Circulation

AHA POLICY STATEMENT

Genetic and Genomic Testing in Cardiovascular Disease: A Policy Statement From the American Heart Association

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ABSTRACT: The rapid advancement of genomic and precision medicine has expanded the role of genetics and genomics in the diagnosis, risk stratification, and management of cardiovascular diseases. With the decreasing cost and increasing accessibility of genetic testing, its clinical utility continues to expand, necessitating updated policies to ensure equitable access, appropriate regulatory oversight, and ethical data stewardship. This policy statement by the American Heart Association provides a framework addressing key policy areas, including equitable implementation of genetic testing, the impact of federal regulations, data privacy concerns, reimbursement for genetic counseling services, and the integration of emerging technologies such as artificial intelligence in cardiovascular genomics into clinical practice. This policy statement underscores the importance of strategic investments in biobanking and genomic research across all populations to enhance variant interpretation and to improve risk prediction models. In addition, it highlights the evolving landscape of pharmacogenomics, polygenic risk scores, and precision public health approaches to cardiovascular disease prevention. By advocating for a multidisciplinary approach that bridges scientific innovation, clinical application, and policy development, this policy statement aims to optimize the benefits of genetic and genomic testing while mitigating disparities and ethical challenges in its implementation.

Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ genetic testing ■ genomic medicine ■ genomics ■ policy

The era of genomic and precision medicine has ushered in an expanding role for genetics and genomics in the care of individuals with and at risk for cardiovascular disease, including stroke. Genetic testing plays a central role in the diagnosis, risk prediction and mitigation, and clinical management of individuals with both heritable cardiac disease and a growing role in acquired cardiac disease.[1,2] Given the falling cost, increased accessibility, and widening indications for use, clinical cardiovascular genetic testing is becoming more available. Furthermore, research-based genetic and genomic science is rapidly growing and propelling the development of entirely new approaches to treating both common and rare cardiovascular diseases. Ensuring that these advances are both broadly accessible and equitably implemented requires thoughtful public policy with collaborators among those in clinical practice; payers; federal, state, and local agencies; nongovernmental organizations; legislatures; and researchers (Figure 1). The goal of this policy statement is to articulate the position of the American Heart Association (AHA) in key areas of public policy concerning genetic (≥1 genes) and genomic (coding and noncoding genome) testing. This policy statement updates a previous AHA policy statement published more than a decade ago[3] and addresses expanding issue areas around genetic and genomic testing, including (1) the role of genetics and genomics in individual and population health, (2) equity in the implementation of genetics and genomic testing in clinical practice, (3) development and support of large biobanks and population genomic studies critical to the advancement of the field, and (4) precision therapeutics. Although data sharing and privacy are central to many aspects of this policy statement, they are addressed in a separately published policy statement[4]

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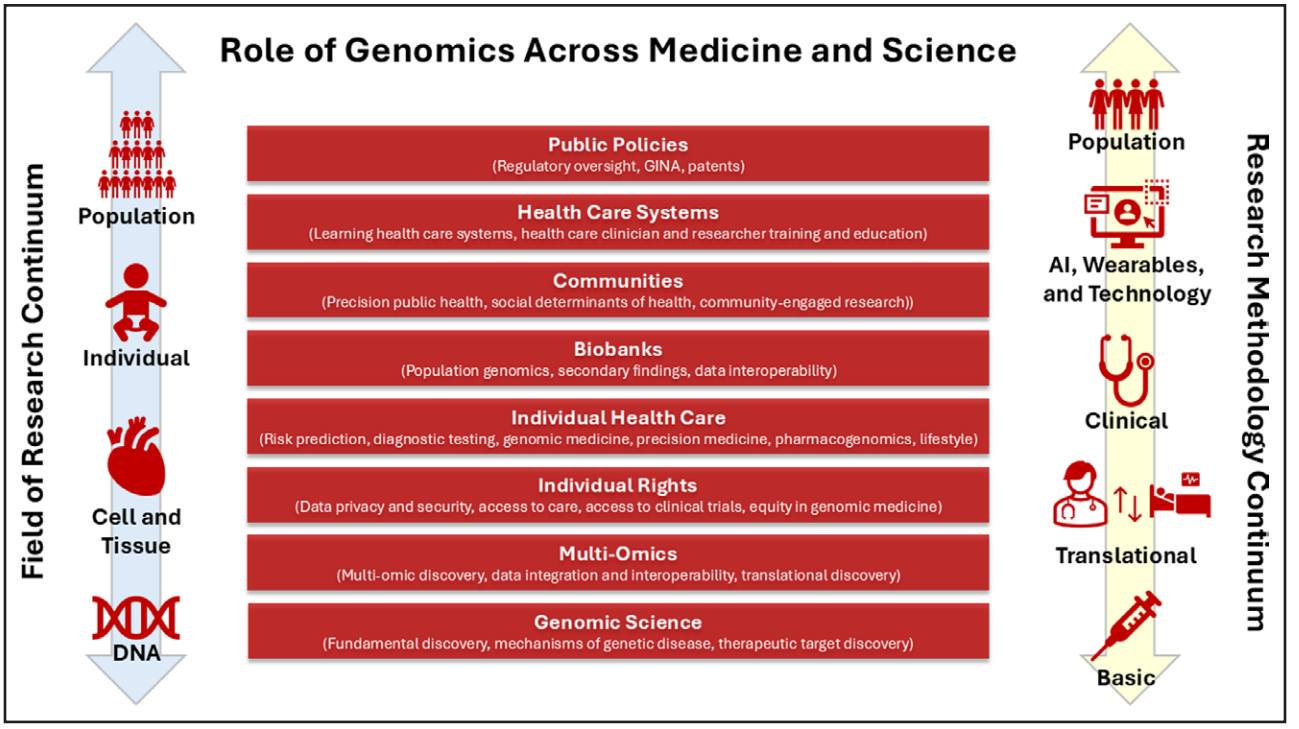

Figure 1. Visual representation of the role of genomics in clinical medicine and cardiovascular sciences.
Genomics is fundamental to understanding cardiovascular disease, spanning a broad spectrum of research fields and methodologies. In addition, genetic and genomic policies influence a similarly wide range of topics within medicine and science. AI indicates artificial intelligence; and GINA, Genetic Information Nondiscrimination Act.

that serves as an important foundation for this content. Furthermore, the policy guidance provided in this policy statement is focused on the US health care and research environment. Overall, this policy statement emphasizes a strong commitment to equitable genetic testing accessibility, effective clinical implementation and discoveries for patients, and amplification of the voices of patients and their families (Figure 2).

