Left Atrium in Heart Failure With Preserved Ejection Fraction
Structure, Function, and Significance
Andrea Rossi, MD; Mihai Gheorghiade, MD; Filippos Triposkiadis, MD; Scott D. Solomon, MD; Burkert Pieske, MD; Javed Butler, MD MPH

Cardiac remodeling is a fundamental part of the heart failure (HF) syndrome, representing a common response to various pathological stimuli that result in changes in the structural and functional properties of the heart. To date, most studies in HF have focused on ventricular remodeling, and much less emphasis has been placed on atrial structural and functional changes. Specifically, in the context of HF with preserved ejection fraction (HFP EF), more attention has recently been placed on the left atrial (LA) remodeling, which is now considered a potential therapeutic target and an end point for evaluation of novel therapies. In this review, we discuss the pathophysiologic and clinical implication of LA remodeling in HFP EF.

Anatomy
Left atrium is a thin-walled structure located in the inflow path from the pulmonary veins to the left ventricle (LV) and is characterized by (a) main body with smooth walls that embryologically is developed from the outgrowth of the pulmonary veins and (b) by a finger-like trabeculated appendage, which is a remnant of the original embryonic left atrium. Distribution of atrial myocyte fibers is highly variable, but some components are relatively constant. In particular, the Bachmann’s bundle is the most superficial group of circumferential myofibers located close to the atrioventricular groove. In this bundle, the electric conduction from right to LA preferentially occurs. Other myocardial longitudinal fibers are likely responsible for upward motion of mitral annulus during atrial contraction.

Function
Mechanical Function
The mechanical function of LA is usually defined by 3 phases of LA volume variations during the cardiac cycle. The reservoir phase takes place during ventricular systole when the LA collects blood coming from the pulmonary veins. This phase is mechanistically determined by LA relaxation and by LV contraction, which moves the mitral annulus toward the apex, resulting in increased LA volume. Atrial compliance allows chamber volume to increase during the reservoir phase, maintaining filling pressures within normal limits. A reduction in atrial compliance increases LA pressure, particularly at the end-ventricular systole (v-wave). In the early diastole, blood stored in LA during the reservoir phase is driven into LV by the high early diastolic atrial–ventricular pressure gradient. Subsequently, direct flow from the pulmonary vein through the atrium into the ventricle takes place (atrial conduit volume). At end-diastole, atrial contraction occurs, forcing blood to fill the LV (Figure 1). Thus, LA contributes importantly to cardiac function, and altered LA diastolic and systolic properties may influence cardiac filling and output.

Neurohormonal Function
Myocytes produce and store natriuretic peptides in intracellular granules as prohormone. Atrial natriuretic peptide is mainly produced in atria and is secreted in the blood stream, exerting many of its actions through the A-type natriuretic peptide receptor, resulting principally in diuresis and vasodilation. Increased atrial volume and stretch are mainly responsible for its release. Natriuretic peptide secretion is also stimulated by paracrine factors, such as endothelin, nitric oxide, angiotensin II, vasopressin, and adrenergic agonists; all systems typically activated in HF. Consequently, atrial endocrine function might be a crucial mechanism to compensate the hemodynamic and neurohormonal disturbances seen in HF.

Regulatory Function
LA is crucial for the volume receptor reflex through its mechanoreceptors located in the venous–atrial junctions. An optimal volume control is essential for cardiovascular function and might be vital in conditions like hemorrhages and HF. This system is regulated on a moment-by-moment basis and works in parallel with other endocrine systems, such as natriuretic peptide, and angiotensin–aldosterone signals for more long-term regulation. The atrial mechanoreceptors are highly efficient, and fluctuation in venous volume of <1% can be signaled to the brain through autonomic nerves. The LA

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also regulates vasopressin production, which is essential for water and electrolyte balance. The primary stimulus for its release is an increase in osmolality, but a nonosmotic activation is possible and is responsible for vasopressin production in pathological conditions, particularly HF. This nonosmotic mechanism is based on activation of atrial baroreceptors as a consequence of filling pressure change.8

