

American Society of Echocardiography Cardiovascular Technology and Research Summit: A Roadmap for 2020

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Abbreviations

ASE = American Society of Echocardiography
DICOM = Digital Imaging and Communications in Medicine
FDA = US Food and Drug Administration
LV = Left ventricular
NIH = National Institutes of Health
TAVR = Transcatheter aortic valve replacement
TEE = Transesophageal echocardiographic
3D = Three-dimensional
TVT = Transcatheter valve therapy
2D = Two-dimensional
VHD = Valvular heart disease

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INTRODUCTION

The promotion of research involving cardiovascular ultrasound is part of the mission of the American Society of Echocardiography (ASE). For years, the ASE has awarded research grants to fund meritorious research by its members. The society's journal, the *Journal of the American Society of Echocardiography*, and the ASE's Annual Scientific Sessions provide venues for the publication and presentation of high-quality research. However, declining availability of federal funding for research has posed challenges for investigators, including those involved with cardiovascular ultrasound. In 2010, Dr. Sanjiv Kaul, then the ASE president, and others believed that a strategic planning session to outline goals and develop an action plan would be valuable to the ASE and its members. Thus, that year, the ASE held the first ASE Technology and Research (as in Technology and Research Summit) Summit in Chicago, preceding the Annual Scientific Sessions of the American Heart Association. To draft a roadmap for cardiovascular ultrasound research, the summit brought together academic echocardiographers, scientists, acoustic physicists, ultrasound engineers from various companies, and a staff member from the National Institutes of Health (NIH). Over the full-day meeting, several research and technology areas of topical interest with a potential for growth in the near future were discussed. These included the assessment of global and regional left ventricular (LV) function, regional myocardial perfusion, molecular imaging, therapeutic ultrasound, peripheral arterial disease, handheld ultrasound, and future technology, including sensor technology, miniaturization, and small-animal imaging systems. Additional emphasis was placed on funding training programs to attract young scientists to the field of echocardiography. A white paper¹ was published in the *Journal of the American Society of Echocardiography* on the basis of the proceedings of that summit. The white paper was shared with the NIH, and a meeting was held to discuss the issues in the report with leadership of the NIH at its Bethesda, Maryland, premises. It was determined at that time that a technology and research summit dedicated to echocardiography would be held every 2 years under the auspices of the ASE.

Additional accomplishments stemming from the 2010 meeting included the partnership with the European Association of

Cardiovascular Imaging for the creation of a standardization task force, the Initiative to Standardize Deformation Imaging, consisting of members of the ASE, the European Association of Cardiovascular Imaging, and the Japanese Society of Echocardiography, engineers from various companies, and scientists from academia. This task force was established to respond to the need to create system-independent means for assessing regional and global cardiac function using tissue-based sampling. This task force has been meeting on a regular basis, and considerable progress has been made in its mandated task. Additionally, a guidelines and standards document concerning handheld and point-of-care ultrasound is nearing completion.

The 2012 summit was developed to build on the success of the 2010 event. With the mission of assessing the state of the art of echocardiography and projecting areas of future growth, the summit focused on a vision for the development of cardiovascular ultrasound technology and clinical research by 2020, including the necessary research infrastructure, with a particular emphasis on three-dimensional (3D) echocardiographic imaging, cardiovascular ultrasound in valvular heart disease (VHD), myocardial deformation, and therapeutic ultrasound. Participants were encouraged to describe the current issues and barriers, plan goals, and develop specific recommendations to chart the future of research and technology in cardiovascular ultrasound. The following sections summarize the summit recommendations, and key recommendations are provided in Table 1.

Selected Readings

1. Kaul S, Miller JG, Grayburn PA, Hashimoto S, Hibberd M, Holland MR, et al. A suggested roadmap for cardiovascular ultrasound research for the future. *J Am Soc Echocardiogr* 2011;24:455-64.

CARDIOVASCULAR ULTRASOUND TECHNOLOGY DEVELOPMENT

The panel discussed three broad goals relating to future ultrasound technology development. These were (1) to use proven technology to improve the quality of patient care, (2) to advance the diagnostic and therapeutic capabilities of ultrasound, and (3) to enhance the future development of cardiovascular ultrasound by increasing collaboration among engineers, scientists, the NIH, the Food and Drug Administration (FDA), and cardiologists.

Goal 1: Use Proven Technology to Improve the Quality of Patient Care

Doppler echocardiography is a highly useful diagnostic test in the evaluation of patients with known or suspected heart disease. The increasing numbers of at-risk cardiac patients in the United States and throughout the world may preclude them from accessing a limited number of centers of excellence for cardiovascular care, but it is reasonable to expect that they can have access to echocardiographic examinations performed with high-quality, affordable echocardiographic instrumentation. Just as advancing electronic technology has enabled handheld or hand-carried echocardiography equipment with satisfactory performance, electronic technology can soon enable the production by many companies of low-cost, highly mobile equipment with two-dimensional (2D) and Doppler echocardiographic

Table 1 ASE roadmap for cardiovascular technology and research

I. Administrative/infrastructure
a. Establish a council to bring together ultrasound engineers, scientists, the NIH, the FDA, and cardiologists
b. Establish a bioengineering research partnership to conduct basic and translational research supporting sonothrombolysis and ultrasound-targeted drug or gene delivery
c. Create an inventory of research training resources
d. Explore the development of imaging registries that interface with other clinical and research data sets
II. Guidelines and standards
a. Develop requirements and standards for echocardiography core labs
b. Develop standards for managing, storing, and assessing large 3D data sets
c. Standardize 3D imaging protocols, measurements, and displays
d. Develop a vendor-independent system to reproducibly, readily, and accurately measure myocardial deformation
III. Software/hardware development
a. Develop intelligent software to improve the quality and efficiency of echocardiographic imaging
b. Develop automated software quantification tools for 3D imaging
c. Improve 3D image quality and transducer design
d. Develop and validate automated methods for quantification of flow
e. Improve catheter and device visualization by echocardiography
f. Develop a vendor-independent automated system to measure myocardial deformation
IV. Research topics
a. Document the value, reproducibility, and feasibility of quantitative echocardiographic biomarkers
b. Conduct clinical trials demonstrating the cost-effectiveness and impact on outcomes of echocardiography
c. Perform clinical trials demonstrating the comparative effectiveness of Doppler echocardiography compared with other imaging modalities in TVT
d. Establish multicenter clinical trials in sonothrombolysis and targeted gene and drug delivery

performance approaching that of the highest performance equipment available today.

Intelligent software should be developed to improve quality and efficiency. Such software, developed jointly by the ASE and industry with encouragement by the NIH and the FDA, can provide real-time feedback during echocardiographic examinations (James B. Seward, MD, personal communication). Perhaps the easiest place to start is with a minimal set of standardized measurements and image and Doppler assessments, tailored to the indications for the examination, which are prompted by the echocardiographic machine and analyzed instantly by machine software. Depending on the initial results, the software could indicate whether the results are normal, or it could prompt additional image or Doppler views or measurements to gain further information required for adequate diagnosis or to resolve inconsistencies in the measurements taken.

The further development of intelligent software and echocardiographic machines with the optimum combination of quality, features, and affordability should be accelerated by the collaboration of engineers from the manufacturers with expert physicians from the ASE to develop products that achieve wide market acceptance. This technology will result in improved safety, accuracy, and quality of patient care.