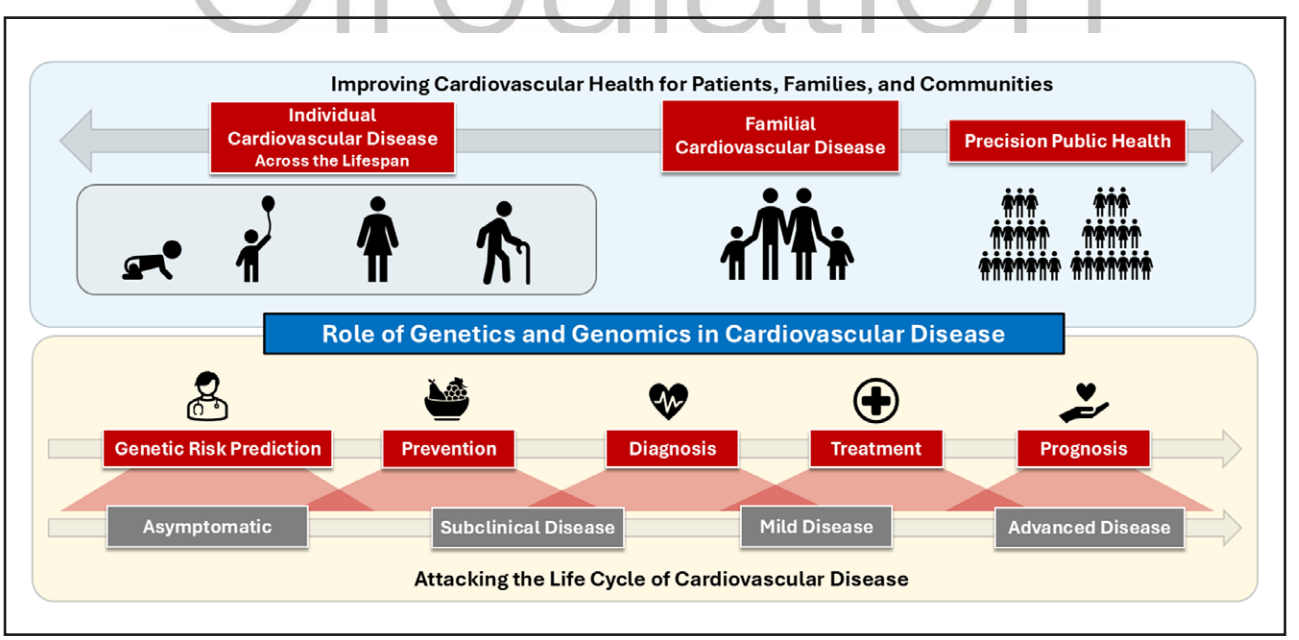

Figure 2. Visual representation of the role of genetics and genomics in cardiovascular disease.
Genetics and genomics play a crucial role in improving cardiovascular health of the individual (across the life span), families, and communities/populations. Furthermore, they contribute to solutions for cardiovascular disease by informing risk prediction, prevention, diagnosis, treatment, and prognosis throughout the disease continuum.

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THE CURRENT POLICY LANDSCAPE AND REGULATORY OVERSIGHT

Multiple pieces of legislation and regulations define the policies relevant to the development and use of genetic tests and the implications of test results for insurability. A major advance in this area in the United States was the bipartisan passage of the Genetic Information Nondiscrimination Act (GINA) in 2008. GINA prohibits the insurance industry from using genetic information when making decisions about health care coverage or setting premiums. In addition, employers are prohibited from using genetic information in job-related decisions (eg, hiring, promotion) or requiring employees to undergo genetic testing. Although GINA represents an important advance that has enabled the increased use of genetic information in clinical practice, its insurance-related protections apply only to health insurance specifically. Other forms of potential discrimination such as life, long-term care, and disability insurance decisions are not protected under GINA. Many US states have laws recognizing the need for informed consent for clinical genetic testing, but most laws were passed years ago before significant advances in genetic technologies occurred.[5] Furthermore, GINA's protections do not apply to small businesses with <15 employees or to federal employees, including members of the armed forces. There is currently a complex interplay between state and federal law and a need to update public policy on informed consent to accommodate new technologies and to ensure that the use and translation of the results optimize patient care and decision-making. Canada and some European countries such as the United Kingdom, Denmark, and France have protections against genetic discrimination, but they are not universal.

Currently, genetic testing is offered by large commercial laboratories and by individual, often hospital-based, laboratories, particularly in academic medical centers. These are known as laboratory-developed tests (LDTs), which fall under the regulatory oversight of the US Food and Drug Administration (FDA).[6] In 2024, the FDA promulgated new oversight rules for LDTs; however, the final rule has raised concerns that access to testing may be reduced and the development of new tests may be slowed. In early 2025, this rule was overturned by a US federal judge, and at the time of this writing, has not been appealed, highlighting the continued uncertainty about implementation of this regulation.[7] Other federal agencies also have enforcement oversight over specific areas relevant to genetic testing. For instance, the Federal Trade Commission oversees unfair trade practices (eg, unsubstantiated claims of efficacy) and informs consumers about direct-to-consumer genetic tests. The Centers for Medicare & Medicaid Services regulates the Clinical Laboratory Improvement Amendments, which dictate the standards laboratories must follow to establish the accuracy of any tests performed. Clinical Laboratory Improvement Amendments requirements include ensuring a "chain of custody" (ie, making sure the sample being tested belongs to the correct patient), best practices, and ongoing validation with appropriate positive and negative controls.

AHA POLICY GUIDANCE

Public policy has an important role in prioritizing and facilitating genomic research, ensuring that all individuals and communities benefit from advances in genomic medicine and supporting equitable access to evidence-based genetic and genomic testing in clinical practice. The Table summarizes key policy guidance across the different priority areas, each of which is addressed in further detail here, including payment and reimbursement, data privacy and sharing, regulatory oversight, research funding, equitable use of and access to testing, precision public health, pharmacogenetics, biobanking, the role of artificial intelligence (AI) and new technologies, common variants and risk prediction, and training and professional education.

Access to Telehealth, Payment, and Reimbursement for Genetic Counselors

The AHA advocates coverage to achieve equitable access to evidence-based genetic and genomic testing for appropriate patient care. This includes support for policies that ensure access to genetic counseling services for all patients with cardiovascular disease and their families. Because the Centers for Medicare & Medicaid Services does not currently recognize certified genetic counselors as health care professionals, they cannot be reimbursed under Medicare for providing services. Legislation has been introduced in the past at the federal level that would have required genetic counselors to be reimbursed for counseling Medicare beneficiaries at 85% of the amount determined under the Medicare Physician Fee Schedule. This has yet to be enacted despite the support of nearly 500 organizations, including the AHA.