Imaging
Echocardiography is the gold standard for LA assessment in practice. For years, 1-dimensional diameter was used to describe LA size, but currently 2-dimensional reconstruction of LA volume is the method of choice. Three-dimensional echocardiography provides even more accurate imaging (Figure 2). Computed tomography for atrial imaging has rapidly expanded because of excellent spatial and temporal resolution, but is limited by radiation exposure and need for contrast. Before atrial fibrillation (AF) ablation, computed tomography offers an efficient roadmap, providing detailed information on LA and pulmonary vein anatomy as well. Magnetic resonance imaging is the most accurate technique for LA volume assessment, with its high spatial resolution and excellent myocardial border detection throughout the cardiac cycle.9 The normal limits for LA diameter and volumes differ according to the imaging modality (Table 1). Although several studies documented a strong association in terms of LA size estimates between

![Figure 1. Phases of left atrial function.](image1)

![Figure 2. Evolution of left atrial imaging.](image2)
echocardiography and both computed tomography and magnetic resonance imaging,\textsuperscript{10} it must be underscored that different cut-off values were defined for each imaging technique.\textsuperscript{11–13}

The ideal method to assess atrial function is invasive assessment of LA pressure and volume. The LA pressure–volume loop consists of an active (A) loop related to LA stroke work and a passive (V) loop representing the total passive elastic energy stored by the LA during reservoir phase.\textsuperscript{14} The slope of the end-systolic pressure–volume relation quantitates change in LA inotropic state. Static compliance of LA may be assessed by the pressure–volume loop by determining the slope of the line between minimal LA pressure of the A loop and the LA maximal pressure in the V loop (Figure 3).

Echocardiography can noninvasively assess atrial volumetric changes throughout the cardiac cycle; however, these are related to both atrial and ventricular function. LA contractility can be assessed by other techniques. Two-dimensional and Doppler echocardiography allows assessment of LA systolic force by Manning’\textsuperscript{s} equation and kinetic energy.\textsuperscript{15} Tissue Doppler measures mitral annulus velocity at different phases. The velocity measured at end-diastole (A’ wave) shows association with invasive parameter of LA systolic function and can estimate atrial contractility.\textsuperscript{16} Tissue Doppler and speckle tracking also allows for evaluation of LA tissue deformation (strain) and rate of deformation (strain rate) at different points, providing estimate of LA systolic (at end ventricular diastole) and diastolic (at ventricular systole) properties.\textsuperscript{17}

**Remodeling**

LA remodeling is related to complex alterations in response to pressure or volume overload (Figure 4). The mechanisms leading to these are not fully understood. Atrial myocyte hypertrophy seen in LA remodeling is likely induced by factors, such as mechanical stretch, growth factors, and cytokines, for example, angiotensin II, endothelin-1, insulin growth factor-1, and interleukin-6.\textsuperscript{18} Increased collagen turnover has been described with atrial remodeling.\textsuperscript{19,20} Atrial fibrosis is determined by mechanical load and activation of renin–angiotensin system; infusion of angiotensin-II leads to atrial fibrosis in the absence of hemodynamic load.\textsuperscript{21} The limited effort to understand LA remodeling may be because of assuming similar pathways in LA to that at the ventricular levels, but experimental models demonstrated qualitative and quantitative differences between the 2.\textsuperscript{22} A more intense inflammatory cellular infiltration, apoptosis, mitogen-activated protein kinases, and transforming growth factor-β activations in atria compared with ventricle has been described, and a more intense fibrosis has been documented at atrial level. These data suggest the need for a more focused study of the mechanisms operating specifically at the atrial levels.