Recommendations

1. Develop cardiovascular ultrasound systems with the optimum combination of quality, features, portability, and affordability.
2. Develop intelligent software to provide real-time feedback during echocardiographic examinations to improve diagnostic quality and time efficiency.

Goal 2: Advance the Diagnostic and Therapeutic Capabilities of Ultrasound

Two-dimensional transducer arrays and high-speed 3D imaging were broadly identified as the most important enabling technolo-

gies that facilitate advancement of the diagnostic and therapeutic capabilities of cardiac ultrasound. The potential directions for new diagnostic and therapeutic capabilities are far-reaching and exciting.

New 2D array transducers (for 3D images), much higher frame rates, greater data acquisition, and greater processing speeds and memory capacities, combined with radically new anatomic and physiologic functional analysis methods and image mapping, will bring about new diagnostic tests that yield far more information than is presently possible. In the future, imaging of cardiac anatomy and function will routinely be done in three dimensions, with strain mapping, electromechanical wave mapping, and synchronization tracking. This will present new challenges and barriers, because the greater amount of additional data will require new evaluation methods and standards, as well as new training and implementation among users and user groups.

New noninvasive ultrasound therapy applications, such as sonothrombolysis, histotripsy, and high-intensity focused ultrasound could make it possible to perform interventions that are currently performed invasively. For example, new noninvasive techniques that make use of high-mechanical index acoustic levels might be able to dissolve intravascular clots using 3D ultrasound transducers. In addition, histotripsy, which makes use of pulsed, high-intensity focused ultrasound, will enable the disintegration of thrombi in deep vessel thrombosis. For conduction problems such as atrial fibrillation, targeted ablation methods will make it possible to resolve these issues noninvasively. These noninvasive techniques could bring new opportunities for treatment that can begin earlier and with abbreviated time for recovery, thus positively affecting patient outcomes. Thus, the technologic development to make this feasible should become a priority.

New quantitative ultrasound tissue characterization could play a significantly greater role in the evaluation of cardiac and vascular tissues for both diagnosis and treatment. This technique uses many

parameters besides backscatter to compute quantitative indices relating to tissue properties. These include the speed of sound, attenuation, strain, temperature, and higher order statistics. For example, it should be possible to noninvasively image and quantitatively identify ischemic and infarcted tissue, as well as clearly delineate coronary stenoses and characterize the size and type (hardness or softness) of plaques, as well as the presence of calcification. It should also be possible to image infarct size and volume, as well as follow the progress of intervention therapy, using of this technique. Beyond this, quantitative ultrasound tissue characterization should also make it possible to evaluate cardiac tissue texture and density, as well as calcifications and the presence of fibrosis, among many other possibilities.

Recommendations.

1. The development of capabilities in 3D imaging of cardiac anatomy and function with strain mapping, electromechanical wave mapping, and synchronization tracking must continue.
2. The much greater amount of resulting data will require development of new evaluation methods and standards and new training and implementation among users.
3. New noninvasive ultrasound therapy applications, such as sonothrombolysis, histotripsy, and high-intensity focused ultrasound, which have great potential for improving outcomes, must continue to be developed.
4. New quantitative ultrasound tissue characterization methods must be further developed to evaluate cardiac and vascular tissues. These image methods offer opportunities for the early detection and treatment of disease.

Goal 3: Develop an Ongoing Forum for Promoting Interaction among Ultrasound Engineers, Scientists, the NIH, the FDA, and Cardiologists

A mechanism to facilitate the ongoing collaboration of noncardiologist scientists and engineers in ASE activities is needed. This would facilitate the two-way communication required to accelerate the development and implementation of techniques, hardware, and software to enhance the capabilities of echocardiography. The ASE was encouraged to develop a mechanism to include such individuals and create a forum for discussion on a regular, ongoing basis.

Additionally, enhancing the awareness of individuals serving in funding and regulatory governmental roles (such as the NIH and the FDA) of current capabilities and future potential of echocardiography for improved patient care is also required to speed technology development. The ASE was encouraged to develop a mechanism to increase the participation of these organizations in the ongoing dialogue regarding technology, device, and drug development.

Recommendation.

1. The ASE should develop a mechanism to include scientists, engineers, and those involved with research funding in forums for discussion on a regular, ongoing basis.

Selected Readings.

1. Lee WN, Provost J, Fujikura K, Wang J, Konofagou EE. In vivo study of myocardial elastography under graded ischemia conditions. *Phys Med Biol* 2011;56:1155-1172.
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CARDIOVASCULAR ULTRASOUND CLINICAL RESEARCH

Numerous issues must be addressed to maintain and expand the use of echocardiography in clinical research. However, among the most important issues are (1) demonstrating that echocardiographic measures can be used as surrogates for outcomes or improved outcomes; (2) the optimization of echocardiographic core lab operations, accuracy, and reproducibility; (3) the development of processes that will ensure that all enrolling sites and operators at the point of research can obtain the proper images required for clinical trials; and (4) the development of a registry of echocardiographic information (and eventually images) that can serve as a platform for quality improvement and clinical research.

Goal 1: Prove That Echocardiographic Measures Can Be Used as Surrogates for Outcome

The strengths of echocardiography remain the quantification of cardiac structure and function by a noninvasive technique that is free of ionizing radiation, relatively inexpensive, universally available, and mobile enough to be performed in almost any venue. However, for it to maintain a key position in clinical research, investigators must ensure that important clinical questions motivate the research rather than hypotheses that just tout the technical capabilities of echocardiography. For example, efforts must be made to demonstrate that echocardiographically quantified parameters correlate with or improve care decisions and outcomes.¹ In particular, the echocardiography community should pursue efforts to satisfy regulatory requirements for establishing the value and practicality of a few select, quantitatively important echocardiographic biomarkers (such as LV ejection fraction and LV mass) by enacting education and policy strategies to ensure their consistency and reproducibility regardless of equipment, patient, or time scanned. In addition, because researchers often must choose a single modality, the relative accuracy and feasibility of echocardiography in clinical research compared with other modalities must be clarified. Funding from federal agencies such as the NIH and the Patient-Centered Outcomes Research Institute is likely to be critical to accomplish these trials. It will also be important to demonstrate that the results obtained in trials comparing imaging modalities are generalizable to the community rather than just reflecting results obtained in academic medical centers.

Recommendations.

1. Design and perform multicenter studies that identify and link the performance of echocardiography and resulting echocardiographic findings to patient outcomes, improved care, and reduced costs.
2. Formally qualify quantitative echocardiographic variables as clinical research biomarkers through a process akin to that followed for radiologic biomarker development (https://www.rsna.org/QIBA_.aspx).
3. Perform research that demonstrates the accuracy of echocardiographic measures such as cardiac chamber size, ventricular systolic and diastolic function, LV mass, and valve function directly compared with other competing modalities.

Goal 2: Develop Standardized Operations for Echocardiography Core Laboratories

Many clinical trials rely on echocardiographic measures confirmed by core laboratories. These uses range from patient qualification for enrollment to quantifying predefined end points in phase 2 and 3 trials of drugs and devices to monitoring of cardiac safety through postmarket surveillance studies. For echocardiography to be the imaging test of choice for these operations, the ASE must demonstrate that echocardiography core labs provide reproducible and reliable data and that these results are comparable and reproducible from core lab to core lab. To demonstrate such reproducibility and adherence to standards, it would be logical to expand on previously defined best practices with the creation of minimal standards for echocardiographic core laboratory operations.² Such standards could be used in the future to inform regulatory policy regarding imaging in clinical trials and, if desired, to create an accreditation process for such core labs.

