24,52] Promote collaboration between academia, industry, healthcare providers (including associated professional organizations and societies), and policy researchers.[20,24] Such partnerships are crucial for the successful translation of biomarker research into clinical and public health practice. Scientific research plays a critical role in the discovery and validation of biomarkers, which emphasizes the importance of coordinated efforts in ensuring the clinical value of novel biomarkers is rigorously demonstrated in both clinical trials and real-life implementation.[24,47] Policy makers also have a vital role in creating an environment conducive to biomarker development and implementation. In the context of cardiovascular health, regulatory bodies can address issues such as reimbursement, approval of companion diagnostics, and the establishment of guidelines for biomarker utilization.[24,52] To effectively link the scientific, industrial, and policy sectors in biomarker development, it is essential to foster collaboration, knowledge sharing, and data-driven approaches. Advocate for continued investment in the research and development of biomarkers. This includes funding for technological innovations and scientific research to enhance the understanding and utility of biomarkers.

6) Ethical Considerations: With the increasing use of biomarker data, protecting patient privacy is paramount. Public policies must establish robust data privacy and security regulations to safeguard sensitive health information.[75] This includes guidelines on data sharing, informed consent, and encryption.[24] Policies should emphasize the ethical considerations in biomarker research and usage, including informed consent, data privacy, and the responsible use of patient data.[24,75] Though these aspects are important to protect everyone, those individuals who are vulnerable to stigma-based inequities may gain particular benefit.[74,75] Furthermore, it is important to raise awareness among healthcare clinicians about discrimination and its impact on patient health, as well as the need for training efforts to reduce stigma in the healthcare setting to avoid perpetuating adverse experiences for patients.[74,75]

Conclusion

Novel CVD and stroke blood-based biomarkers could advance the prevention and treatment of these diseases, potentially revolutionizing patient care and public health strategies. However, there are thousands of blood-based biomarkers that have been developed and investigated, but only few have met standards to be used clinically in the diagnosis, prognosis and risk stratification of CVD in adults.[51] Furthermore, the growing fields of individualized medicine and -omics technology (genomics, proteomics, and metabolomics) have ushered in many more potential measures of cardiometabolic risk that may improve disease risk assessment.[56] **Table 2**, below, provides a summary of the key guidance from this review. Importantly, public policies should focus on validation, education, promoting equity, cost-effectiveness, and data security to maximize the potential benefits of these biomarkers for all populations. The American Heart Association supports public policies that fund robust research for validation and cost-effectiveness, equitable access to these novel biomarkers in the context of clinical care, patient and professional education, and data security to optimize the benefits of novel biomarker use in patient care and clinical research.

Table 2: Key Guidance for the American Heart Association's Public Policy Development of Novel Blood Cardiovascular and Stroke Biomarkers

Guidance	Description

CVD Novel Biomarkers

Prioritize Novel Biomarker Research	Encourage and support extensive research in the field of CVD and stroke biomarkers.
Advocate for Testing and Validation Standardization	Push for strict validation protocols and standardization of biomarker testing.
Promote Collaborative Development Pathways	Work to coordinated academics/science, industry, clinical experts, policy and regulatory bodies.
Promote Equitable Access	Develop policies that ensure equitable access to those novel biomarkers that meet the standards for use in clinical practice.
Advocate for Ethical Practices	Uphold high ethical standards in the development and application of biomarkers.
Foster Public and Professional Education	Implement initiatives to educate both the public and healthcare professionals about the benefits, limitations, and ethical considerations of biomarker use.
Promote Continuous Monitoring and Evaluation	Establish mechanisms for ongoing monitoring and evaluation of biomarker use in clinical settings.

References

1. Naik A, Adeleye O, Koester SW, Winkler EA, Hartke JN, Karahalios K, Mihaljevic S, Rani A, Raikwar S, Rulney JD, et al. Cerebrospinal Fluid Biomarkers for Diagnosis and the Prognostication of Acute Ischemic Stroke: A Systematic Review. *International Journal of Molecular Sciences*. 2023;24:10902. doi: 10.3390/ijms241310902
2. Chen X, Li S, Chen W, Xu F, Wang Y, Zou G, Ren B. The Potential Value of D-Dimer to Fibrinogen Ratio in Diagnosis of Acute Ischemic Stroke. *Journal of Stroke and Cerebrovascular Diseases*. 2020;29:104918. doi: https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104918
3. Montaner J, Ramiro L, Simats A, Tiedt S, Makris K, Jickling GC, Debette S, Sanchez J-C, Bustamante A. Multilevel omics for the discovery of biomarkers and therapeutic targets for stroke. *Nature Reviews Neurology*. 2020;16:247-264. doi: 10.1038/s41582-020-0350-6
4. Thomas MR, Lip GYH. Novel Risk Markers and Risk Assessments for Cardiovascular Disease. *Circulation Research*. 2017;120:133-149. doi: 10.1161/circresaha.116.309955
5. Califf RM. Biomarker definitions and their applications. *Experimental Biology and Medicine*. 2018;243:213-221. doi: 10.1177/1535370217750088
6. FDA-NIH Biomarker Working Group. *BEST (Biomarkers, EndpointS, and other Tools) Resource*. Silver Spring (MD): Food and Drug Administration (US); Bethesda (MD): National Institutes of Health (US); 2016-.
7. Lyngbakken MN, Myhre PL, Røsjø H, Omland T. Novel biomarkers of cardiovascular disease: Applications in clinical practice. *Critical Reviews in Clinical Laboratory Sciences*. 2019;56:33-60. doi: 10.1080/10408363.2018.1525335
8. Zola H. Novel biomarkers. *Pathology*. 2009;41:41. doi: https://doi.org/10.1097/01268031-200941001-00087
9. Markus A, Valerie S, Mira K. Promising Biomarker Candidates for Cardioembolic Stroke Etiology. A Brief Narrative Review and Current Opinion. *Frontiers in Neurology*. 2021;12. doi: 10.3389/fneur.2021.624930