**Table 1. Reference Limits for Left Atrial Dimension and Volume for the Various Imaging Modalities**

<table>
<thead>
<tr>
<th>Modality</th>
<th>Echocardiography</th>
<th>Computed tomography</th>
<th>Cardiac magnetic resonance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left atrial volume, mL</strong></td>
<td>Women ≤52</td>
<td>80±20 (76, 85)</td>
<td>73±15 (44–102)</td>
</tr>
<tr>
<td><strong>Left atrial volume/m², mL/m²</strong></td>
<td>Men ≤58</td>
<td>41±9 (39, 43)</td>
<td>40±7 (27, 53)</td>
</tr>
<tr>
<td><strong>Left atrial area, cm²</strong></td>
<td>≤28</td>
<td>21±4 (14, 28)</td>
<td>23±2 (17, 29)</td>
</tr>
<tr>
<td><strong>Left atrial dimension, cm</strong></td>
<td>Women ≤3.8</td>
<td>3.2±0.5 (2.2, 4.2)</td>
<td>3.2±0.5 (2.2, 4.2)</td>
</tr>
<tr>
<td><strong>Left atrial dimension, cm/m²</strong></td>
<td>Men ≤4.0</td>
<td>1.7±0.3 (1.2, 2.3)</td>
<td>1.7±0.3 (1.2, 2.3)</td>
</tr>
</tbody>
</table>

**Figure 3.** The left atrial pressure volume curve. The left atrial pressure volume curve is characterized by 2 loops. The A loop represents left atrial pump function at left ventricular end-diastole and the V loop is the expression of the reservoir function of left atrium. LA indicates left atrial; and MV, mitral valve.

**Figure 4.** Left atrial remodeling. Left atrial remodeling is frequent in conditions characterized by atrial volume or pressure overloads and in presence of increased heart rate. The pathophysiologic pathways behind these stressors are complex and diverse and lead to a wide range of adaptive and maladaptive changes. LA indicates left atrial.
Stages of Heart Failure
In 1 study, 47.6% of asymptomatic patients at clinically high risk for HF had mild and 16.5% had moderate to severe diastolic dysfunction.25 The progression from diastolic dysfunction to HFpEF is a complex and unresolved issue, where progression of LV disease in terms of relaxation and elastic recoil, change in load and stiffness, and vascular elasticity impairment and concomitant extracardiac factors may lead to symptom development.24 Emerging evidences suggest that LA might also play a significant role in this transition. In the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction trial) echocardiographic substudy,25 it was demonstrated that, in HFpEF, LA dilation was seen in 66% of the patients. Although LV hypertrophy is also seen in these patients, when LV mass was compared between asymptomatic hypertensive patients and HFpEF patients, a nonsignificant difference was observed,26 and LV mass evaluation did not distinguishing these patients.27 On the contrary, there was a significant difference in LA size between HFpEF and asymptomatic hypertensive patients.

In patients with LV hypertrophy, a prolonged relaxation time leads to greater dependence on atrial contribution at end-diastole for an optimal filling.28 This is, particularly, important in the presence of reduced diastolic filling time because of increased heart rate, for example, during exercise, and an impairment of atrial systolic function may compromise filling and cardiac output with effort. Interestingly, late anular diastolic velocity, a measure of atrial contractility, increases in hypertensive subjects with isometric handgrip29 and by exercise,30 but was unchanged in HFpEF. Consequently, impaired LA contractility because of increased atrial afterload or intrinsic atrial myopathy31 might explain reduced cardiovascular efficiency with effort in HFpEF. Resting LA function, defined as total LA strain, is an independent correlate of exercise tolerance, whereas LV mass and ejection fraction did not predict exercise duration in HFpEF.32

Beside impaired contractility, patients with HFpEF have modification of LA diastolic properties. A reduced systolic LA strain, a surrogate of chamber compliance during the reservoir phase, emerged as the only parameter able to distinguish asymptomatic patients with diastolic dysfunction from HFpEF.33 LA function impairment in HFpEF may precede LA remodeling.34 One study reported that 59% of HFpEF patients have severe atrial dysynchrony, accounting for worse hemodynamic profile, and a beneficial effect of LA pacing on hemodynamic and exercise tolerance has been shown.35 LA enlargement can predict functional impairment,36 and LA volume is associated with risk of hospitalization for HF.37