In addition to ensuring high-quality data output from core labs, there are issues surrounding the logistics and regulatory compliance of transmitting, processing, and archiving thousands of images and data sets. A network of core labs working with technology developers should establish the necessary minimum standards for this aspect of core lab and clinical research operations.

Recommendations.

1. A task force should be formed to develop core lab minimum standards for operations and set minimum standards for reproducibility (within and between labs).
2. Perform research establishing core lab best practices and reproducibility standards, including demonstrating their validity in improving the scientific goals and efficiency of trials.

Goal 3: Optimize Imaging at Points of Research

Because echocardiography is ubiquitous in clinical care, extraction of the images from the clinical care environment for use in clinical research would be an important advance. For this to succeed, standardization of image protocols, measurement conventions, and reports are necessary along with simple tools to ensure that patients' health information is protected. These steps will enable the creation of large-scale registries or research imaging networks. In such a model, data elements from the echocardiographic report or database (rather than the actual images) could be transferred to central repositories and then used for a wide variety of investigations. However, such a model can succeed only if high-quality, standardized images are obtained and universal definitions and quality standards are used for reporting results. For example, all sites participating in such an imaging network would need to classify findings in an identical fashion. This is in contrast to the current state of affairs, whereby some laboratories report moderate mitral regurgitation and others report it as 3+ mitral regurgitation, and the criteria used to determine the severity of the regurgitation vary significantly.

Research must be performed to identify and refine those educational tools that most effectively and efficiently teach sonographers and echocardiographers proper image acquisition and measurement conventions for research applications. This may take the form of webinars, the use of social media sites for interactive training, and even instructional videos that can be viewed on smart phones and other portable communication devices.

In addition, research efforts should explore the creation of "smart" echocardiographic machines with embedded real-time

decision support. Such tools could initially include "ideal image" templates for operators to mimic and searchable guidelines. More advanced tools could include automated methods that show the user when an image is adequate for the particular research application. This may take the form of on-screen schematics of properly aligned images, prompts that inform the sonographer when an image matches a model image for that required view, notification that a 3D data set is adequate for cropping and quantification, integration of wireless communication capabilities on the machine for the sonographer to communicate with core labs, and easy-to-use tools that anonymize and transfer Digital Imaging and Communications in Medicine (DICOM) image sets to research archives. Also critical will be automated measurement capabilities that reduce measurement variability and ensure uniformity of measurements across different echocardiography machines. Last, electronic health record modules are required for seamless transfer of the results to a database.

Recommendation.

1. Develop real-time tools that can be used by imagers in clinical echocardiography laboratories to ensure that reproducible, standard images can be obtained for research applications.

Goal 4: Create Echocardiographic Data Registries

Registries currently exist for many cardiovascular procedures, such as angioplasty, cardiac surgery, device implantation, and some aspects of care, including acute coronary syndromes and outpatient care.^{3,4} These registries have been important tools to assess and improve the quality of care and are valuable platforms for clinical research. To date, imaging registries have been hampered by a lack of data standards and limited use of electronic health records. However, these barriers are being addressed, and there is increasing need for such data from both the regulatory and health care reform sectors, making such an undertaking more feasible in the future. Such registry data would be accessible to the research community, facilitating a broad range of clinical research on the effectiveness of echocardiography for the improvement of patient management and outcomes.

Recommendations.

1. Perform research to identify important echocardiographic variables for a cardiovascular imaging registry.
2. Complete efforts to develop and disseminate a full set of echocardiographic data elements formally approved by Clinical Data Interchange Standards Consortium and Health Level 7 and published in the Cancer Data Standards Registry and Repository hosted by the National Cancer Institute.
3. Develop standardized echocardiographic reports that enable seamless transfer of report data to cardiovascular imaging registries.
4. The ASE should explore the operational and financial feasibility of creating a national echocardiography registry.

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RESEARCH INFRASTRUCTURE

There is a consensus for the need to build a research pipeline in echocardiography both within the United States and globally. Moreover, there is a great need to improve the recording, storing, and sharing of Doppler echocardiographic images and linking them with other data sources.

Goal 1: Fostering Training and Early Career Development: Grants, Fellowships, and Other Mentorship Opportunities

Opportunities for training and early career development research funding are available across a range of potential sources, including the NIH, foundations, academic institutions, industry, and professional societies and include grants, fellowships, and other mentorship opportunities.¹⁻³ The currently available training programs are summarized in the [Appendix](#).

NIH funding opportunities include two broad areas of relevance, both of which can be initiated by the investigator community using existing funding mechanisms: institutional training grants (T series) and individual career development grants (K series). Adaptations of traditional models for institutional training grants may be well suited to echocardiographic research and include multi-institutional training grants (e.g., T32) that would bring together relevant expertise and resources across geographically proximate institutions, cross-department training grants (involving radiology, cardiology, etc.), and multimodality imaging training grants aligned with how fellows are currently being clinically trained. These types of grants could also increase the potential pool of fellows for postdoctoral research training awards. Both institutional training grants and career development grants allow the pursuit of courses and didactics in research design, methodology, and analysis.

The American Heart Association early career development program provides another opportunity for career development grants, and other funding opportunities are available through the American College of Cardiology and the Agency for Healthcare Research and Quality. Industry or foundation funding for training may allow a specific focus or facilitate bringing together different disciplines (e.g., clinical and engineering). Other important opportunities include training opportunities for foreign institutions and international trainees (e.g., applications to the Fogarty International Center at the NIH for training), as well as US institutions looking to exceptional international training sites for research training models (e.g., imaging research training programs in Canada funded by the Canadian Institutes of Health Research).

Although the potential to diversify funding may be an important opportunity as different funders may be willing to take on different aspects of funding, the tight fiscal environments facing funders and institutions could pose a barrier in the near term as grant competition stiffens. Other barriers include (1) the paucity of grants that are specifically designated for echocardiography, (2) the limited number of trainees who could be enrolled as part of institutional

training grants, and (3) the declining interest among fellows in academic research careers in echocardiography. It is therefore of the utmost importance to champion echocardiographic research and appropriate funding opportunities to attract a pipeline of fellows to the field.

Recommendations.

1. Create and maintain an inventory or mini-registry of research training resources by surveying the echocardiographic research community to collect such data. Resources catalogued could include investigators or labs with training grants, training components available in these labs (e.g., animal and molecular laboratories, statistical and cost-effectiveness expertise), the aspects of these resources that could be shared or made available to others through potential e-training or e-mentoring initiatives, and a listing or network of potential research mentors. This could be hosted on the ASE Web site.
2. Enhance communication among laboratories and institutions that are performing training to facilitate the development of joint initiatives such as training grant applications, development of an echocardiography research fellowship curriculum, and research mentoring.
3. The ASE must serve as a champion for echocardiography and echocardiographic research in the eyes of trainees and funding groups.

Goal 2: Informatics: Enhance Recording, Storing, and Sharing of Echocardiographic Images and Data

Future opportunities to improve informatics include developing imaging repositories that are interoperable, intercommunicable, and compliant with the Health Insurance Portability and Accountability Act and can be linked to other clinical data and research data sets.⁴⁻⁶

Cutting-edge grid-based computing or cloud computing may present viable opportunities to efficiently share data. Some barriers to sharing data include the fact that there is no single image repository that researchers can access. Individual studies and trials traditionally have used core laboratories, which retain their own images. Although images are being accepted into repositories such as the National Heart, Lung, and Blood Institute's BioLINCC, and efforts are under way at the NIH to explore storage of large databases of information (including imaging), such repositories are currently limited.