Furthermore, telehealth offers the opportunity to expand access of care to patients with cardiovascular disease, particularly to genetic counseling services. At present, state and federal laws governing telehealth across state lines complicate the use of telehealth for genetic counseling, genetic testing, and communication of genetic testing results because health care professionals must navigate heterogeneous regulatory requirements based on location. This includes issues of licensure, reciprocity agreements, interstate compacts, privacy and security, and patient access.[8] To this end, to ensure that all cardiovascular patients and their families can access the vital services, including access to

Table. Key Policy Guidance for Public Policy Priorities in Genetic and Genomic Testing

Issue area	Key policy guidance
Telehealth, payment, and reimbursement	Genetic/genomic testing should be covered and adequately reimbursed by private and public payers when there is consensus and evidence-based guidance for its use Telemedicine should be widely accessible and adequately reimbursed by payers to increase access to care Efforts to harmonize the complex and heterogeneous landscape of telehealth, which often varies from state to state, should be supported with a goal of providing comprehensive access to care for patients
Genetic counseling	Genetic testing should be integrated into clinical care delivery through a team-based approach to optimize patient care with adequate reimbursement and payment for the services of each relevant clinician/professional Legislation/regulation should be supported that allows board-certified genetic counselors to receive reimbursement for their services from Medicare, Medicaid, and private insurers Medicare, Medicaid, and private insurers should include genetic counseling as a billable service under telehealth Access to genetic counseling should be created for all individuals with, or at familial (or genetic) risk, for cardiovascular disease Telehealth has the potential to expand access to genetic counseling services and should be a widely available option for all patients
Data privacy and sharing	Federal law should provide a baseline of protection and enforcement for individuals whose genetic information is collected and used Entities that collect genetic information and researchers who use it must adhere to the highest ethical standards, including being respectful of the people from whom the data are derived and acting as responsible stewards of this valuable common resource Entities that collect genetic information and researchers who use it should be transparent about the potential and actual future uses of the data with patients and other contributors Awareness, education, and involvement of patients in genetic research that is vital to fostering important future discoveries should be encouraged Medical and scientific researchers, research institutions, and publishers should commit to making genetic information–derived research findings and innovations widely accessible, providing access to supporting data of sufficient quality to validate and replicate research findings and data documentation that permits the reuse and interoperability of the data The AHA supports digital platforms that aggregate and analyze genetic and clinical data to advance precision medicine for rare cardiovascular diseases, with safeguards ensuring privacy, transparency, patient ownership, and informed consent
Regulatory agency oversight	Because of the complexity of genetic testing and its interpretation, testing requires regulatory oversight by an authority capable of fully evaluating both analytical validity and especially clinical validity FDA Rule 21 CFR Part 809 may be one approach to help improve diagnostic accuracy of genetic testing through improved regulatory oversight As the FDA continues its regulatory role in genetic testing, the effort should be appropriately resourced and have sufficient authority to ensure efficient test reviews while maintaining access to tests that have established clinical validity. This is critical to prevent this regulatory role from becoming a barrier to genetic testing access and innovation.
GINA	Legislative safeguards should be included for (1) life insurance underwriting, (2) long-term care insurance, and (3) disability insurance to protect individuals from discrimination based on genetic risk, family history, or both. This will help maximize the development and utility of genetic testing in health care, allowing people to undergo such testing without facing financial or other penalties. Protections against discrimination should be provided for individuals of all ages according to not only their genetic risk but also their actual health status and health history. These provisions, which protect patients from discrimination, are outlined in the Affordable Care Act and other state and federal regulations.
Genetic patents	Naturally occurring genetic variants cannot be patented because they are a product of nature Methods and technologies developed to test for biomarkers, which can be genetic markers, may be appropriate for patent protection Expert-informed policy is needed to clarify patent eligibility for genetic testing advances, balancing innovation protection with limits on claims over naturally occurring DNA sequences
Genetic testing use and access	Barriers to accessing affordable and accurate genetic testing such as cost and access to testing should be identified and addressed by policymakers Access not only involves the availability of the test itself but also includes carefully interpreted results. This requires (1) enhancing genomic information from traditionally underrepresented ancestral groups, (2) ensuring access to health professionals who can accurately interpret testing results, and (3) ensuring access to health professionals with the expertise to communicate genetic test results and their implications. Expanding genetic/genomic studies to encompass diverse ancestries is critical for improving the accuracy of diagnostic testing for all individuals Implementation science approaches must be used to understand the optimal ways to use genomic medicine interventions across different populations
Research funding	Strategic investments from federal, not-for-profit, and private entities, among others, should be made in research and health care infrastructure development. Engagement and recruitment of individuals across all communities, data generation, and methodological innovations are necessary to fully realize equitable genomic medicine. New paradigms in the management and prevention of genetic cardiovascular disease require the full scope of research methodologies, from preclinical discovery science to prospective clinical trials

(*Continued*)