Hemodynamic Derangements
LA remodeling with volume or pressure overload may normalize wall stress and reduce atrial and pulmonary pressures,38 but studies have demonstrated a positive association between LA volume and pulmonary pressure.38 This paradoxical effect is likely secondary to modification in LA compliance. LA remodeling is often associated with increased interstitial fibrosis causing LA compliance impairment during reservoir phase. Patients with low peak atrial longitudinal strain during the reservoir phase, an indirect measure of compliance, are characterized by interstitial fibrosis and increased atrial endocardial thickness.37 Accordingly, in HFpEF, a strong and inverse association is observed between atrial strain during reservoir phase and pulmonary pressure.33

Atrial Fibrillation
One study demonstrated that ≤75% of HFpEF patients develop AF.39 The loss of atrial contraction in HFpEF explains the reduced exercise tolerance in HFpEF with AF. A lower stroke work with effort in AF may be related to reduced LV stroke volume, which is partly related to atrial contraction. In chronic lone AF, abnormal atrial histological findings are observed, including inflammatory features compatible with myocarditis, noninflammatory cardiomyopathy, and presence of patchy fibrosis.40 In an experimental model of sustained AF, profound structural changes were found in the atrial myocytes similar to those found in hibernating myocardium.41 Furthermore, in a group of patients with AF and no other structural and functional cardiac abnormalities, a significant increase in atrial volume was observed.42 In patients with history of AF, impairment in LA function may be present even with sinus rhythm and normal LA volume.43 LA enlargement is frequent in HF44 and is considered a cause of incident AF as well. Atrial stretch is associated with increased dispersion of refractoriness and modifications of anisotropic and conduction properties, increasing the likelihood of AF.45 It has been shown that LA dilation is characterized by increased activity of stretch-activated channels responsible of AF vulnerability.46 Increased neurohormonal alterations lead to interstitial fibrosis, which in turn leads to heterogeneity of atrial repolarization and increase the dispersion of refractoriness favoring re-entry circuits predisposing to AF.

Clinical Implication
Risk Prediction
LA enlargement is associated with increased mortality47 in asymptomatic people. The association between LA size and various cardiovascular disease, for example, HF, coronary disease, AF, and stroke, may partly explain the link between LA and outcome. In the general population, a 30% increase in LA volume is associated with a 43% greater risk of AF. In patients at risk for AF, for example, those undergoing cardiac surgery, LA volume >32 mL/m² is associated with 6.5-fold increase risk of postoperative AF.49 In elderly patients, an enlarged LA is associated with a 2-fold increased risk of incident HF.50

Diagnosis
The European Society of Cardiology51 recommend that 3 conditions must be met for HFpEF diagnosis: (1) HF symptoms or sign, (2) normal or near-normal ejection fraction, and (3) evidence of elevated filling pressure (wedge pressure or Doppler E/E′ ratio or natriuretic peptide level). In the majority of HFpEF studies, LA size is mild to moderate enlargement (Table 2). LA volume is determined mainly by LV diastolic dysfunction.61 The relatively load-independency of a dilated LA provides an important advantage over Doppler parameters that are related to filling pressures. Also, LA volume is a long-term marker of ventricular pressure.62 This is crucial as patients with HFpEF may have normal filling pressure at rest.
with disproportionate increase during effort. Thus, LA imaging may provide important clue for HFpEF diagnosis.

Prognosis
LA volume is a marker of increased morbidity and mortality for various cardiac diseases, including HF. A large meta-analysis showed that LA dilation was associated with 2.4-fold increase risk of mortality, independent of ejection fraction, restrictive mitral filling, functional class, and age. LA size is modified in HFpEF, and the degree of atrial dilation is associated with increased mortality (Figure 5).