The current challenges in sharing data predominantly concern retrieval and software intercommunicability problems, because software formats are frequently proprietary. Creating open software bridges to DICOM may represent an opportunity to manipulate images acquired from different machines. DICOM is the current standard, but it has some drawbacks, including not being customized for echocardiography. Pushing for additional specific standards for echocardiography represents a worthwhile endeavor and opportunity to foster intercommunicability.^{5,6} It is acknowledged that some flexibility would be lost in the process of creating standards and industry representatives emphasize that revised standards take a long time and significant financial investment to develop. Thus, it is critical from their perspective to have a user group committed to standards that would be stable for a long period of time. By taking a stance on the development of these standards, the ASE could influence this to happen.

With regard to the organization of data, the ability to effectively categorize and communicate what is stored for retrieval and use is important. The ability of end users to recognize and access different images for different purposes is another important consideration. Last, the ability to link imaging data to other clinical, electronic

health record, and claims data should provide important research opportunities. Leveraging such data linkages could represent ripe opportunities for early stage investigators to submit ancillary studies and proposals using secondary data analysis to funders such as the NIH. In particular, the National Heart, Lung, and Blood Institute currently offers two relevant funding opportunities currently active (one for ancillary study proposals and a second for secondary data analysis).

Recommendations.

1. The ASE should work with manufacturers, clinicians, and researchers to promote standard access to image data, DICOM standards specific for echocardiographic image storage and reporting, and open-source software bridges to DICOM or peer-to-peer standards to foster intercommunicability using DICOM.
2. Foster the development of one or more image repositories that will allow researchers to access images from multiple sites and sources for analyses as well as to link imaging data to other clinical data sets.

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THREE-DIMENSIONAL ECHOCARDIOGRAPHIC IMAGING

Over the past decade, 3D echocardiography has gone through tremendous technological evolution, resulting in a worldwide recognition of this imaging modality and anticipation of its future central role in clinical echocardiography. The development of matrix-array transthoracic transducers has resulted in near real-time volume data sets. The development of fully sampled real-time 3D transesophageal echocardiographic (TEE) probes¹ has resulted in excellent image quality and ease of use. The visually striking, easy-to-interpret images provide new clinically useful information. In addition, the success of percutaneous procedures for the treatment of structural heart disease, such as mitral valve repair and closure of perivalvular leaks, relies heavily on 3D TEE guidance.² Access to 3D technology has been facilitated by the recent increase in the number of vendors.

These advancements have led to the development of new ASE guidelines for the acquisition and display of 3D echocardiographic images.³ These guidelines define the clinically recommended uses of 3D imaging, including quantification of LV volumes and ejection fraction, assessment of mitral valve anatomy and stenosis, and guidance of transcatheter procedures.

However, unlike the TEE applications, 3D transthoracic methodology has been lagging in its clinical dissemination, at least in part because of work flow issues. The following approaches may help overcome this problem.

Goal 1: Develop Automated Quantification and Improve Image Display

Most current tools for the quantification of LV volumes and ejection fraction require manual initialization of the endocardial boundaries in multiple planes extracted from the 3D data sets, which is usually performed offline on dedicated computer workstations.⁴ Because this methodology is time-consuming, it impedes optimal clinical work flow and consequently remains limited mostly to research, despite its proven benefits in accuracy and reproducibility.

Recommendations.

1. Automated quantification software tools that could be used immediately as the images are acquired must be developed. This is needed not only for the left ventricle but for the right ventricle, atria, and valves. This would serve as the basis for development of algorithms for segmenting various structures of interest for visualization and quantification.
2. Adaptive imaging is needed for automatic display of standard planes or 3D renderings without problems of misalignment such as foreshortening.
3. Software development for the automated analysis of left atrial volumes would contribute to more accurate diagnosis of diastolic dysfunction.⁵
4. Further software development for comprehensive and immediate assessment of the mitral valve apparatus and aortic valve annulus is needed to guide intervention in the operating room and catheterization lab.
5. Improvement of color Doppler regarding both visualization and quantification of flow is needed to support more accurate assessment of regurgitant flow volume.

Goal 2: Standardize 3D Methodology

For 3D echocardiography to be widely used, standardization of image acquisition protocols, display strategies, indices to be measured, the phases of cardiac cycles in which measurements should be performed, and the exact definitions on where to measure and which formulas and identifiers will be used are essential. Although the published guidelines³ serve as the foundations for this, further refinements will occur according to the specific tools developed for automated quantification.

Recommendation.

1. To support the standardization effort, the 3D DICOM format should be adopted.

Goal 3: Improve Image Quality and Transducer Design

Further improvements in spatial and temporal resolution of transthoracic 3D images are critical, because to date, the image quality of 2D planes extracted from 3D data sets is inferior to that of native 2D images acquired with dedicated 2D transducers. Achieving this goal would greatly facilitate the practice of echocardiography, because the acquisition of a single data set followed by semiautomated slicing would be adequate to display the standard 2D views currently used for complete echocardiographic evaluation, including, for example, stress echocardiography. Image quality in specific patient populations could also be improved by developing a range of 3D transducers, including probes with smaller footprints that use higher imaging frequencies for pediatric patients or higher power output for technically difficult adult patients. Further miniaturization of 3D TEE probes could potentially eliminate the need for general anesthesia during percutaneous procedure guidance, as well as allow this methodology to be expanded to include very young pediatric patients. This could have an impact on the outcomes of complex intracardiac repairs in these patients. The development of 3D vascular probes with higher imaging frequencies would improve on the current diagnostic capabilities of

atherosclerotic carotid disease, because it would allow easier evaluation of disease burden. Furthermore, optimization of contrast-enhanced 3D imaging would make this technology useful in difficult patients and also for 3D stress testing.

Recommendations.

1. Improve the spatial and temporal resolution of transthoracic 3D images.
2. Develop a variety of transthoracic and transesophageal 3D transducers to optimally image patients of varying sizes and perform vascular imaging.
3. Optimize 3D contrast imaging.

Goal 4: Improvement of Work Flow

Clinical work flow would benefit considerably from the use of transthoracic 3D transducers capable of acquiring both 3D and 2D images. This would allow integration of the 3D and 2D parts of the study in the digital information storage and review systems by structure rather than by the dimensionality of the images. This would also eliminate the need to export images into third-party workstations for further specialized analyses. Fusion of 3D echocardiographic images with other imaging modalities, such as computed tomography, magnetic resonance, or fluoroscopy, would likely result in enhanced diagnostic applications as well as improved guidance of complex interventions. Training and education in 3D echocardiography plays an important role in the routine adoption of this modality. The support of the ASE remains crucial.

Recommendations.

1. Develop transthoracic transducers capable of acquiring both 3D and 2D images.
2. The ASE must continue training and education in 3D echocardiography.

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CARDIOVASCULAR ULTRASOUND IN VALVULAR HEART DISEASE

In the United States, 2.5% of the population has moderate or severe VHD, 1.4% has bicuspid aortic valve, and 2.5% has mitral valve prolapse.^{1,2} Furthermore, rheumatic heart disease remains common in developing countries. Worldwide, it is estimated that 500 to 600 million people have VHD. VHD thus represents a major public health problem that should be addressed.