Table. Continued

Issue area	Key policy guidance
Biobanking	Large population registries have become important drivers of innovation and clinical care and require long-term sustained support Ensuring interoperability of the data is crucial to catalyze research discoveries. Data interoperability should be prioritized to facilitate discovery across different research methodologies and biobanks.
Precision public health	Additional genomics research must prioritize the inclusion of diverse study populations. Building research leadership capacity within all communities and engaging communities in the planning and design stages of studies will be critical to this effort. Advances in data science must be leveraged to promote the use of novel datasets beyond genomics in discovery efforts. This approach will permit the analysis of communities that are currently underrepresented in research and of novel covariates and outcomes. Health services research should seek to understand how genomic information may follow a patient throughout their health care journey with a goal of optimizing their health care. Furthermore, the economic impact and sustainability of genomic medicine should be explored.
Secondary findings/ incidentally identified genetic variants and predictive genomics	Rigorous interpretation of secondary findings/incidentally identified variants is key to proper risk prediction Identification of a genetic finding that is likely to be associated with development of heritable cardiovascular disease in an individual who has agreed to return of these findings should trigger an individualized evaluation by a multidisciplinary team of experts Additional research and tools are needed to more accurately predict disease penetrance of incidentally identified cardiovascular genetic variants
Pharmacogenetics and pharmacogenomics	Key stakeholders, including professional societies, the FDA, the Clinical Pharmacogenetics Implementation Consortium, the Pharmacogenomics Research Network, pharmacy benefits payers (including CMS), and patients should be brought together to reach consensus on clinically actionable pharmacogenomic findings. Establishing such consensus can be facilitated by the NIH and other bodies through prioritization of ongoing research in this field. Implementation will require federal assistance in fostering the development of health information technology, particularly in the interoperability of electronic health records with advanced informatics capabilities and systems that can interface with pharmacy professionals
Common variants and polygenic risk prediction	Research funding is necessary to genotype and accurately phenotype across diverse communities. This will maximize PRS performance broadly and will be important to establish variant pathogenicity (eg, variants rare in 1 population [suggesting pathogenicity] may be common in others [suggesting nonpathogenicity]). Standardization in reporting and requirements for clinical use and a flexible regulatory framework that can accommodate ongoing innovation in genetic risk prediction are needed. It is important to support infrastructure investments and to ensure consistency in genomic data management, iterative analysis, and defined criteria for rereporting. An individual's polygenic risk should not lead to genetic discrimination (eg, affect insurability).
AI and genomic technologies	Understanding population-level cardiovascular genomics is essential for informing AI algorithms. By providing more complete and representative data, researchers can improve the effectiveness and accuracy of these algorithms. It is also crucial to discuss the significance of explainable AI and to validate the predictive and diagnostic algorithms developed with AI. Data privacy and security regulations must be in place to ensure that genomics and AI-driven insights used in health care do not lead to adverse outcomes for individuals such as insurance coverage denial based on their genetic predispositions. Expanding coverage for AI-powered genomic-based diagnostics has the potential to make personalized cardiovascular care more accessible. It is important to implement the FDA's frameworks for Good Machine Learning Practice to guide the development of safe and effective AI tools in the health care sector Increasing participation from all communities in genetic research is vital for creating more accurate AI models and reducing biases in risk assessments and care
Genome editing and gene therapy	Gene editing offers curative potential for monogenic cardiovascular diseases but requires strict ethical, safety, and regulatory oversight Gene therapy using viral or nonviral delivery mechanisms is an emerging modality in cardiovascular medicine, necessitating further long-term safety and efficacy studies for regulatory oversight
Training and professional education	Integration of genetics and genomics into clinical education of all health care professionals is critical to ensuring broad and equitable implementation of genomic medicine A formal pathway for physician training in cardiovascular genetics and genomics should be established to ensure quality of training and standards for practice. Such a pathway is needed to galvanize creation of a subspeciality around genetics, genomics, and precision health within cardiology and pediatric cardiology. Effective clinical training and educational material development require the participation of multiple disciplines, including genetic counselors, nurses with specialized training, and pharmacists.

AHA indicates American Heart Association; AI, artificial intelligence; CMS, Centers for Medicare & Medicaid Services; FDA, US Food and Drug Administration; GINA, Genetic Information Nondiscrimination Act; NIH, National Institutes of Health; and PRS, polygenic risk score.

genetic counselors, the AHA supports the following policy principles: (1) Medicare, Medicaid, and private insurers should provide coverage for genetic counseling services provided by board-certified genetic counselors. (2) Medicare, Medicaid, and private insurers should include genetic counseling as a billable telehealth service. (3) Access to genetic counseling services should be made available to all patients with or at risk for cardiovascular disease and their families. (4) Within worksite health promotion programs, genetic counseling services should be voluntary, available to all employees, and in compliance with federal and state regulations. (5) Telehealth has the potential to expand access to genetic counseling services and should be a widely available option for patients. (6) Reimbursement policies should ensure full parity for integrated telehealth services, recognizing their equivalent clinical value in health care delivery.

Data Privacy and Sharing

A previous AHA policy statement[4] articulated important principles for data privacy and data sharing that are relevant and integral to public policy on genetic testing. These principles highlight the importance of informed consent and privacy protections and seek to address the collection of health and genetic information and researchers' use of these data. Furthermore, they highlight the importance of maintaining the highest standards of ethical behavior, including being respectful of the people from whom the data are derived, and highlight the need for being responsible stewards of genomic data. Decisions to proceed with genetic testing, in either the clinical or research area, should take into consideration and address patient/parental attitudes about genetic testing. Furthermore, this decision should be balanced with the ethical obligation to ensure informed decision-making, particularly when refusal may lead to preventable outcomes such as heart failure or sudden cardiac death in the patient being tested or in family members.

Entities that collect health information and biological specimens and researchers who use them should be transparent about potential and actual future uses with patients, researchers, and other data contributors. For example, failure to properly obtain consent and to provide appropriate levels of disclosure about the future use of materials undercuts the ethical foundation on which research discoveries are necessarily based. Promoting awareness, education, and involvement of patients in genetic research is encouraged to enable important future discoveries. Medical and scientific researchers, research institutions, and publishers should commit to making research findings and innovations derived from health information widely accessible. This includes providing access to supporting data of sufficient quality to validate and replicate research findings and ensuring that data documentation allows reuse and interoperability. Federal law should provide a consistent baseline of protection and enforcement for individuals whose health information is collected and used.

Last, digital health care platforms that aggregate and analyze genetic and clinical data play a critical role in advancing precision medicine, particularly for rare cardiovascular diseases. The AHA supports robust privacy protections, transparency in data sharing, and the preservation of patient ownership and informed consent to ensure ethical and equitable use of such platforms.

Regulatory Agency Oversight

Traditionally, genetic testing was not subject to extensive regulation. However, with the rise in test volume, the FDA established new rules in 2024 (21 CFR Part 809),[9] reclassifying LDTs as medical devices. This shift put LDTs under more robust FDA approval. There was a 4-year phase-in process for this regulation, but the court decision has put its implementation into question. A potential benefit of this rule would be improved diagnostic accuracy of testing, reducing misdiagnosis and leading to less undertreatment and overtreatment of genetic disease. However, the benefits of the rule could be dampened by 2 significant exemptions that remove premarket review requirements and most quality-system requirements for LDTs that (1) predate May 6, 2024, and (2) are developed by academic health centers and used in house for unmet patient needs.[10] These exemptions may reduce the public health benefit of the regulatory oversight.

On the other hand, some members of Congress and professional societies have expressed concerns that complying with the new regulation will be time-consuming and costly, potentially having the unintended consequence of raising the cost of and reducing access to testing. Another major argument is that the added complexity could hinder the ability to introduce new tests. There may be further efforts by Congress or the FDA to address implementation and enforcement of this rule. The AHA advocates for oversight of LDTs to ensure the quality and accuracy of genetic testing. This oversight should be balanced by the recognition that this new regulatory framework should be pragmatic, leveraging the oversight that the Clinical Laboratory Improvement Amendments already provide, and should meet the increasing needs for broader testing access and enable genetic testing innovation.