10. Jickling GC, Sharp FR. Biomarker Panels in Ischemic Stroke. *Stroke*. 2015;46:915-920. doi: 10.1161/strokeaha.114.005604
11. Montalescot G, Guedeney P, Tijssen J. A Multi-Biomarker Score for a Global Approach of Risk: Time for a Change?∗. *Journal of the American College of Cardiology*. 2022;80:898-901. doi: https://doi.org/10.1016/j.jacc.2022.06.018
12. Li W, Shao C, Zhou H, Du H, Chen H, Wan H, He Y. Multi-omics research strategies in ischemic stroke: A multidimensional perspective. *Ageing Research Reviews*. 2022;81:101730. doi: https://doi.org/10.1016/j.arr.2022.101730
13. Skov J, Kristiansen K, Jespersen J, Olesen P. Status and perspectives of biomarker validation for diagnosis, stratification, and treatment. *Public Health*. 2021;190:173-175. doi: 10.1016/j.puhe.2020.11.002
14. Horvath AR, Kis E, Dobos E. Guidelines for the use of biomarkers: Principles, processes and practical considerations. *Scandinavian Journal of Clinical and Laboratory Investigation*. 2010;70:109-116. doi: 10.3109/00365513.2010.493424
15. Salzano A, Marra AM, D'Assante R, Arcopinto M, Bossone E, Suzuki T, Cittadini A. Biomarkers and imaging: complementary or subtractive? *Heart Failure Clinics*. 2019;15:321-331.
16. Myhre PL, Lyngbakken MN, Tveit SH, Røsjø H, Omland T. Cardiac imaging and circulating biomarkers for primary prevention in the era of precision medicine. *Expert Review of Precision Medicine and Drug Development*. 2019;4:299-308. doi: 10.1080/23808993.2019.1660162
17. Castro AMJ. Biomarkers in heart failure. *CorSalud (Revista de Enfermedades Cardiovasculares)*. 2019;11:317-325.
18. Ravassa S, Delles C, Currie G, Díez J. Biomarkers of Cardiovascular Disease. In: *Textbook of Vascular Medicine*. Springer International Publishing; 2019:319-330.
19. Elliott P, Cowie MR, Franke J, Ziegler A, Antoniades C, Bax J, Bucciarelli-Ducci C, Flachskampf FA, Hamm C, Jensen MT. Development, validation, and implementation of biomarker testing in cardiovascular medicine state-of-the-art: proceedings of the European Society of Cardiology—Cardiovascular Round Table. *Cardiovascular research*. 2021;117:1248-1256.
20. Mayer CC, Climie R, Hametner B, Bruno R-M. The european cost action VascAgeNet fostering innovation-When industry comes to science. 2020.
21. Salzano A, D'Assante R, Israr MZ, Eltayeb M, D'Agostino A, Bernieh D, De Luca M, Rega S, Ranieri B, Mauro C. Biomarkers in heart failure: clinical insights. *Heart Failure Clinics*. 2021;17:223-243.
22. Vea A, Llorente-Cortes V, de Gonzalo-Calvo D. Circular RNAs: a novel tool in cardiovascular biomarker development. *Non-coding RNA Investig*. 2018;2:39.
23. Badianyama M, Mpanya D, Adamu U, Sigauke F, Nel S, Tsabedze N. New biomarkers and their potential role in heart failure treatment optimisation—An African perspective. *Journal of Cardiovascular Development and Disease*. 2022;9:335.
24. Figtree GA, Vernon ST, Nicholls SJ. Taking the next steps to implement polygenic risk scoring for improved risk stratification and primary prevention of coronary artery disease. *European Journal of Preventive Cardiology*. 2022;29:580-587.
25. Ekkert A, Šliachtenko A, Grigaitė J, Burnytė B, Utkus A, Jatužis D. Ischemic Stroke Genetics: What Is New and How to Apply It in Clinical Practice? *Genes*. 2021;13:48. doi: 10.3390/genes13010048
26. Wlodarczyk L, Szelenberger R, Cichon N, Saluk-Bijak J, Bijak M, Miller E. Biomarkers of Angiogenesis and Neuroplasticity as Promising Clinical Tools for Stroke Recovery Evaluation. *International Journal of Molecular Sciences*. 2021;22:3949. doi: 10.3390/ijms22083949
27. Marcovecchio ML. Importance of Identifying Novel Biomarkers of Microvascular Damage in Type 1 Diabetes. *Molecular Diagnosis & Therapy*. 2020;24:507-515. doi: 10.1007/s40291-020-00483-6
28. Vajpeyee A, Wijatmiko T, Vajpeyee M, Taywade O, Pandey S, Chauhan PS. Clinical Usefulness of Cell-Free DNA as a Prognostic Marker in Acute Ischemic Stroke. *The Neurologist*. 2020;25:11-13. doi: 10.1097/nrl.0000000000000249