Imaging is necessary to optimize the management of VHD. Because of its versatile, noninvasive, radiation-free, widely available, and low-cost nature, Doppler echocardiography is currently the primary imaging means of assessment. However, changes that have occurred in the spectrum and management of VHD during the past decades have brought new requirements and challenges to Doppler echocardiography. These changes include an increase in the proportion of elderly patients (a group with frequent comorbidities), improvements in the safety and efficacy of valve surgery, and the development of transcatheter valve therapy (TVT). This new and rapidly evolving field requires comprehensive and quantitative assessment of valve anatomy and function in three dimensions to identify the patients and valvular lesions that can be addressed by the specific TVT and to guide the procedure and assess its results.

Goal 1: Improve Doppler Echocardiography to Better Quantify the Severity of Valve Dysfunction and to Enhance Risk Stratification and Clinical Decision Making in VHD

There is a need to develop high-resolution 3D imaging technologies that permit precise description of valve anatomy and lesions. This development should enable accurate estimation of valve leaflet dimensions, thickness, and coaptation distance as well as quantification and localization of calcifications and small lesions. Moreover, 3D imaging technology must be improved and adapted to allow assessment, quantification, and modeling of valve kinematics. These analyses should also be feasible by transthoracic echocardiography.

Improved methods of quantifying the severity of valve dysfunction are needed. Two-dimensional color Doppler flow imaging has limited accuracy to assess valve regurgitation severity. Although various quantitative methods such as the proximal isovelocity surface area method have greatly improved prognostication of mitral or aortic regurgitation,³ these methods are subject to technical pitfalls and other limitations. Furthermore, the quantitative methods may be difficult to apply and/or may be inaccurate in patients with eccentric or multiple regurgitant jets as well as in patients with prosthetic valves. Parameters of aortic stenosis severity such as the peak jet velocity or transvalvular gradients are dependent on the magnitude of transvalvular flow, which may vary.⁴ The aortic valve effective orifice area is much less flow dependent than the gradient but requires the estimation of stroke volume, which may be subject to measurement errors. Recent studies suggest that exercise stress echocardiography provides incremental prognostic value beyond resting echocardiography and exercise testing alone.⁴ However, the quantification of valvular dysfunction and its impact on size and function of cardiac chambers during exercise is technically demanding and may be less reliable.

These challenges highlight the urgent need for the development of simple and accurate methods to quantitate antegrade and retrograde flow across valves. Automated or semiautomated quantification of mitral inflow and aortic valve outflow stroke volume would greatly facilitate and enhance the estimation of quantitative parameters of valvular stenosis or regurgitation at rest and during exercise. Three-dimensional real-time volume color-flow Doppler echocardiography and backscattered Doppler power analysis have shown promise. However, further technological development and clinical validations are necessary.

Doppler echocardiography has an important role in assessing the consequences of valvular dysfunction on the dimensions and function of cardiac chambers. Hemodynamic parameters such as stroke volume index, cardiac index, and pulmonary arterial pressure have been shown to be powerful risk markers in VHD, and there is

a need for automated or semiautomated methods allowing accurate and rapid quantification of these parameters. Three-dimensional echocardiography may improve cardiac chamber quantification in patients with VHD, but its clinical utility remains limited by suboptimal image resolution and by the labor-intensive nature of the measurements. High-resolution transthoracic 3D imaging with analysis tools allowing rapid, user-friendly, and accurate quantification of cardiac chamber geometry and function are needed.

Recent studies also suggest that LV longitudinal strain measured by speckle-tracking imaging is superior to standard echocardiographic parameters to detect and quantify myocardial dysfunction and contractile reserve as well as to predict symptoms and outcomes in VHD. However, to enable the implementation of myocardial strain parameters into VHD practice, it is necessary to (1) standardize and optimize the technologies for 2D and 3D strain acquisition and measurements and (2) conduct large multicenter prospective studies to validate the optimal cut-point values of strain parameters for the identification of significant myocardial dysfunction and the recommendation of valve intervention in different types of VHD. The strain parameters that appear most promising in the context of VHD are global LV longitudinal strain and LV systolic torsion. Three-dimensional speckle-tracking has the potential to provide a true "global" assessment of LV longitudinal and rotation function, but this technology needs to be further optimized and validated.

Recommendations.

1. Develop and validate high-resolution 3D imaging technologies, feasible by transthoracic echocardiography, to provide precise description and quantification of valve anatomy, lesions, and kinematics.
2. Develop and validate automated or semiautomated Doppler echocardiographic methods for the accurate quantification of antegrade and retrograde flow across valves at rest and during exercise.
3. Improve quantitative 3D volumetric assessment of all four cardiac chambers.
4. Standardize and validate myocardial strain parameters and criteria for the identification and quantification of LV and right ventricular systolic dysfunction in VHD.

Goal 2: Improve the Evaluation and Treatment of Patients Undergoing Transcatheter Valve Procedures

TVTs, including transcatheter aortic valve replacement (TAVR) and mitral valve repair, have brought new responsibilities and challenges for imagers. Doppler echocardiography has an important role in patient selection, procedural planning and guidance, and postprocedural evaluation.^{5,6} Multidetector computed tomography, cardiac magnetic resonance imaging, or fluoroscopy may complement and, in some situations, replace Doppler echocardiography. Doppler echocardiography must be further studied and adapted to the rapidly growing and changing field of TVT.

Patient selection and procedure planning for TAVR requires a comprehensive and quantitative assessment of the aortic annulus and root, and high-resolution 3D imaging is crucial to achieve this goal.^{5,6} Accurate measurement of the aortic annulus is key to the selection of optimal prosthesis size and the prevention of paravalvular regurgitation; this is better achieved by 3D rather than 2D imaging, regardless of the imaging modality used. The echocardiographic methods and criteria used to measure annular dimensions and select prosthesis size for TAVR must be better defined and standardized. Randomized clinical trials are needed to compare 3D TEE imaging with multidetector computed tomography or cardiac magnetic reso-

nance imaging for the estimation of aortic annular size and the prevention of paravalvular regurgitation and aortic annular complications. Quantitative assessment of valve kinematics in three dimensions and in a continuous way would greatly enhance the assessment of appropriateness of the valvular lesion for catheter-based therapy intended to reduce mitral regurgitation as well as the evaluation of adequacy of the results.

Although fluoroscopy is the mainstay technique for TVT procedural guidance, TEE imaging is useful to guide and monitor the procedure and to rapidly identify complications. Real-time 3D imaging clearly offers major advantages, particularly for more complex procedures such as percutaneous mitral valve repair, in which switching from 2D to 3D imaging significantly reduces procedural time and radiation exposure.^{5,7} However, there is currently a trend to move toward "totally" percutaneous valve procedure without general anesthesia, which implies the elimination of standard TEE probes. The potential alternatives include miniaturized transnasal echocardiographic probes or intracardiac echocardiography. Such developments should include high-quality and real-time 3D imaging technology to ensure optimal communication with interventional cardiologists. Another interesting future direction is the development of transthoracic probes that allow high-resolution 3D imaging during the procedure. Such development requires major improvement in the image quality and the implementation of strategies to reduce radiation exposure for imagers.