Needed Updates to the GINA

GINA was enacted when many practitioners and patients had limited awareness of the implications of genetic and genomic testing. Since that time, there has been a dramatic increase in our understanding of genetic variants as drivers of cardiovascular phenotypes, as well as a rise

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in genetic and genomic testing volumes, awareness of variable penetrance, and cascade screening practices. This rapidly expanding use of testing can generate difficult decisions for patients and their families. Probands in whom a clinical or genetic diagnosis has been established may face denial of life, disability, and long-term care benefits. This situation can make family members hesitant to undergo cascade screening, which can ultimately put them and their relatives at greater risk. For these reasons, we advocate for amending GINA to apply more broadly, especially across insurance benefits, to facilitate effective screening and disease risk assessment for treatable cardiovascular diseases.

Genetic Patents

The current landscape of patents on genetics and genomics is highly variable, is based on country-specific laws, and is evolving. In the United States, the landmark ruling from the Supreme Court on *Association for Molecular Pathology v Myriad Genetics, Inc* in 2013 found that naturally occurring DNA sequences and isolated human genes cannot be patented.[11] This ruling effectively invalidated existing gene patents and expanded the ability of companies to conduct diagnostic genetic testing. In Australia, similar rulings apply such that naturally occurring nucleotide sequences are not patent eligible.[12] Conversely, many European countries still allow patents on isolated genomic DNA and associated testing methods,[13] increasing the risk of patent infringement for genetic testing laboratories and adding to a complex global landscape where patentability varies regionally.

Previous AHA policy[3] has highlighted the importance of a more "liberal nonexclusive licensing practice" so that there is wide accessibility for rapid and accurate genetic testing. This policy remains valid in the face of rapid expansion of genetic and genomic sequencing in cardiovascular disease. Furthermore, continued efforts in some areas to patent naturally occurring DNA sequences may lead to restricted access and increased cost of genetic testing. A single entity responsible for diagnostic genetic testing may also limit innovations that improve diagnostic accuracy. This runs counter to the AHA's position that genetic and genomic testing should be widely accessible, affordable, and accurate. Conversely, methods and technologies developed to test for biomarkers, which can be genetic markers, may be appropriate for patent protection. Last, there is complexity in distinguishing which genetic testing methods and technologies qualify for patent protection, particularly as AI and integrative risk models emerge. Although current US law generally permits patents on novel laboratory methods and engineered reagents but excludes interpretations of naturally occurring DNA sequences, clearer policy guidance is needed.

The Use of and Access to Genetic and Genomic Testing

Genetic and genomic testing is a powerful tool to augment clinical evaluation, serving both predictive and diagnostic purposes. Although the use of testing in clinical settings has grown, this increase has not been equitably distributed across all populations. Indeed, equitable access to genetic and genomic testing is essential for advancing precision medicine and addressing health disparities for all cardiovascular disease.[14] Lack of genetic diversity has been linked to inaccurate interpretation of variant pathogenicity. Among genetic variants that were seemingly diagnostic (interpreted as likely pathogenic/pathogenic) for association with cardiomyopathy development and then later downgraded to a variant of uncertain significance, the majority were common among non-European ancestries and rare among individuals of European ancestry. Thus, because of limited non-European healthy reference alleles, these variants were likely "overcalled" when inappropriately compared with individuals of European ancestry.[15,16] This inaccurate classification of variants, assigning disease risk when none is present or vice versa, has the potential to lead to inaccurate diagnoses of serious cardiovascular diseases. Cascade genetic screening in the family can amplify this issue by ascribing inaccurate disease risk to those relatives. Moreover, recent population genomic studies in underevaluated populations such as African communities highlight a variable burden of diagnostic variants across groups.[17] Expanded genetic diversity can also inform therapy development; genetic discovery in underrepresented communities can lead to breakthrough new therapies. The current rise of PCSK9 (proprotein convertase subtilisin/kexin 9) inhibitors to treat atherosclerotic disease was fueled by genetic discoveries made from various communities.[18]

Although the benefits from an ethical and research perspective are clear, significant barriers remain in the access and use of genetic testing.[19] To address these inequities, policies should support equitable and broad access to genetic and genomic testing for all populations, including those of non-European ancestry,[20,21] low-income groups,[22] and rural-dwelling communities.[23] Furthermore, policies aimed at increasing access to genetic and genomic testing should encompass both access to testing and access to accurately interpreted results by qualified health care professionals. To achieve this, investments should focus on enhancing genomic datasets from underrepresented ancestral groups and on training health care professionals to appropriately initiate, interpret, and implement genetic testing.[24] In addition, policies should prioritize the creation of reimbursement pathways, including expanded insurance coverage and public health programs, to decrease existing geographic and financial barriers to genetic

testing and genetic counseling. Last, to further support equity in access to genetic and genomic testing, health systems must intentionally engage with diverse communities to build trust and to develop culturally sensitive testing initiatives that meet the unique needs of different populations.[20] These measures will help maximize the benefits of genetic testing such as accurate diagnoses and early identification of at-risk individuals while minimizing disparities across all populations.[25]

Support for Research Funding

Funding for cardiovascular genetic and genomic research plays a pivotal role in advancing medicine for cardiovascular disease, enabling the development of innovative prevention and management strategies. Strategic investments in research and health care infrastructure are essential to drive breakthroughs in preclinical discovery science and to catalyze the translation of these findings into both clinical practice and precision public health. Research funding across the full continuum of methodologies is critical: from basic preclinical discovery science to translational research, clinical sciences, clinical trials, and population-based outcomes research. Equally important is the commitment of funding agencies to engage and recruit diverse communities, ensuring equitable genomic medicine by fostering inclusivity in data generation and research participation. When methodological innovations are prioritized and gaps in representation are addressed, research funding can unlock new paradigms in cardiovascular care, ultimately improving outcomes for patients worldwide.

Biobanks

Significant investments in the creation, maintenance, and analysis of large-scale cohorts have led to important advances in understanding the genetic basis of cardiovascular disease and stroke, as well as many other common and rare diseases.[3] Efforts such as the Exome Aggregation Consortium[26] and its successor, the larger Genome Aggregation Database,[27] have helped molecular geneticists prioritize putative pathogenic variants by focusing on those that are uncommonly observed in diverse unselected populations. The UK Biobank, a volunteer-based prospective cohort of ≈500 000 phenotyped and sequenced adults living in the United Kingdom, is broadly available to researchers and, largely because of its scale, has revolutionized our understanding of common and rare genomic variants in health and disease.[28] This cohort has been molecularly enriched through collaborations with pharmaceutical industry partners and analysis enabled by a subscription-model cloud-based trusted research environment.