29. Pulignani S, Borghini A, Andreassi MG. microRNAs in bicuspid aortic valve associated aortopathy: Recent advances and future perspectives. *Journal of Cardiology*. 2019;74:297-303. doi: 10.1016/j.jjcc.2019.03.005
30. Paul S, Harshaw-Ellis K. Evolving Use of Biomarkers in the Management of Heart Failure. *Cardiology in Review*. 2019;27:153-159. doi: 10.1097/crd.0000000000000224
31. Desiree W, Eleni M, Maria B, Nikola K, Matthias D, DANIELLE MG, Tobias B, Christian M. Mortality prediction in acute heart failure: scores or biomarkers? *Swiss Medical Weekly*. 2020;150:w20320.
32. Castiglione V, Aimo A, Vergaro G, Saccaro L, Passino C, Emdin M. Biomarkers for the diagnosis and management of heart failure. *Heart Failure Reviews*. 2022;27:625-643. doi: 10.1007/s10741-021-10105-w
33. Pinilla L, Barbé F, Guerra JM, Llorente-Cortés V, de Gonzalo-Calvo D. Epigenetics in precision medicine of cardiovascular disease. In: *Epigenetics in Precision Medicine*. Elsevier; 2022:347-368.
34. Sarhene M, Wang Y, Wei J, Huang Y, Li M, Li L, Acheampong E, Zhengcan Z, Xiaoyan Q, Yunsheng X. Biomarkers in heart failure: the past, current and future. *Heart failure reviews*. 2019;24:867-903.
35. Wankhede NL, Rai KKR, Anandpara TM, Hirave KS, Trivedi RV, Kale MB, Umekar MJ, Wadher KJ. Biomarkers of Cardiovascular Disease and Future Directions: A Review. *Int J Pharm Sci Rev Res*. 2023;79:54-67. doi: 10.47583/ijpsrr.2023.v79i02.011
36. Adusumalli R. Biomarkers for early diagnosis and management of cardiovascular diseases. *Advances in Bioscience and Clinical Medicine*. 2022;10:16-20. doi: 10.7575/aiac.abcmed.v.10n.1p.16
37. Vekic J, Zeljkovic A, Al Rasadi K, Cesur M, Silva-Nunes J, Stoian AP, Rizzo M. A New Look at Novel Cardiovascular Risk Biomarkers: The Role of Atherogenic Lipoproteins and Innovative Antidiabetic Therapies. *Metabolites*. 2022;12:108. doi: 10.3390/metabo12020108
38. Leite AR, Borges-Canha M, Cardoso R, Neves JS, Castro-Ferreira R, Leite-Moreira A. Novel Biomarkers for Evaluation of Endothelial Dysfunction. *Angiology*. 2020;71:397-410. doi: 10.1177/0003319720903586
39. Wong Y-K, Tse H-F. Circulating Biomarkers for Cardiovascular Disease Risk Prediction in Patients With Cardiovascular Disease. *Frontiers in Cardiovascular Medicine*. 2021;8. doi: 10.3389/fcvm.2021.713191
40. Serra R, Jiritano F, Bracale UM, Ielapi N, Licastro N, Provenzano M, Andreucci M, Rizzuto A, Mastroroberto P, Serraino GF. Novel biomarkers in cardiovascular surgery. *Biomarkers in Medicine*. 2021;15:307-318.
41. Li X, Xu L, Xu Z. The diagnostic and prognostic performance of Lp-PLA2 in acute ischemic stroke. *Medicina Clínica*. 2021;156:437-443. doi: https://doi.org/10.1016/j.medcli.2020.11.034
42. Smith ER, Hewitson TD, Holt SG. Diagnostic Tests for Vascular Calcification. *Advances in Chronic Kidney Disease*. 2019;26:445-463. doi: 10.1053/j.ackd.2019.07.001
43. Esteve-Pastor MA, Roldán V, Rivera-Caravaca JM, Ramírez-Macías I, Lip GYH, Marín F. The Use of Biomarkers in Clinical Management Guidelines: A Critical Appraisal. *Thrombosis and Haemostasis*. 2019;119:1901-1919. doi: 10.1055/s-0039-1696955
44. Cipollini V, Troili F, Giubilei F. Emerging Biomarkers in Vascular Cognitive Impairment and Dementia: From Pathophysiological Pathways to Clinical Application. *International Journal of Molecular Sciences*. 2019;20:2812. doi: 10.3390/ijms20112812
45. Wang S-W, Liu Z, Shi Z-S. Non-Coding RNA in Acute Ischemic Stroke: Mechanisms, Biomarkers and Therapeutic Targets. *Cell Transplantation*. 2018;27:1763-1777. doi: 10.1177/0963689718806818
46. Ioannou A, Papageorgiou N, Falconer D, Rehal O, Sewart E, Zacharia E, Toutouzas K, Vlachopoulos C, Siasos G, Tsioufis C, et al. Biomarkers Associated with Stroke Risk in Atrial Fibrillation. *Current Medicinal Chemistry*. 2019;26:803-823. doi: http://dx.doi.org/10.2174/0929867324666170718120651
47. Makris K, Haliassos A, Chondrogianni M, Tsivgoulis G. Blood biomarkers in ischemic stroke: potential role and challenges in clinical practice and research. *Critical reviews in clinical laboratory sciences*. 2018;55:294-328.
48. Lanfermann S. Novel Biomarkers in Heart Failure with Reduced and Preserved Ejection Fraction in the General Population. In: Staats-und Universitätsbibliothek Hamburg Carl von Ossietzky; 2020.