Reverse Atrial Remodeling
As recently pointed out by a consensus article on HFpEF, another potential application of LA volume is as a therapeutic target. LA remodeling may identify patients who might improve with, and aid in monitoring the response to, novel pharmacological and nonpharmacological therapies. In patients with end-stage renal disease, a progressive increase of LA volume is associated with incident cardiovascular events. LA reversal remodeling is possible and has been described after surgery for mitral valve diseases and in hypertensive patients with ACE-inhibitors. In hypertensive patients with LV hypertrophy, both an increase and a decrease of LA size during follow-up were associated with onset of AF. In patients with HF undergoing resynchronization therapy, LA improvement is associated with decreased risk for atrial arrhythmias and improved survival. In HFpEF, benefit with carvedilol

Table 2. Left Atrial Remodeling in Heart Failure With Preserved Ejection Fraction Studies

<table>
<thead>
<tr>
<th>Patients</th>
<th>Patients</th>
<th>Echocardiographic Inclusion Criteria</th>
<th>LA Volume, mL/m²</th>
<th>LA Area, cm²</th>
<th>LA Diameter, cm</th>
<th>LA Classification (ASE/EAE)</th>
</tr>
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<tbody>
<tr>
<td>TOPCAT52</td>
<td>935</td>
<td>EF&gt;40</td>
<td>29.8±12.5</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>PARAMOUNT53</td>
<td>292</td>
<td>EF&gt;40</td>
<td>35.9±13.5</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Aldo-DHF54</td>
<td>422</td>
<td>EF&gt;50 and DD or AF</td>
<td>28±8</td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>RELAX55</td>
<td>216</td>
<td>EF&gt;50</td>
<td>44 (35, 59)</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>CHARM56</td>
<td>312</td>
<td>EF&gt;40</td>
<td>41.3±14.7</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>I-PRESERVE57</td>
<td>745</td>
<td>EF&gt;45</td>
<td>23±6</td>
<td></td>
<td></td>
<td>1</td>
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<tr>
<td>PEP-CHF57</td>
<td>850</td>
<td>2 over: EF&gt;40 or LAD &gt;40 or IVT ≥12</td>
<td>4.5 (1.4, 4.8)</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>He58</td>
<td>128</td>
<td>EF&gt;55</td>
<td>3.9±0.5</td>
<td>1</td>
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<tr>
<td>Gupta/ARIC59</td>
<td>85</td>
<td>EF&gt;50</td>
<td>3.4 (3.1, 3.8)</td>
<td>N</td>
<td></td>
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<tr>
<td>Tribouilloy60</td>
<td>368</td>
<td>EF&gt;50</td>
<td>4.1±0.7</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Northwestern61</td>
<td>402</td>
<td>EF&gt;50 and DD grade ≥2</td>
<td>34±14</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>Kaneko63</td>
<td>301</td>
<td>EF&gt;55</td>
<td>4.13±1.0</td>
<td>1</td>
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<td></td>
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<tr>
<td>Yamamoto64</td>
<td>245</td>
<td>EF&gt;40</td>
<td>4.4±0.8</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>Rossi65</td>
<td>183</td>
<td>EF&gt;45</td>
<td>4.1±1.0</td>
<td>1</td>
<td></td>
<td></td>
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</tbody>
</table>

LA classification used cut off value for left atrial size identified by American (ASE) and European (EAE) Society of Echocardiography: N, normal (left atrial diameter, ≤2.3 cm/m²; area, ≤20 cm²/m²; volume, ≤28 mL/m³); 1, mildly enlarged (left atrial diameter, ≤2.6 cm/m²; area, ≤30 cm²/m²; volume, ≤33 mL/m³); 2, moderately enlarged (left atrial diameter, ≤2.9 cm/m²; area, ≤40 cm²/m²; volume, ≤39 mL/m³); 3, severely enlarged (left atrial diameter, ≥3.0 cm/m²; area, ≥40 cm²/m²; volume, ≥40 mL/m³). AF indicates atrial fibrillation; Aldo-DHF, aldosterone receptor blockade in diastolic heart failure; ARIC, Atherosclerosis Risk In Communities; CHARM, Candesartan in Heart failure: Assessment of reduction in mortality and morbidity; DD, diastolic dysfunction; EF, ejection fraction; I-PRESERVE, the Irbesartan in Heart Failure with Preserved Ejection Fraction trial; IVT, interventricular septum thickness; LA, left atrial; LAD, left atrial diameter; PARAMOUNT, Prospective Comparison of ARNI With ARB Management of Heart Failure With Preserved Ejection Fraction; PEP-CHF, The Perindopril in Elderly People with Chronic Heart Failure; RELAX, the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; and TOPCAT, Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist.