The device and imaging companies should work together to develop ultrasound probes, technologies, and software geared to specific TVT procedures on one hand and to improve the echogenicity and visibility of catheters and devices on the echocardiographic images on the other hand. In particular, the development of fusion imaging between 3D echocardiography and fluoroscopy is a priority, as it would (1) enhance understanding of anatomy relevant to intervention; (2) improve navigation of guidewires, catheters, and delivery systems; and (3) accelerate the assessment of results and the recognition of anatomy-device interaction and other complications. An automatic mapping system would optimize the communication between interventionalists and imagers and would facilitate the procedural guidance. Virtual reality technology may help optimize the selection of the implantation route and the model and size of device as well as to anticipate and prevent intraprocedural complications.

After TVT, Doppler echocardiography is the method of choice to evaluate the functional integrity of transcatheter heart valves and devices.^{5,6} However, TVT leads to challenges in terms of imaging and flow dynamics. Percutaneous mitral valve repair for mitral regurgitation creates two distinct mitral valve orifices, making quantification of residual mitral regurgitation more difficult. Paravalvular regurgitation is common after TAVR and has been associated with reduced survival. The estimation of paravalvular regurgitation severity is challenging because of the presence of multiple and/or eccentric jets and because of the acoustic shadowing caused by the prosthesis stent. In this context, standard quantitative methods for color Doppler flow imaging are less reliable. There is an urgent need for the development of new Doppler echocardiographic methods that allow accurate and reliable estimation of residual regurgitation severity after TVT. The measurement of the vena contracta area of the regurgitant jet(s) by 3D color Doppler is currently one of the most promising and feasible approaches for this purpose.⁷ Three-dimensional real-time volume color-flow Doppler echocardiography and back-scattered Doppler power analysis are also attractive approaches that could allow automated, fast, and reliable quantification of residual

regurgitation but require further technological development and clinical validation.

Recommendations.

1. Develop echocardiographic technologies customized and optimized for specific transcatheter valve procedures.
2. Improve catheters and devices so that they become more visible and traceable on echocardiography.
3. Develop technologies that allow high-quality, real-time 3D imaging without general anesthesia.
4. Develop fusion imaging and virtual reality technologies that integrate 3D echocardiography with other imaging modalities, in particular with fluoroscopy and multidetector computed tomography, to enhance and facilitate the planning and guiding of transcatheter valve procedures.
5. Perform clinical trials demonstrating the efficacy and cost-effectiveness of Doppler echocardiography compared with other imaging modalities in patient selection for TVT as well as procedure planning, guiding, and evaluation.

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MYOCARDIAL DEFORMATION ECHOCARDIOGRAPHY

Myocardial deformation by echocardiography provides a quantitative assessment of regional and global systolic and diastolic function and deformation of any chamber of the heart. A growing body of evidence suggests that it is superior to conventional echocardiographic measures of function. In a range of cardiac conditions, including but not limited to coronary artery disease, cardiomyopathy, and cardiac arrhythmias, deformation parameters have been demonstrated to yield incremental functional and prognostic information compared with conventional echocardiography. Despite a plethora of data from in vitro models, animal models, small clinical studies, and larger clinical trials, the adoption of deformation echocardiography in routine clinical practice has been slow.

The key issues addressed were (1) identifying the barriers to the routine clinical implementation of deformation echocardiography, (2) establishing the technological advances needed to achieve the clinical and research goals for deformation echocardiography, and

(3) determining specific research directions to examine the potential role of strain in clinical practice.

Goal 1: Formulate a Strategic Approach to Technology Development to Achieve a Standardized Methodology That Enables Routine Clinical Use of Deformation Echocardiography

A key barrier to the routine use of deformation echocardiography is the vastly different acquisition techniques and analysis packages offered by each vendor. Not only is the use of deformation echocardiography not intuitive, it is unwieldy and operator dependent, therefore lending itself to artifacts and variability in results from operator error. For example, to obtain and analyze a spectral Doppler signal, the process is much more uniform: place a sample volume at a particular site, activate the Doppler, and record the signal. Similarly, analysis involves placing a caliper at the peak or tracing the signal outline. A similar standardized work flow would greatly enable wider adoption of strain. There is recognition that each vendor may have unique strengths. Also, expert users may desire additional and more sophisticated analysis options. However, for routine clinical applications, a standardized approach would facilitate use. The challenge is to balance innovation with throughput in this era of diminishing reimbursements for echocardiography and the push to keep clinical units more productive with fewer resources. Future directions include the incorporation of deformation echocardiography into a blended imaging system or in adaptive imaging wherein deformation mapping would assist in regionally targeted delivery of gene or polymer or stem cell therapies. There is excitement about 3D deformation echocardiography, although more data are needed to better understand its value over tissue Doppler and 2D-based deformation. Similarly, although assessment of torsion and twist mechanics has provided new insights into cardiac physiology, there remains an important opportunity for demonstration of its incremental clinical value.

Recommendations.

1. Promote and support active vendor engagement in the ongoing Initiative to Standardize Deformation Imaging with a view to achieve a robust and standardized deformation echocardiography system in a time-sensitive manner.
2. Develop technology strategies for user-friendly deformation echocardiography that need no additional dedicated images.
3. Devise image noise management approaches and allow higher frame rate imaging to maximize the information yield in resting and stress studies.
4. Continue the discussion on structured reporting standards and engagement of the DICOM committee to incorporate deformation parameters.
5. Pursue technological advances that permit the incorporation of deformation echocardiography into multimodal imaging platforms that include magnetic resonance, computed tomography, and positron emission tomography.

Goal 2: Facilitate the Implementation of Deformation Echocardiography as Part of the Standard Clinical Echocardiographic Examination

Although the introduction of speckle-tracking technology has addressed some of the key barriers by allowing semiautomated analysis programs on the basis of standard B-mode images, major impediments to implementing deformation echocardiography on a wider scale and in routine clinical practice remain. They are (1) a lack of fundamental knowledge about the deformation concept, (2) a lack of training and analysis skills, (3) varying vendor platforms with differing

normal value ranges (discussed under goal 1), and (4) a lack of reproducibility in key deformation parameters (discussed under goal 3).

Recommendations.

1. Expand deformation concept education in core echocardiography training programs and in ASE-sponsored courses and conferences.
2. Expand and increase the frequency of hands-on workshops for deformation image acquisition and analysis.

Goal 3: Generate a Body of Evidence Demonstrating the Incremental Clinical Value of Deformation Echocardiography in Common Cardiovascular Conditions Compared with Conventional Echocardiography

For myocardial deformation indices to become a routine part of the echocardiographic examination, research studies are essential to prove the following hypotheses: (1) deformation parameters add significant incremental information compared to existing functional indices, and (2) deformation parameters are acquired and analyzed easily and reproducibly in a time-efficient manner.

There is a growing body of research evidence that global longitudinal strain in particular carries incremental prognostic value compared with wall motion assessment and ejection fraction alone in a variety of cardiovascular pathologies, such as valvular disease, cardiomyopathies, chemotherapy-induced cardiotoxicity, and coronary artery disease or myocardial infarction. Furthermore, deformation parameters may detect subtle abnormalities of regional myocardial function not otherwise feasible by conventional means.

Three significant barriers must be overcome to demonstrate the incremental clinical value of deformation echocardiography. First, standardization of strain acquisition, analysis, and values (goal 1) is needed. Next, large multicenter studies are needed. Most of the published deformation studies are small, single-center studies. In contrast, the value of LV ejection fraction has been validated in an extensive body of literature. Finally, there are no data on how best to incorporate deformation information in actual clinical decision making.