49. Correale M, Monaco I, Brunetti ND, Di Biase M, Metra M, Nodari S, Butler J, Gheorghiade M, Failure MPSoDDfH. Redefining biomarkers in heart failure. *Heart Failure Reviews*. 2018;23:237-253.
50. Liem DA, Cadeiras M, Setty SP. Insights and perspectives into clinical biomarker discovery in pediatric heart failure and congenital heart disease—a narrative review. *Cardiovascular Diagnosis and Therapy*. 2023;13:83-99. doi: 10.21037/cdt-22-386
51. Sipos B, Jirak P, Paar V, Rezar R, Mirna M, Kopp K, Hoppe UC, Berezin AE, Lichtenauer M. Promising Novel Biomarkers in Cardiovascular Diseases. *Applied Sciences*. 2021;11:3654. doi: 10.3390/app11083654
52. Saleh S, George J, Kott KA, Meikle PJ, Figtree GA. The Translation and Commercialisation of Biomarkers for Cardiovascular Disease—A Review. *Frontiers in Cardiovascular Medicine*. 2022;9:897106.
53. Kamtchum-Tatuene J, Jickling GC. Blood biomarkers for stroke diagnosis and management. *Neuromolecular medicine*. 2019;21:344-368.
54. Halushka PV, Goodwin AJ, Halushka MK. Opportunities for microRNAs in the Crowded Field of Cardiovascular Biomarkers. *Annual Review of Pathology: Mechanisms of Disease*. 2019;14:211-238. doi: 10.1146/annurev-pathmechdis-012418-012827
55. Eltelbany M, Shah P, deFilippi C. Biomarkers in HFpEF for Diagnosis, Prognosis, and Biological Phenotyping. *Current Heart Failure Reports*. 2022;19:412-424.
56. Tahir UA, Gerszten RE. Omics and Cardiometabolic Disease Risk Prediction. *Annual Review of Medicine*. 2020;71:163-175. doi: 10.1146/annurev-med-042418-010924
57. Omran F, Kyrou I, Osman F, Lim VG, Randeva HS, Chatha K. Cardiovascular Biomarkers: Lessons of the Past and Prospects for the Future. *International Journal of Molecular Sciences*. 2022;23:5680. doi: 10.3390/ijms23105680
58. Oikonomou E, Zografos T, Papamikroulis G-A, Siasos G, Vogiatzi G, Theofilis P, Briasoulis A, Papaioannou S, Vavuranakis M, Gennimata V, et al. Biomarkers in Atrial Fibrillation and Heart Failure. *Current Medicinal Chemistry*. 2019;26:873-887. doi: http://dx.doi.org/10.2174/0929867324666170830100424
59. Quispe R, Das T, Michos ED. Biomarkers. In: *Precision Medicine in Cardiovascular Disease Prevention*. Springer International Publishing; 2021:31-64.
60. Anghel L, Sascău R, Zota IM, Stătescu C. Well-known and novel serum biomarkers for risk stratification of patients with non-ischemic dilated cardiomyopathy. *International Journal of Molecular Sciences*. 2021;22:5688.
61. Sopic M, Vilne B, Gerdts E, Trindade F, Uchida S, Khatib S, Wettinger SB, Devaux Y, Magni P. Multiomics tools for improved atherosclerotic cardiovascular disease management. *Trends in Molecular Medicine*. 2023.
62. Kiyosawa N, Watanabe K, Morishima Y, Yamashita T, Yagi N, Arita T, Otsuka T, Suzuki S. Exploratory Analysis of Circulating miRNA Signatures in Atrial Fibrillation Patients Determining Potential Biomarkers to Support Decision-Making in Anticoagulation and Catheter Ablation. *International Journal of Molecular Sciences*. 2020;21:2444. doi: 10.3390/ijms21072444
63. Tekesin A, Tunç A. Inflammatory markers are beneficial in the early stages of cerebral venous thrombosis. *Arquivos de Neuro-Psiquiatria*. 2019;77:101-105. doi: 10.1590/0004-282x20190001
64. Zhao J, Wang Q, Zhu R, Yang J. Circulating Non-coding RNAs as Potential Biomarkers for Ischemic Stroke: A Systematic Review. *Journal of Molecular Neuroscience*. 2022;72:1572-1585. doi: 10.1007/s12031-022-01991-2
65. Ke C, Pan C-W, Zhang Y, Zhu X, Zhang Y. Metabolomics facilitates the discovery of metabolic biomarkers and pathways for ischemic stroke: a systematic review. *Metabolomics*. 2019;15. doi: 10.1007/s11306-019-1615-1
66. Saenz-Pipaon G, Martinez-Aguilar E, Orbe J, Gonzalez Miqueo A, Fernandez-Alonso L, Paramo JA, Roncal C. The role of circulating biomarkers in peripheral arterial disease. *International Journal of Molecular Sciences*. 2021;22:3601.