Countries and health care systems are increasingly developing mega biobanks.[29] In the United States, initiatives such as the National Institutes of Health All of Us Research Program,[30] the Million Veteran Program,[31] and the National Heart, Lung, and Blood Institute's Trans-Omics for Precision Medicine Program[32] have formed alongside multiple increasingly large health care system–based biobanks. The rapid growth of these extensive resources is also enabling approaches that combine data across different datasets.[33] However, there are barriers to such combined analyses, including varying consent mechanisms and regulatory requirements (eg, European privacy rules) and inconsistent phenotyping approaches (eg, varying definitions of common diseases such as type 2 diabetes). Expanding these resources to better include non-European ancestry populations will enhance discovery that benefits all and should be prioritized. Furthermore, accessibility of these biobanks to the research community varies widely, which can hinder broad use of the data for the advancement of cardiovascular research.

A major goal of these biobanks is to improve the interpretation of genetic variants during diagnostic testing. The accuracy of genetic testing relies on effectively capturing genetic variations in both healthy and diseased individuals. For example, a variant may be considered pathogenic on the basis of its rarity in one population, but it could be re-evaluated as nonpathogenic if it is common in another population that is not primarily affected by the disease. In addition, the characterization of pathogenic alleles across diverse populations will improve our ability to classify variants accurately. As genotyping and sequencing are increasingly being performed in asymptomatic individuals, new approaches to actionable screening, surveillance, and prevention are being considered. These studies will require prospective trials to better understand the benefits, costs, and risks involved.

The accurate representation and integration of full genomic features within health care records are still not well established. Advances in using genetic variant information in health care continue to evolve, with new sequencing technologies, reference representations, and variant calling methods refining diagnostic accuracy. Likewise, genetic variant interpretation is similarly iterative, improving with new sequence references across diverse ancestries and communities, new functional/experimental data (eg, multiplexed assays of variant effects), and new in silico prediction tools (eg, AI-based pathogenicity prediction tools).[34] A "learning health system," a health care system that uses data and scientific evidence to improve patient care, represents a major potential tool to accommodate these dynamic considerations. New paradigms in management and prevention require a rigorous and reproducible level of evidence for implementation. It is crucial to invest strategically in research and health care infrastructure development, to engage and recruit individuals from diverse communities, to generate data, and to innovate methodologies to fully realize equitable genomic medicine.

Precision Public Health

Precision public health is a field that applies the principles of precision medicine, integrating multiple data sources such as genomics, social determinants of health, and digital technologies to improve health outcomes. The concept of precision public health was first described in 2016 by a group of thought leaders from the Centers for Disease Control and Prevention, National Institutes of Health, and US Public Health Service.[35] The proposal stressed the importance of multidisciplinary collaboration in public health efforts, including the role of geneticists. Furthermore, it highlighted the importance of prevention over treatment and the integration of advanced information technologies into the practice of public health. More recently, precision public health has been described as "considering the interplay between genetic, lifestyle and the environment to improve disease prevention, diagnosis and treatment on a population level, thereby delivering the right interventions to the right population at the right time."[36] In this recent iteration, the most pressing needs identified for the expansion of precision public health include data sciences, emerging AI technologies, capacity building, equity research, and implementation science. These identified needs for expansion inform AHA policy guidance on the inclusion of diverse study populations in future genetic research, support for data science advances permitting efficient use of novel types of data in genomic analyses, and support for research examining the implementation of genomic medicine. Among many areas of future research, there is a particular need for health services research to understand how genomic information may follow a patient on their health care journey to optimize care, treatment strategies, and disease prevention. This should be done with appropriate privacy protections. Furthermore, additional understanding of the economic impact and sustainability of this type of genomic health care is needed.

Secondary Findings/Incidentally Identified Genetic Variants and Predictive Genomics

With the expansion of broad clinical exome and genome sequencing and the growth of population-based genomic sequencing efforts, an increasing number of clinically actionable, incidentally identified genetic variants have been reported. Also known as secondary findings, these variants, particularly those in cardiovascular disease–associated genes, represent actionable genetic information in individuals in whom heritable cardiovascular disease was not a concern at the time of sequencing (eg, diagnostic exome genetic testing in infants and children).

The identification of such variants in asymptomatic individuals holds the promise of uncovering genetic disease risk before symptomatic disease develops, potentially preventing tragic outcomes such as sudden cardiac death. This promise forms the foundation of true genomic risk prediction (also known as the genome-first approach to heritable cardiovascular diseases[37]) and represents an exciting advancement in the field of genomic medicine. The American College of Medical Genetics and Genomics, among other groups and efforts,[38] has provided critical guidance on interpreting these variants and reporting them back to the referring health care professional or study participant, provided that the individual has consented to the return of findings. Variants that fall into "actionable genes" and are considered to be likely pathogenic or pathogenic are eligible to be reported back to the ordering clinician.[39–41]

Although the rate of secondary findings in cardiovascular disease–associated genes is generally 0.5% to 1% of individuals, this rate is significantly higher than the frequency of manifest disease.[42,43] This disparity suggests that most of these variants are low-penetrance alleles. In other words, the majority of individuals identified as being at risk for heritable cardiovascular disease will not develop the disease. Furthermore, the genetic basis of many heritable cardiovascular conditions, even those believed to be monogenic/mendelian, is increasingly appreciated as being more complex. For example, genetic modifier variants influence how disease progresses and the age at disease onset.[44] Myriad nongenetic factors such as medications and environmental exposures can alter disease onset, presentation, and severity.[45] These factors pose a major challenge for implementing predictive genetics, particularly in cardiovascular disease. The tension is avoiding excessive or unnecessary testing for those at low/no risk while identifying those in whom a diagnosis and appropriate follow-up (including cascade screening) are beneficial. Indeed, the identification of disease-associated variant in an individual who is ostensibly healthy and will not manifest evidence of disease may have unintended consequences for emotional well-being of the individual, place them at risk of genetic discrimination (ie, negatively impact insurability), and impose a financial burden for a lifetime of clinical follow-up. This is further compounded should the variant be found in other members of the family who also do not demonstrate evidence of disease.

Last, educating researchers, clinicians, and research participants, key stakeholders in predictive genetics, about the nuances of variant interpretation remains a significant hurdle. The AHA has provided guidance on this topic, highlighting the need for a multidisciplinary approach to both presequencing and postsequencing counseling and a customizable, individualized evaluation for individuals when a secondary variant is found.[46] New models, including population-based genomic risk prediction tools, high-throughput functional analyses, and AI, have shown promise in advancing variant interpretation.[47,48] Further research is needed to improve variant interpretation and, more important, to understand

the drivers of disease penetrance in genetic conditions. Addressing these gaps will be essential for the broad implementation of predictive genetics.