Recommendations.

1. Using an easy-to-use deformation image acquisition system that is standardized across vendors (goal 1), develop a large standardized normal value database. Establish the reproducibility of the parameters.
2. Formulate and execute large randomized, controlled, blinded, outcomes-based studies that test the potential incremental value of the standardized deformation echocardiographic examination.
3. Build on validation-based and outcomes-based studies to design testable algorithms of clinical decision making that incorporate deformation parameters. One iteration of these studies would be to study the economic impact of using deformation-based parameters in clinical decision making.

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THERAPEUTIC ULTRASOUND

Sonothrombolysis, targeted drug or gene delivery using carrier microbubbles, and the establishment of clinical trials for these applications were discussed.

Goal 1: Develop a Bioengineering Research Partnership in Sonothrombolysis

In the presence of a commercially available intravenous microbubble infusion, animal studies have demonstrated that high-mechanical index impulses from a modified diagnostic ultrasound transducer can produce thrombus dissolution. In acute myocardial infarction, rapid (within 30 min) epicardial recanalization of the infarct vessel has been achieved with this approach, using only low doses of fibrinolytic agents. Other in vivo studies have demonstrated that the guided high-mechanical index impulses may be able to recanalize thrombosed vessels and/or mitigate microvascular no reflow, even in the absence of a lytic agent. The term used for this process is *sonothrombolysis*. The portability and safety of sonothrombolysis makes it an exciting new approach in the treatment of acute coronary syndromes and ischemic stroke. Beyond this, sonothrombolysis has the potential to be used in other clinically relevant pediatric and adult situations, such as treating catheter-related thrombi or graft and shunt thrombosis.

Clinical application of sonothrombolysis is contingent on several factors, ranging from basic understanding of the mechanisms for thrombus dissolution to achieving first in human trials that will explore the feasibility, safety, and efficacy of sonothrombolysis in a busy emergency room environment. This translational effort requires multidisciplinary expertise that engages basic science, bioengineering, regulatory, and commercial interests. Because of the scale of such an endeavor, we recommend using the bioengineering research partnership concept (<http://grants.nih.gov/grants/guide/pa-files/PAR-10-234.html>) to develop a translational multidisciplinary research team. Not only is the bioengineering research partnership a mechanism for funding through the NIH, but its conceptual design is ideal for the sequence of steps required to successfully incorporate sonothrombolysis into routine clinical care. The bioengineering research partnership would establish a national network focused on overcoming the barriers and challenges to the clinical implementation of sonothrombolysis. These include (1) determining the mechanisms for sonothrombolysis and their relation to other ultrasound-induced phenomena, such as nitric oxide release and sonoporation; (2) establishing the optimal ultrasound parameters for sonothrombolysis within the microvasculature and how this may prevent microvascular obstruction; (3) identifying the optimal transducer design technology for sonothrombolysis (e.g., micromachined technology vs piezoelectric crystals); and (4) establishing, in conjunction with the FDA, an investigational device exemption that will explore the safety, feasibility, complementarity, or potential superiority of sonothrombolysis over

emergent percutaneous catheter-based interventions in treating acute coronary syndromes. To achieve these goals, a stepwise approach will be required that first incorporates the expertise already in place at several institutions, followed by collaborations with the FDA and the NIH in formulating the first in human studies. The National Heart, Lung, and Blood Institute Clinical Trials Pilot Studies (R34) (<http://grants.nih.gov/grants/guide/pa-files/PAR-13-002.html>) can serve as a mechanism for funding these initial feasibility trials. A similar multicenter and institutional effort will also be developed in treating ischemic stroke, only here, collaborations will need to include the expertise of neurologists and radiologists in developing this research partnership.

Recommendation.

1. Establish a bioengineering research partnership or translational multidisciplinary research team to develop sonothrombolysis and a stepwise plan to incorporate it into clinical care.

Goal 2: Develop High-Yield Areas in Targeted Drug or Gene Delivery

Preclinical studies have shown the potential for targeted drug or gene delivery using carrier microbubbles and high-mechanical index ultrasound application. Genes or proteins and drugs can be incorporated within microbubbles, attached on their surface or administered unattached along with microbubble agents into the systemic circulation, where they freely pass through the microcirculation. Externally applied high-power ultrasound can then be used to destroy the microbubbles within the microcirculation of the tissue of interest, producing biologic effects that result in deposition and targeted transfection or delivery of the therapeutic agent. The ability to use the transducer to dually image the target as well as destroy microbubbles within the tissue of interest allows optimal temporal and spatial targeting of microbubble destruction. Multiple therapeutic applications have been studied, including angiogenesis in ischemic heart and vascular disease, anticancer therapies, antifibrotic therapies in progressive nephropathy, and islet cell regeneration in diabetes. The ability to deliver genes and drugs using a noninvasive theranostic approach that is easily repeated while limiting off-target side effects of systemic delivery offers an exciting new avenue for targeted delivery of therapeutic agents to any organ accessible to ultrasound.

Considerable work needs to be done before successful translation of ultrasound-targeted drug or gene delivery becomes a clinical reality. More preclinical studies need to be performed to (1) optimize ultrasound parameters (power, transit frequency, and pulse duration) and delivery settings to maximize transfection while minimizing adverse tissue biologic effects, (2) determine the most effective method to "load" targets onto microbubbles, and (3) choose the key target(s) to progress to phase I clinical trials in selected disease states that have the greatest chance of early success.

Other barriers to the clinical translation of ultrasound microbubble-mediated gene and drug delivery include the need for carrier microbubbles and ultrasound delivery platforms designed specifically for human use. The solutions for these problems must be developed in conjunction with industry and regulatory agencies and used in the next generation of preclinical studies. The ability to simultaneously image the tissue being insonified during delivery is important to confirm therapeutic application. This "theranostic approach" should be built into the design of therapeutic

ultrasound platforms. These results will inform and provide key efficacy and safety data in support of first-in-human trials. Given the body of work performed to date and ease of ultrasound-targeted delivery, the focus should be turned to high-yield applications such as (1) treatment of diabetes with gene delivery to the pancreas, (2) cancer therapies, and (3) ischemic cardiac and peripheral arterial disease.

The barriers to the successful translation of ultrasound targeted drug or gene delivery are very similar to those that exist for sonothrombolysis. Again, a translational multidisciplinary research team including international collaborators is recommended.

Recommendation.

1. Establish a bioengineering research partnership or translational multidisciplinary research team to develop ultrasound targeted drug or gene delivery and a stepwise plan to incorporate it into clinical care.

Goal 3: Establish Multicenter Clinical Trials in Sonothrombolysis and Targeted Delivery

The goals of the basic and translational studies exploring sonothrombolysis and targeted drug or gene delivery are ultimately to conduct multicenter clinical trials exploring their effectiveness in their proposed high-yield areas. For sonothrombolysis, this would involve trials examining the effect of ultrasound and microbubbles in the emergent treatment of acute coronary syndromes and ischemic stroke. For targeted drug and gene delivery, this would include targeted ultrasound delivery in the treatment of diseases such as type I diabetes, advanced peripheral and coronary vascular disease, and cancer. Multicenter studies would serve as the springboard for a new field of ultrasound-guided treatment for life-threatening disorders. Such noninvasive treatment modalities would greatly expand the number of patients who could be treated effectively. Barriers to reaching these goals include the lack of funding sources to financially support large clinical trials and a lack of established communications with regulatory and funding agencies or venture capitalists.