67. Sun Y, Miller MM, Yaghi S, Silver B, Henninger N. Association of Baseline Cardiac Troponin With Acute Myocardial Infarction in Stroke Patients Presenting Within 4.5 Hours. *Stroke*. 2020;51:108-114. doi: 10.1161/strokeaha.119.027878
68. Csecsei P, Varnai R, Nagy L, Molnar T, Illes Z, Farkas N, Szapary L. L-arginine pathway metabolites can discriminate paroxysmal from permanent atrial fibrillation in acute ischemic stroke. *Ideggyógyászati Szemle*. 2019;72:79-88. doi: 10.18071/isz.72.0079
69. Stege NM, De Boer RA, Van Den Berg MP, Silljé HHW. The Time Has Come to Explore Plasma Biomarkers in Genetic Cardiomyopathies. *International Journal of Molecular Sciences*. 2021;22:2955. doi: 10.3390/ijms22062955
70. Sun J, Lv X, Gao X, Chen Z, Wei D, Ling Y, Zhang J, Gu Q, Liu J, Chen W, et al. The association between serum uric acid level and the risk of cognitive impairment after ischemic stroke. *Neuroscience Letters*. 2020;734:135098. doi: https://doi.org/10.1016/j.neulet.2020.135098
71. Florijn BW, Bijkerk R, Kruyt ND, Van Zonneveld AJ, Wermer MJH. Sex-Specific MicroRNAs in Neurovascular Units in Ischemic Stroke. *International Journal of Molecular Sciences*. 2021;22:11888. doi: 10.3390/ijms222111888
72. Trentini A, Manfrinato MC, Castellazzi M, Bellini T. Sex-Related Differences of Matrix Metalloproteinases (MMPs): New Perspectives for These Biomarkers in Cardiovascular and Neurological Diseases. *Journal of Personalized Medicine*. 2022;12:1196. doi: 10.3390/jpm12081196
73. Hackler E, Lew J, Gore MO, Ayers CR, Atzler D, Khera A, Rohatgi A, Lewis A, Neeland I, Omland T, et al. Racial Differences in Cardiovascular Biomarkers in the General Population. *Journal of the American Heart Association*. 2019;8. doi: 10.1161/jaha.119.012729
74. Diamond LM, Dehlin AJ, Alley J. Systemic inflammation as a driver of health disparities among sexually-diverse and gender-diverse individuals. *Psychoneuroendocrinology*. 2021;129:105215.
75. Panza GA, Puhl RM, Taylor BA, Zaleski AL, Livingston J, Pescatello LS. Links between discrimination and cardiovascular health among socially stigmatized groups: A systematic review. *PloS one*. 2019;14:e0217623.

Appendix A

Summary of the conclusions and recommendations from each of the articles addressing the factors for the integration on novel blood biomarkers into clinical practice.

Article	Year	Article Type	CVD/Stroke	Biomarker use	Conclusions/Recommendations
Naik, et al.	2023	Review	Ischemic Stroke	Diagnosis & Prognosis	Cost-effective
					High sensitivity/Specificity/AUC
					NPV/PPV/Diagnostic Accuracy
					Accessibility (safety & comfort to collect sample)
					Generalizable
Castro	2019	Review	Heart Failure	Diagnosis/Prognosis/Management	Have reasonable cost and completion time
					Provide information not yet available for clinical evaluation
					Must be useful in making medical decisions
Sipos, et al.	2021	Review	CVD	Diagnosis/Prognosis/Management	Reliability & Reproducibility
					Clinical Relevance
					Rapid Results

CVD Novel Biomarkers

Saleh, et al.	2022	Review	CVD	Diagnosis/Prognosis/Management	Personalized Assessment - phenotype/genetic predisposition
					Should provide greater predictive value than established tests or add to predictive value by improving sensitivity/specificity
					Useful for screening of conditions lacking such tools/practical to apply to an asymptomatic population
					Demonstrate improved outcomes (treatment guidance)
					Timely/Financially practical
Ravassa, et al.	2019	Review	CVD	Risk/Prognosis/Diagnosis/Management	Reliable/Repeatable
					Standardized methodologies
					High Specificity/Sensitivity
					Easily interpretable
					Cost effective
					validated in independent populations
					Should add incremental information beyond traditional risk or disease factors
Elliot, et al.	2021	Other	CVD	risk/diagnosis/prognosis/management	Superiority over standard of care
					Meet defined clinical need
					Improve efficacy or safety of patient management
					Practical and scalable
					Reproducible
					Cost effective
					Easily accessible (e.g., blood or urine)
Mayer, et al.	2020	Other	Vascular disease		Ease of use
					Standardized methodology
					Cost effective
					Incremental value additive to or over standard of care
					Clearly define reference values
					Improvement in clinical outcomes
Salzano, et al.	2019	Review	Heart Failure	Diagnosis/Prognosis/Management	Ideal should be suited for precision medicine approach
					Cost-effectiveness
					Clinical utility
					Widely available
Serra, et al.	2021	Review	Cardiovascular Surgery	Risk stratification	Easily measurable
					Add new information
					Improve clinical management
					Cost effective
					Support patient-tailored strategies
Salzano, et al.	2021	Review	Heart Failure	Risk/Diagnosis/Prognosis/Management/Phenotyping	Accurate and Repeatable
					Reasonable cost
					Timely
					Provide additional information, not already available
					Clear cut-offs