Figure 5. Prognostic significance of left atrial remodeling. The associations between hazard ratios (HR; y-axis) for mortality in previous studies by left atrial size (blue boxes) and ejection fraction (green boxes) are shown over a wide range of ventricular systolic function as defined by ejection fraction (EF; x-axis). Left atrial size maintained a significant association with mortality independently of the mechanisms underlying ventricular dysfunction. Note that the hazard ratios cannot be compared across studies because different methodologies were used to quantify left atrial size.
was amplified in patients with dilated LA, suggesting that LA might be used to select HFpEF patients who might have more benefit from therapy. Recently, the Prospective Comparison of ARNI With ARB Management of Heart Failure With Preserved Ejection Fraction trial showed that angiotensin receptor
naprilysin inhibitor compared with valsartan significantly reduced both natriuretic peptide levels and LA volume. The ongoing Safety and Efficacy Study of Four Dose Regimens of BAY1021189 in Patients With Heart Failure and Preserved Ejection Fraction Suffering From Worsening Chronic Heart Failure trial also includes changes in natriuretic peptide levels and LA volume as primary outcome measures in patients treated with vericiguat versus placebo. Finally, based on these data, the Efficacy and Safety of LCZ696 Compared to Valsartan on Morbidity and Mortality in Heart Failure With Preserved Ejection Fraction trial will use LA enlargement as an eligibility criteria for enrolment (http://clinicaltrials.gov/ct2/show/study/NCT01920711).

Conclusions
LA structure and function is easily assessable and holds promise to provide incremental value to existing parameters for diagnosis, management, and research for patients with HFpEF. With the growing burden of HFpEF, a projected increase over time with aging population, and with no known therapy with proven efficacy, new prevention and treatment strategies for HFpEF are needed. LA might be useful both for identifying patients with those at risk for HFpEF and may be a marker for target for novel therapies. Further research on the importance and clinical utility of LA in patients with HFpEF is needed.

Disclosures
Drs Rossi, Triposkiadis, Solomon, and Pieske have no relevant conflict of interests. Dr Gheorghidea reports following relationships: Abbott Laboratories, Astellas, AstraZeneca, Bayer Schering Pharma AG, Cardiventis Ltd, Cor Thera, Cytokinetics, CytoPhex, Inc, DebioPharm S.A., Errekappa Therapeutics, GlaxoKline, Ikaria, Intersection Medical, INC, Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Ono Pharmaceuticals USA, Otsuka Pharmaceuticals, Palatin Technologies, Pericor Therapeutics, Protein Design Laboratories, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Sticares InterACT, Takeda Pharmaceuticals, and Trevena Therapeutics, and has received significant support from Bayer Schering Pharma AG, DebioPharm S.A., Medtronic,Novartis Pharma AG, Otsuka Pharmaceuticals, Sigma Tau, Solvay Pharmaceuticals, Sticares InterACT, and Takeda Pharmaceuticals. Dr Butler reports research support from the National Institutes of Health, European Union, and Health Resources Service Administration and is a consultant to Amgen, Bayer, BG Medicine, Cardiocell, Celladon, Gambro, GE Healthcare, Medtronic, Novartis, Ono Pharma, Takeda, Trevena, and Zensun.

References


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