Recommendations.

1. Within the next 3 years, obtain necessary basic and translational data to serve as the basis for first-in-human pilot studies, to establish safety and potential efficacy.
2. For each potential clinical trial, a specific business plan should be developed and proposals put forth to NIH and the FDA for trial design.

Selected Readings.

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3. Smith AH, Kuliszewski MA, Liao C, Rudenko D, Stewart DJ, Leong-Poi H. Sustained improvement in perfusion and flow reserve after temporally separated delivery of vascular endothelial growth factor and angiopoietin-1 plasmid deoxyribonucleic acid. *J Am Coll Cardiol* 2012;59:1320-1328.
4. Chen S, Shimoda M, Wang MY, Ding J, Noguchi H, Matsumoto S, Grayburn PA. Regeneration of pancreatic islets in vivo by ultrasound-targeted gene therapy. *Gene Ther* 2010;17:1411-1420.

5. Carson AR, McTiernan CF, Lavery L, Grata M, Leng X, Wang J, et al. Ultrasound-targeted microbubble destruction to deliver siRNA cancer therapy. *Cancer Res* 2012;72:6191-6199.

SUMMARY

To realize the great potential of ultrasound for improving patient outcomes and offering novel therapy, closer partnerships among scientists, engineers, and those involved with research funding are needed. Improvements in technology, developed with these partnerships, will be necessary to advance 3D echocardiography, deformation imaging, and the quantitative assessment of VHD. Stepwise

research studies will advance the development of sonothrombolysis and drug and gene delivery. The development of intelligent software offers the potential to improve the quality and efficiency of echocardiographic examinations. With demonstration of the value, reproducibility, and feasibility of quantitative echocardiographic biomarkers, users can then make the strong argument that echocardiography is a superior technology as a research tool for clinical trials in which large numbers of subjects must be imaged efficiently, cost-effectively, and safely. The leadership of the ASE will discuss the recommendations put forth in this document and formulate an action plan. Research remains an important mission of ASE, and the society must find a way to continue to expand and advance this endeavor to meet the needs of our patients.

APPENDIX**National Heart, Lung, and Blood Institute (NHLBI)
Research Training Opportunities**

Individual National Research Service Awards for Predoctoral and Postdoctoral Training. F30–NHLBI Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral MD/PhD Fellows: This program supports individual predoctoral fellowships for combined MD and PhD training in research areas relevant to the mission of the NHLBI. Applications will be accepted from (1) students currently enrolled in a combined MD and PhD program and (2) current medical or graduate students seeking admission to a combined program that provides research training in areas relevant to the NHLBI's mission. Awards to these applicants are contingent on subsequently being enrolled in a combined MD and PhD program.

F31–Individual Predoctoral Fellowships (F31) to Promote Diversity in Health-Related Research: This program supports individuals from backgrounds underrepresented in biomedical science, including members of underrepresented racial and ethnic groups, individuals with disabilities, and individuals from disadvantaged backgrounds enrolled in programs leading to PhD, MD and PhD, or other combined degrees in the biomedical or behavioral sciences.

F32–Individual Postdoctoral National Research Service Award: The F32 program offers health scientists the opportunity to receive full-time research training for up to 3 years in areas that reflect the national need for biomedical, clinical, and behavioral research in cardiovascular, pulmonary, and hematologic diseases. These grants are not intended for study leading to MD, DO, DDS, or equivalent professional degrees, nor do they support residency training.

Institutional Ruth L. Kirschstein National Research Service Awards. T32–Institutional National Research Service Award: This program enables research institutions to support predoctoral and postdoctoral research and short-term training in the areas of heart, lung, and blood diseases. Trainees are selected through local review procedures established by the program director at the grantee institution. The maximum training period for predoctoral individuals is 5 years. The maximum training period for postdoctoral individuals is 3 years. Research training is pursued full-time, and trainees in clinical areas are expected to confine their clinical duties to those that are part of their research training. Trainees must be US citizens, noncitizen nationals, or legal permanent residents of the United States.

T35–Short-Term Institutional Research Training Grant: This program provides funds to research institutions to make awards to individuals in health professional schools for research opportunities that would not be available through their regular courses of study. Awards are made to training institutions by national competition. Trainees are selected by the grantee institution and must be US citizens, noncitizen nationals, or legal permanent residents of the United States.

Individual Career Development Awards (K Awards). K01–Mentored Career Development Award to Promote Faculty Diversity/Re-Entry in Biomedical Research (K01): This award supports junior faculty members from underrepresented backgrounds, including members of racial and ethnic groups, individuals with disabilities, and individuals from disadvantaged backgrounds, at US institutions to enhance their research skills in areas of interest

to the NHLBI and to increase the number of highly trained investigators from diverse backgrounds.

K08–Mentored Clinical Scientist Development Award: The K08 award enables candidates holding professional degrees (e.g., MD, DO, DVM, or equivalent degrees) to undertake 3 to 5 years of special study and supervised research with the goal of becoming independent investigators. The award also allows awardees to pursue research career development programs suited to their experience and capabilities under mentors who are competent to provide guidance in the chosen research areas.

K23–Mentored Patient-Oriented Research Career Development Award: The K23 award supports the career development of investigators who are committed to patient-oriented research. It provides support for supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research.

K24–Midcareer Investigator Award in Patient-Oriented Research (K24): The K24 award provides support for clinicians to further their research and mentoring of outstanding patient-oriented investigators. It will enable them to expand their potential for significant contributions to their fields and to act as mentors for beginning clinical researchers. This award provides protected time to enable clinicians to carry out these activities.

K25–Mentored Quantitative Research Career Development Award: The goal of the K25 program is to foster interdisciplinary collaboration in biomedical and behavioral research by supporting supervised research experiences for scientists with quantitative and engineering backgrounds. This award provides research and career development opportunities for scientists and engineers with little or no biomedical or behavioral research experience who are committed to establishing themselves in careers as independent biomedical or behavioral investigators.

K99/R00–NIH Pathway to Independence Award: The Pathway to Independence Award is designed to facilitate a timely transition from a mentored postdoctoral research position to a stable independent research position with independent NIH or other independent research support at an earlier stage than is currently the norm. The award will provide up to 5 years of support consisting of two phases. The initial phase will provide up to 2 years of mentored support for postdoctoral research scientists. This phase will be followed by up to 3 years of independent support contingent on securing an independent tenure-track or equivalent research position.

R25–Short-Term Training Program to Increase Diversity in Health-Related Research: The NHLBI's Short-Term Research Education Program to Increase Diversity in Health-Related Research is designed to promote diversity in undergraduate and health professional graduate student populations by providing short-term research education support to stimulate career development in cardiovascular, pulmonary, hematologic, and sleep disorders research.

Additional Sources. NIH Grants & Funding Web site: <http://grants.nih.gov/grants/oer.htm>

NIH Loan Repayment Programs to stimulate research training in five areas: <http://www.lrp.nih.gov/index.aspx>

NHLBI Research Training and Careers Web site: <http://www.nhlbi.nih.gov/training/index.htm>

NHLBI Division of Cardiovascular Sciences Office of Research Training and Career Development: (301) 435-0535, <http://www.nhlbi.nih.gov/about/dcvd/index.htm>