					Support clinical decision making
Wong & Tse	2021	Review	CVD	Primary & Secondary Risk Stratification	Cost effective
					Accurate and repeatable risk stratification
					Validated across populations (at large-scale)
					Optimize decision-making and therapeutic management
Vea, et al.	2018	Review	CVD	Diagnosis/Prognosis	Measurable in routine practice
					High accuracy & reproducibility
					Add new information not otherwise available
					Reasonable cost
					Standardized methodology & processes
					Validation across large, diverse population
Badianyama, et al.	2022	Review	Heart Failure	Treatment	Cost-effective
					validated on diverse (racial/ethnic) populations
					Cardiac-specificity
Tahir & Gerszten	2020	Review	Cardiometabolic Disease	Risk Prediction	Standardization of methodologies
					Diverse cohorts
					external validation
					Demonstrate improved risk prediction over traditional markers
					High sensitivity/specificity (discrimination)
Figtree, et al.	2022	Review	CAD	Risk Prediction	Ease of implementation/use
					clinic benefit
					cost-effectiveness
					Provide additive information to traditional risk scores
					Validated with diverse population
					Provide clear decision support
Myhre, et al.	2019	Review	CVD	Primary Prevention	Cost effectiveness (Benefit>cost)
					Ease of measurement (Non-invasive & Safe)
					Positively impact clinical management/decision making
					Provide superior information to existing tests
Li W, et al.	2022	Review	Ischemic Stroke	Stroke Differentiation/Treatment	Easily accessible (i.e., available in 'biofluids')
					High sensitivity/specificity
					Provide data not available otherwise
					Repeatable & verifiable
					Cost-effective
					Standardized methodologies (collection, processing, analysis)
Omran, et al.	2022	Review	CVD	Screening/diagnosis/prognosis/treatment	High specificity/sensitivity
					Clear clinical usefulness
					Clear advantage over established markers
					Standardized methodologies (including commercial availability)
Zhao, et al.	2022	Meta-Analysis	Ischemic Stroke	diagnosis	Consistent results from studies
					Clear clinical applicability

					High sensitivity/specificity/AUC (discrimination)
					Validation across diverse populations
Ekkert, et al.	2021	Review	Ischemic Stroke	Risk/Prevention	Objective findings
					Consistent results
					Clear applicability in clinical practice
					Provide information above traditional markers
					Cost effective
Wlodarczyk, et al.	2021	Review	Stroke Recovery	Recovery	Safe and non-invasive
					Measurement repeatable
					Cost-effective
					Quick results
					Not interfering with applied therapies
Stege, et al.	2021	Review	Genetic Cardiomyopathy	Diagnosis/Management	Provide clear clinical utility
					Clearly defined reference limits
					Strong predictive power
Li X, et al.	2021	Case-Control Study	Ischemic Stroke	diagnosis/prognosis	Safe & non-invasive
					Objective results
					High sensitivity/specificity
					Validated in a diverse population
Marcovecchio	2020	Review	Microvascular Damage	Risk prediction/disease progression	high sensitivity/specificity
					Replace or improve predictive power of established markers
					Accessible & easy collection
					Validated in two or more independent populations
					Standardized procedures
					Cost effective
Chen, et al.	2020	Cohort Study	Ischemic Stroke	diagnosis	High specificity to support diagnosis
					Economical
					Simple
					Quick
Montaner, et al.	2020	Review	Stroke	diagnosis/prognosis/management	Standardized assays
					Support clinical decision making
					Cost effective
					High sensitivity/specificity
					Validation in large cohort (ethnic and geographical diversity)
Kiyosawa, et al.	2020	Cohort Study	Atrial Fibrillation	Prognosis/management	Stable in body fluids (blood)
					Provide objective information for decision making in clinical practice
					Provide clear clinical value
					Standardization of methodologies (validation and analysis)
					Discriminate patients at high risk and/or suited for therapies (precision, accuracy, specificity, sensitivity)
Leite, et al.	2020	Review	Endothelial Dysfunction	diagnosis/prognosis	Representative of underlying disease
					Reproducible
					Useful to clinical judgment

					Correlated with disease severity
					Quantified by simple and low-cost methods
Vajpeyee, et al.	2020	Cohort Study	Ischemic Stroke	Diagnosis/Prognosis	Clear cut-point
					Accurate and high sensitivity/specificity
					Cost-effective
Smith, et al.	2019	Other	Vascular Calcification	Diagnosis/prognosis	Relatively non-invasive
					Economic
					Discriminatory
					Temporal stability
					Add information over established markers
Sun, et al.	2020	Cohort Study	Stroke Associated AMI	Diagnosis	High discriminatory value
					Clear clinical implication
Ke, et al.	2019	Review	Ischemic Stroke	Risk/Diagnosis	Multiple independent validations
					Consistent, repeatable
					Validated with diverse groups, which includes diverse controls
Esteve-Pastor, et al.	2019	Other	CVD	Disease Management	Simple and practical
					Contributes to clinical decision-making
					Relatively stable
					Repeatability
					Rapid results
					Uniformity in recommendation
					External validation to maximize generalizability
Pulignani, et al.	2019	Review	Valvular Disease	Diagnosis/Prognosis	Disease-related accuracy
					Cost-efficient
					Consistency of results
					Validation in large well-defined cohorts
Cipollini, et al.	2019	Review	Vascular Disease	Diagnosis/Prognosis	Quantify a definite biologic state
					Easily assessed
					Low-cost
					Data normalization
					Standardized methodology
					Patient friendly procedure
Csecsei, et al.	2019	Case-Control Study	Endothelial disfunction		Consistent results
					Temporal stability
Kamtchum-Tatuene & Jickling	2019	Review	Stroke	Diagnosis & Management	High sensitivity & specificity
					Discriminate between disease, disease-mimics, and healthy controls
					Very rapid test results
					Add to routine care
					Clear diagnostic cut-off
Tekesin & Tunç	2019	Case-Control Study	Cerebral Venous Thrombosis		Reference values
					validation in large population
					Temporal stability