Pharmacogenetics and Pharmacogenomics

Genetic testing intended to inform optimal medication use, known as pharmacogenomics, is becoming increasingly mainstream, although its adoption has been slower than initially expected. Because a single pharmacogenomics genetic evaluation may inform a lifetime of medication use, there is tremendous value in the broad implementation of pharmacogenomics at the bedside. Despite this, pharmacogenomics still suffers from several key barriers and has important distinctions compared with other forms of genetic testing, particularly compared with tests used to identify inherited genetic diseases and their associated phenotypes. To date, the field of pharmacogenomics has focused mostly on common genetic variants with large effect sizes that affect medication pharmacokinetics. This traditional approach has achieved significant clinical applications that enhance the safety, effectiveness, and efficiency of medication use.[49–51] This focus is logical in that a large proportion of medications are influenced by a small number (ie, 10-20) of key enzymes/transporters and molecular targets (eg, *VKORC1* altering warfarin drug response). Because these variants are common, >90% of humans carry at least 1 impactful variant in at least 1 key pharmacogenomics gene. The FDA currently lists >600 individual drug-gene interactions as having potential clinical impact. More modernized approaches to pharmacogenomics aim to better understand pharmacodynamic effects, to develop multigene or model-based prediction methods, to use unbiased/genome-wide association studies approaches to identify interactions, and to link these findings to polygenic score methods.[52–56] Although these more complex approaches hold great future potential, most are not yet primed for current clinical implementation. In contrast, the more well-known pharmacokinetic effects of drug-metabolizing variants have many specific examples with clinical utility.

At the time of the last genetic testing policy statement, several key barriers to the implementation of pharmacogenomic testing in clinical practice were enumerated. These challenges included the timeliness of pharmacogenomics test results, the need for improved evidence and decision support for prescribers, methods to deliver this information at an impactful time (ie, integration into clinical workflow), and continued educational needs (ie, health care professionals are generally not adequately prepared to use pharmacogenomics information fully). Over the past decade, this landscape has changed significantly. Although achieving greater consensus and a deeper knowledge base remains an eternal pursuit, several of these key issues have been significantly mitigated. Specifically, the rapidly decreasing cost and increasing throughput of genetic testing have made preemptive pharmacogenomics testing a more practical solution for ensuring timely availability of test results. Some data suggest that patients prefer this approach.[57] Since 2018, the FDA has approved direct-to-consumer pharmacogenomics testing. The Human Genome Institute estimates that 26 million individuals have used commercial genetic testing. However, preemptive pharmacogenomics testing can introduce a potentially long lag time (years) between the test and the initiation of a drug; this can be a particular problem if the patient moves health care systems. Similarly, the near-universal adoption of electronic health records has enabled the creation of pharmacogenomic solutions that provide real-time notifications and decision support to health care professionals when pharmacogenomics data are available. An implementation science–based approach may facilitate the widespread use of pharmacogenomics, particularly in the setting of clinical decision support tools. Last, guidelines and decision support have also continued to mature and expand, offering helpful evidence summaries and recommendations by the Clinical Pharmacogenomic Implementation Consortium for various areas of pharmacotherapy, including cardiovascular disease.[58,59]

Despite these positive innovations, further progress is required for widespread implementation, and some previously cited challenges remain salient. Specifically, the pharmacogenomic knowledge base remains inadequate to guide many potential applications, highlighting the need for more data, particularly from diverse populations. Moreover, despite substantial evidence supporting specific applications, there is significant variability in health care professionals' and experts' perspectives on the level of evidence required for action, which may hinder true consensus building.[60] At the same time, and perhaps most critically, health care professionals remain inadequately prepared from an educational standpoint to efficiently use pharmacogenomics information in routine clinical care.

Common Variants and Polygenic Risk Prediction

Common cardiovascular diseases such as coronary artery disease, stroke, atrial fibrillation, venous thromboembolic disease, calcific aortic disease, and heart failure are heritable conditions. Genome-wide association studies are increasingly expanding and refining the catalog of common variants (often defined as allele frequency >1%) across hundreds of gene regions associated with each condition. Each individual variant typically confers a modest increase in risk, ranging from a <1% to 10% to 20% relative increase. This modest effect on disease risk can limit the clinical utility of genotyping individual common variants for prognosis purposes. Polygenic risk

scores (PRSs), which use multiple common variants in risk prediction, have gained significant attention and are described in a recent AHA scientific statement.[54] The increasing size and diversity of genome-wide association studies, coupled with methodological innovations, have enhanced the performance of PRSs. For example, a recent PRS for coronary artery disease identified that 1 in 5 individuals is at a >3-fold risk for developing coronary artery disease.[61] The effect estimates are generally more pronounced in younger individuals.[62] However, a significant limitation exists in that genotyped datasets often overrepresented individuals of European ancestry, resulting in the best performance of PRSs among this group. This further highlights the urgent need for greater diversity in PRS studies, particularly among traditionally underrepresented communities.[63,64]

Although the diagnostic yield from PRS to identify previously unrecognized high-risk individuals continues to increase, several key issues remain. First, clinical offerings for PRS are expanding but vary widely in terms of the number and type of variants included, weighting of these variants, methods of derivation, training datasets used, and reporting approaches. Furthermore, the transparency of these metrics varies, which hinders consistent interpretability and consequently actionability.[65] Currently, there is no single canonical PRS for any trait,[65] but integrative approaches appear promising.[66]

Second, the cost-effectiveness of PRS remains unknown. Although the costs of PRS testing continue to decrease, an abnormal test finding may generate additional studies and prompt new therapies. The relative benefits, costs, and potential harms associated with testing asymptomatic individuals remain poorly understood. A single-site clinical trial showed that coronary artery PRS disclosure led to reduced cholesterol levels at 6 months,[67] and a 9.5-year follow-up indicated a reduction in major adverse cardiovascular events.[68] Furthermore, larger multisite trials are needed across the breadth of potential cardiovascular PRSs.

Third, unlike monogenic testing, which is performed largely for affected individuals, the implications of PRSs for life and long-term disability insurance in asymptomatic individuals have not been established, and a role if any for cascade screening has not been established. Fourth, although PRSs can predict disease progression and disease onset,[69] the clinical role of these scores for individuals with established cardiovascular disease is still largely unknown. This extends from common cardiovascular disease to rare heritable cardiovascular diseases such as cardiomyopathies and ion channelopathies, many of which are classically considered monogenic/mendelian.[44,70,71]

Although germline genotypes are static, genetic risk prediction remains inherently dynamic and requires consideration of many new policies. PRSs continue to show increasingly predictive capabilities, providing notable opportunities to interrupt disease development early in the pathogenesis process. Although this is tremendously promising, there are still barriers for broad clinical implementation. For example, recent evidence has suggested that a well-established PRS that performs similarly at the population level still demonstrated marked variability when applied at the individual level.[65] Further work is necessary to genotype and accurately phenotype cardiovascular traits across diverse communities to maximize the PRS performance and to best understand settings in which it is most useful. In addition, prospective trials are necessary to define the most efficacious PRS paradigms. Standardization in reporting and requirements for clinical use, along with a flexible regulatory framework that accommodates ongoing innovations in genetic risk prediction, is needed. There is a need for infrastructure investment and field consistency in genomic data management, iterative analysis, and clearly defined criteria for rereporting findings. Last, as a PRS reaches the bedside, it is critical that an individual's polygenic risk does not lead to genetic discrimination.