					High sensitivity/Specificity
Wang, et al.	2018	Review	Ischemic Stroke		Easy collection
					High sensitivity/specificity
					Non-invasive
Halushka, et al.	2019	Review	CVD	Risk/diagnosis/prognosis	Well validated for their intended purpose
					High sensitivity/specificity (discrimination)
					Rapid measurement
					Clear cut-off
					Standardized methodologies
					Temporal stability
					Validated on large, well-characterized populations
Paul & Harshaw-Ellis	2019	Review	Heart Failure	Disease Management	Cost effective
					Non-invasive measurement
					Objective interpretation
Oikonomou, et al.	2019	Review	Heart failure related Atrial Fibrillation	Risk	Validation on large patient cohorts
					Clear clinical role
					Independent information above or additive to existing measures
Ioannou, et al.	2019	Review	Stroke risk in Atrial Fibrillation	Risk	Objectively quantifiable
					Improve accuracy of risk stratification (additive to or above existing measures)
					Safe
					Clear clinical benefit
Lyngbakken, et al.	2019	Review	CVD	risk/diagnosis/prognosis	Results available in a reasonable timeframe and cost
					Reliably measurable
					Add information to existing markers or assessments
					Validated with metrics of discrimination, calibration, and reclassification
					Strong and consistent association with disease
					Improve clinical management and decision-making
					Serial measurements should reflect treatment response and risk
Makris, et al.	2018	Review	Ischemic Stroke	Risk/Diagnosis/differentiation/Prognosis	Accurate and reproducible
					Standardized methodologies
					Acceptable to the patient
					Easy to interpret
					High sensitivity/specificity
					Changes disease management
					Available reference standard
					Consistently provides independent information that is above or additive to existing markers
					Validated in large patient cohorts
Desiree, et al.	2020	Review	Acute Heart Failure	Prognosis	Reproducible results
					Reasonable result turn-around time

					Reasonable cost
					Add new and clinically useful information
					Specific understanding of the pathophysiology of the biomarker
					Able identify patients at very high risk
					High accuracy for prognosis
Castiglione, et al.	2022	Review	Heart Failure	Diagnosis & Management	Measured accurately
					Easily available and interpretable
					Reasonable cost
					Results should be available quickly
					Biological variation should be well defined/Sources of error known
					Should give information on an important disease pathway
					Provide information not otherwise available
					Should guide diagnosis, risk stratification, or management
Lanferman n	2020	Cross-Sectional Study	Heart Failure	Diagnosis/Prognosis	Methodologies well-tested and established
					Easily measurable in a timely manner and reasonable cost
					Add new information independently and/or in additional to other markers or examinations
					Clear cut-off values
					Aid in disease management
					Identify causes of HF
					Diagnose and risk stratify disease
Pinilla, et al.	2022	Review	CVD	Prevention/Diagnosis/Management	Accurate, Reliable, reproducible
					Add new information not already available
					Assists in clinical decision-making and risk assessment
					Cost-effective (including benefit to healthcare system)
					Easily measurable in routine practice
Quispe, et al.	2021	Review	CVD	Prognosis/disease progression	Repeatedly and accurately measured
					Provide information on normal biological and pathological processes
					Change clinical management by guiding shared decision-making
Anghel, et al.	2021	Review	Dilated Cardiomyopathy	risk stratification/Prognosis	Repeated with cost-effective methods
					Provides more information compared to other tests
					Clinically useful for decision making
Correale, et al.	2018	Review	Heart Failure	Prognosis	Should be accurate and standardized
					Acceptable for the patient
					Easy to interpret for clinicians
					Sensitive and highly specific for the outcome
					Incremental value above/beyond standard measures
Wankhede, et al.	2023	Review	CVD	Risk/Disease management	Be accurate and have therapeutic impact with early intervention

					Provide incremental information over and above existing measures
					Be cost-effective
Saenz-Pipaon, et al.	2021	Review	PAD	Diagnosis/Outcome assessment	Validated on Large diverse cohorts
					Validated over longer follow-up periods
					Demonstrate clear clinical utility
Sarhene, et al.	2019	Review	Heart Failure	Diagnosis/Management	Ideally in constant circulation
					Have incremental value over existing measures
					Provide clear clinical utility (diagnosis, risk stratification, and management) with demonstrated effective clinical outcomes (decision-making and clinical care)
					Be prospectively validated
					Be able to determine the presence of HF Syndrome, assess severity, and foresee risk of disease progression
					Be cost-effective
					Evaluation on a wide range of patient characteristics
					Have defined biological variability and low analytical precision
					Allow repetitive and precise measurements with a rapid processing time
Eltelbany, et al.	2022	Review	HFpEF	Pathophysiology/diagnosis/Prognosis	Valid measure with rapid turnaround at reasonable cost
					Provide new and beneficial information
					Assist in decision making process
					Should reflect an important pathophysiologic pathway
					Thorough validation through standardized methodologies
					Assays used should be robust
Sopic, et al.	2023	Review	ASCVD	Management	Validation through standard study design and methodologies
					Clear guidelines on preanalytical considerations to ensure coherence, accuracy, and reproducibility.
					Provide more information to better stratify patients
					Standardized Data integration algorithms to collect comprehensive data sets, with strong safeguards to prevent bias related to ethnicity, gender, and socioeconomic status
					Standardized data interpretation
Adusumalli	2022	Review	CVD	Diagnosis and Management	Accurate and reproducible
					Stabile
					Easily accessible assay
					Reasonable cost
					high throughput
					Rapid turnaround
					Adds new information to existing tests

					Provide strong link to disease
					Clinically useful for patient management
Liem, et al.	2023	Review	Pediatric Congenital Heart Disease	Diagnosis/Management	Objectively quantified
					Reproducible
					Repeatedly measured over time and follow-up
					Defined cut-offs and reference ranges for specific indications
					less invasive and safe
					Easily measured at relatively low costs
					Addresses a defined clinical need
					validation across appropriate cohorts
Vekic, et al.	2022	Review	ASCVD	Residual CV Risk	Predict clinically significant outcomes and patient response to therapy
					Cost-effective
					Focused toward personalized medicine

Appendix B

Summary of the conclusions and recommendations from each of the articles addressing the public policy concerns of novel blood biomarkers.

Article	Year	Article Type	CVD/Stroke	Biomarker use	Conclusions/Recommendations
Florijn, et al.	2021	Review	Ischemic Stroke	Risk/Management	More studies need to be done to validate biomarkers in women
					Compelling evidence for sex-specific microRNAs that could predict silent cerebral ischemia and identify effective therapeutic strategies for women
Saleh, et al.	2022	Review	CVD	Diagnosis/Prognosis/ Management	Patents laws - 1) differs from nature/natural processes; 2) consists of inventive concepts; 3) significantly differs from routine practice
					Need to develop a viable commercially incentivized pathway
					Clear pipeline linking scientific, industrial, and regulatory bodies
Elliot, et al.	2021	Other	CVD	Risk/Diagnosis/Prognosis/Management	Demonstrated technical, preclinical, & clinical validation
					Demonstrated clinical utility
					Demonstrated stability
					Clear development pathway
Mayer, et al.	2020	Other	Vascular disease		Pathway between academia, industry, society (i.e., patients), and government
Wong & Tse	2021	Review	CVD	Primary & Secondary Risk Stratification	Health policy needs to be informed by cost-effectiveness
Tahir & Gerszten	2020	Review	Cardiometabolic Disease	Risk	Lack of diversity and representation of historically underrepresented groups
					Clear pathways from discovery to validation are crucial

CVD Novel Biomarkers

Figtree, et al.	2022	Review	CAD	Risk	Clear clinical pathways (science/academics, health economics, policy)
					Enable clinical environment for evidence-based integration
					Ethical considerations (consent, identification of High-risk populations)
					clinical, policy, and consumer leaders need to work close together regarding disclosure of genetic risk
Li W, et al.	2022	Review	Ischemic Stroke	Stroke Differentiation/ Treatment	Proven effectiveness in clinical practice
					Use of Machine Learning/AI
Makris, et al.	2018	Review	Ischemic Stroke	Risk/Diagnosis/ Differentiation/Prognosis	Team of academics/scientists select biomarkers that show promise to standardize/harmonize
					Biomarkers must fulfill specific criteria, including promise for lab automation
					IFCC lead standardization/harmonization process with industry involvement
Hackler, et al.	2019	Cross Section Study	ASCVD	Risk	Racial differences in biomarkers reflect different pathological pathways (may contribute to or mediate racial differences in disease risk)
Panza, et al.	2019	Review	Cardiovascular Health	Risk	Social discrimination (race, weight, sexual orientation) and related stigma are strongly correlated with biomarkers of adverse cardiovascular health
					CDC/WHO recognize stigma as a public health priority because of potential to accelerate disease process
					Lack of studies examining non-black racial/ethnic groups and discrimination
					Impact of discrimination based on age, gender (transgender or questioning), or bisexual orientation is understudied
Diamond, et al.	2021	Review	Systemic Inflammation	Risk	Extensive variation in type and severity of health disparities in sexually-diverse and gender-diverse populations
					Need for more biologically-specific research through which social stigmas (across diverse manifestations) influence disease-relevant processes
					Need to define sexual- and gender-diverse populations more broadly (e.g., trans-male, trans-female, asexual, intersex)
Sopic, et al.	2023	Review	ASCVD	Disease Management	Safeguards to ensure diversity to prevent bias based on ethnicity, gender, and socioeconomic status.
					Safeguards to protect patient privacy/confidentiality (appropriate de-identification and secure transfer protocols)
					Researchers, analytic specialists, clinicians, data scientists need to work together
					Regulatory approval through established procedures
Trentini, et al.	2022	Review	CVD	Prognosis/Progression	Studying sex differences is paramount in the era of precision medicine.

					Sex usually considered confounding factor to correct statistical models. Sex differences (across the lifespan) should be evaluated in biomarker studies.
					Systematic disaggregation and analysis by sex is important for biomarker translation into clinical practice.