AI and Genomic Technologies

AI aims to replicate human thought processes, learning capacities, and methods of knowledge storage.[72] The integration of AI technologies into cardiovascular genomics is beginning to change how researchers analyze genetic data and interpret findings, aiming to develop personalized treatment strategies. The increasing volume of genetic data arising from the rapid growth of genomic research, fueled by reduced sequencing costs and advanced sequencing technologies, presents significant challenges for traditional statistical methods used to analyze complex genetic interactions.[73,74] AI methods are designed to train programs to recognize relationships in big data. Datasets are often intricate and multifaceted, enabling automated reasoning and inference. AI-driven technologies encompass a broad range of concepts, including machine learning, deep learning, cognitive computing, and natural language processing.

These technologies have begun to play a transformative role in genomic research.[73,75] Emerging machine learning techniques such as transfer learning (which leverages a pretrained model to improve performance on a new, related task) and multiview learning (which uses multiple datasets or perspectives to enhance model performance) can be applied to cardiovascular genomics.[52] For example, AI has the potential to enhance cardiovascular genomics by identifying genetic variants, predicting their impacts, and correlating genomic data with clinical outcomes.[76] Furthermore, natural language processing has been used to discover gene-disease associations related to heart failure[77] and to generate clinical recommendations while analyzing genomic data.[78] The applications of AI in cardiovascular genomics have been

well summarized.[73,78,79] Furthermore, a recent scientific statement from the AHA outlined best practices for AI/machine learning algorithms in the field of cardiovascular genetics.[80] With these best practices, AI has the potential to streamline data analysis and to enhance predictive models in cardiovascular diseases.[81]

Cardiovascular genomics presents a challenge in the development of AI resulting from the heterogeneity of clinical variables linked to disease and the genomics data themselves, which often involve complex interactions between a person's genetics and environmental factors that influence biological processes such as gene regulation.[82] Advanced methodology has been proposed that integrates traditional bioinformatics, classic statistics, and multimodal AI/machine learning techniques to identify the functional impacts of multiomics interactions, including genomics, transcriptomics, metabolomics, structural biology, and advanced phenomics, among other modalities. This holds promise in identifying novel biomarkers, establishing their assessment for cardiovascular disease development, and contextualizing these predictions to the clinical setting.[83]

Despite the promising advancements in AI-driven cardiovascular genomics to accelerate the discovery of complex interactions that inform future prevention and treatment efforts, several challenges remain. The AHA believes that AI-driven technologies are best advanced through several key efforts. These include improving genomic variant calling and interpretation, conducting deep clinical phenotyping of research cohorts, and supporting interdisciplinary approaches to develop rigorous AI-based platforms. Efforts to integrate data across research platforms, a key feature of data interoperability, are key, as are broad initiatives to provide diverse datasets that are representative of diverse patient communities. Data privacy and security are paramount. Careful consideration of potential group harms such as insurance coverage denial attributable to AI-predicted genetic predisposition is key to making the benefits of AI-driven technologies available to all.

Genome Editing and Gene Therapy

Advances in genome editing, gene therapy, and reproductive technologies, including human cloning, have introduced both significant opportunities to improve cardiovascular care and ethical challenges. Although gene therapy approaches such as viral vector–mediated delivery of therapeutic genes or genome editing technologies such as CRISPR-Cas9 hold promise for treating challenging and life-threatening cardiovascular diseases, their long-term safety, off-target effects, and equitable access remain unanswered.[84] Addressing these issues is central to the successful implementation of cardiovascular genetic therapy to the clinical domain. Human germline editing and reproductive cloning present distinct ethical and regulatory concerns. These concerns center around heritable modifications, consent across generations, potential for unintended genomic modifications, and potential misuse of this technology for nontherapeutic applications.

Training and Professional Education

The AHA 2012 policy statement[3] highlighted that physicians, nurses, genetic counselors, and pharmacists play an important role in genomic medicine. However, it highlighted that individuals in these professions have not received adequate genomics training to fully realize their potential in this field. Thus, given the rapid technological advances, continuing genomics education was felt to be critical for the effective practice of genomic medicine in the long term. These issues continue today, and the rapid advances in genomic testing, in both clinical settings and direct-to-consumer markets, have only intensified the need for education. Since 2012, numerous courses and educational offerings have been developed, primarily using short distance-learning approaches that are feasible for busy health care professionals. Notable comprehensive courses include a genetics curriculum developed specifically by the AHA titled "From Concepts to Practice: A Guide to Cardiovascular Genomics"[85] and a series of short continuing medical education/certified nurse educator modules hosted by The Jackson Laboratory and Northwestern Medicine, Feinberg School of Medicine called "Implementing Cardiogenomics in Clinical Practice,"[86] among other programs.[87] These offerings reflect a multidisciplinary approach to clinical genetics and genomics, involving the collaborative efforts of health care professionals, scientists, and genetic counselors.

Despite these offerings, a large gap remains between the current education of clinical professionals and the knowledge base needed to successfully practice in the genomic medicine era. Dedicated training pathways for physicians, genetic counselors, and other clinicians are needed to standardize training and to ensure expertise among individuals who care for cardiovascular genetic patients or use aspects of genetics/genomics in their practice. As genomic and precision medicine advances, ensuring that all health care professions are educated in core principles of genetics and genomics is key. These core principles need to be formally established in a field/profession–specific manner and include domains such as fundamentals of genetic testing, variant interpretation, and heritable disease–specific topics. Furthermore, educational offerings that are rigorous, affordable, and accessible are needed to ensure continued professional education in a rapidly evolving field. Ultimately, a dedicated training pathway and expanded education of this field to all physicians trained in cardiology and pediatric cardiology should form the foundation of a distinct subspecialty that centers on genetics, genomics, and precision health.

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CONCLUSIONS

Tremendous strides are being made in genomics, offering the promise of individualizing and optimizing clinical cardiovascular care for all patients. However, there are barriers to securing long-term support for the research efforts that are driving these fields forward, as well as challenges in ensuring that the benefits of these discoveries are implemented broadly and equitably for both patients and the community at large. The current focus on accessibility of rigorous genetic testing and expansion of research tools and biobanks and an expanded focus on the equitable implementation of genomic discoveries offer ways to surmount these barriers.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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