Welcome to Circulation Reports (Circ Rep). Thank you very much for taking a look at the preparation issue (Vol. 0). As reported by the Editor-in-Chief of the Circulation Journal (Vol. 81, Issue 1, 2017), the inaugural issue of Circulation Reports (Circ Rep), a new on-line only, Open Access Journal, will be published on January 10, 2019. Circulation Reports (Circ Rep) is a sister journal of the Circulation Journal, an official Journal of the Japanese Circulation Society. In this preparation issue, I will describe how and why the new journal is to be launched and what types of manuscripts will be published.

It is 82 years since the first issue of the Circulation Journal was published. Its impact factor in 2016 was 3.544. The acceptance rate is around 25%, but almost 1,500 manuscripts are submitted every year from all over the world. It has been discussed that we should make an opportunity to publish excellent manuscripts that are rejected because of limitations of space. Today, the internet is the most powerful tool for publication and exchange of opinions. In line with this trend, the Japanese Circulation Society has decided to launch an on-line only, Open Access new journal to contribute to further advances in cardiovascular medicine.

Today, researchers in cardiology require new methods and analyses from medical engineering, medical informatics, and medical economics, besides the conventional physiology, pharmacology, molecular biology and epidemiology. To prevent cardiovascular diseases, nutrition, exercise, team medicine, healthcare systems, social medicine and comprehensive management of cardiovascular risk factors are important. Circulation Reports (Circ Rep) will consider all types of original research articles, including studies in these new areas, related to cardiovascular diseases. I hope that Circulation Reports (Circ Rep) will serve as a forum to discuss the tasks and problems in cardiovascular medicine and research by accepting statements and opinions from physicians and non-physicians. Thus, Circulation Reports (Circ Rep) will cover a wide range of topics that are of interest to not only cardiovascular physicians and researchers but also to non-physicians.

Next, I will outline concretely how to submit your manuscripts to the new Journal. Circulation Reports (Circ Rep) will consider not only de novo manuscripts but also excellent manuscripts unable to be published in the Circulation Journal. Such manuscripts will be rapidly transferred to the Circulation Reports (Circ Rep) editorial system to ensure their timely publication. The editorial team consists of domestic and international associate editors, who are relatively young experts in each area. Some manuscripts may be accepted without further review. Accepted manuscripts will be published on-line as “papers in press” without delay and published monthly with numbers of volume, issue, and pages. From January 2018, Circulation Reports (Circ Rep) will mainly publish accepted manuscripts transferred from the Circulation Journal.
New types of articles that will be accepted by *Circulation Reports (Circ Rep)* include Protocol Papers, Brief Reports, and Statements/Opinions (Table), which are not considered in the *Circulation Journal*. However, no case reports will be published in *Circulation Reports (Circ Rep)*, as with the *Circulation Journal*. Accepted manuscripts will undergo statistical review before on-line publication so that all articles in *Circulation Reports (Circ Rep)* are reliable based on appropriate statistical methods.

The following categories are specific to *Circulation Reports (Circ Rep)*.

- Cardiovascular Nursing
- Exercise Physiology
- Health Services and Outcomes Research
- Medical Economy
- Medical Education
- Medical Engineering
- Medical Policy
- Metabolism
- Nutrition
- Obesity

### Table. Types/Categories of Papers Accepted by Circulation Reports

<table>
<thead>
<tr>
<th>Article type/category</th>
<th>Form and content of article</th>
<th>Total word counts</th>
<th>Word count in abstract</th>
<th>No. of tables/figures/ supplementary files</th>
<th>No. of references</th>
<th>Other</th>
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<tr>
<td>Brief Report</td>
<td>Brief Reports are brief but complete highly significant findings reported in a shorter format of 4,000 words or less; this strictly enforced word limit includes all text (title page, main text, references, legends, and table). Brief Reports are limited to 4 display items (figures and/or tables)</td>
<td>≤4,000 words</td>
<td>≤220 words</td>
<td>No more than 4 tables/figures</td>
<td>No limitation</td>
<td>3–5 key words</td>
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<tr>
<td>Statement/Opinion Article</td>
<td>Statement/Opinion articles should focus on a topic about which the authors have personal thoughts, beliefs, or feelings</td>
<td>≤3,000 words</td>
<td>≤220 words</td>
<td>No more than 4 tables/figures</td>
<td>No limitation</td>
<td>3–5 key words</td>
</tr>
<tr>
<td>Protocol Paper</td>
<td>Protocol Papers should report planned or ongoing studies. Manuscripts that report work already carried out will not be considered as a Protocol Paper</td>
<td>≤3,000 words</td>
<td>≤220 words</td>
<td>No more than 4 tables/figures</td>
<td>No limitation</td>
<td>3–5 key words</td>
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Below contents are to be common with *Circulation Journal*

<table>
<thead>
<tr>
<th>Article type/category</th>
<th>Form and content of article</th>
<th>Total word counts</th>
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<th>No. of references</th>
<th>Other</th>
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<tr>
<td>Clinical Investigation</td>
<td>Rapid Communications are reports of novel findings of particular importance and/or current interest and will be accepted if they merit immediate publication. The manuscripts normally occupy no more than 3 journal pages. Provide both a short title and 3 key words (see Regular Paper section). Please refer to the General Instructions for Authors regarding reference style and other manuscript requirements</td>
<td>≤6,000 words</td>
<td>≤220 words</td>
<td>No more than 8 tables and figures No more than 3 supplementary files</td>
<td>No limitation</td>
<td>3–5 key words</td>
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<tr>
<td>Experimental Investigation</td>
<td></td>
<td>≤6,000 words</td>
<td>≤220 words</td>
<td>No more than 8 tables and figures No more than 3 supplementary files</td>
<td>No limitation</td>
<td>3–5 key words</td>
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<tr>
<td>Rapid Communications</td>
<td></td>
<td>≤1,000 words</td>
<td>≤100 words</td>
<td>No more than 2 tables/figures</td>
<td>No more than 15</td>
<td>3 key words</td>
</tr>
<tr>
<td>Images in Cardiovascular Medicine</td>
<td>The manuscript should contain a novel color image with scientific impact. The total number of color figures is limited to 1 (in addition to 2 supplementary files if needed). Submission of tables is not encouraged. The manuscript normally occupies 1 journal page. Please remove &quot;Case Report&quot; from manuscript titles/subheadings. Please refer to the General Instructions for Authors regarding reference style and other manuscript requirements. <em>Circulation Journal</em> ceased accepting simple Case Reports from 31st October 2008</td>
<td>≤250 words</td>
<td>No abstract</td>
<td>1 figure No tables No more than 2 supplementary files</td>
<td>No more than 3 references</td>
<td></td>
</tr>
<tr>
<td>Review Article (Invited)</td>
<td>These are invited articles (not an open submission) by internationally recognized authorities on various topics</td>
<td>≤6,000 words</td>
<td>≤220 words</td>
<td>No more than 8 tables/figures No more than 3 supplementary files</td>
<td>No limitation</td>
<td>Upon request from the Editor</td>
</tr>
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The official home page of *Circulation Reports (Circ Rep)* will be found on the website of the Japanese Circulation Society (http://www.j-circ.or.jp/) early in September 2018. Submission and publication are completely on-line only.

The editorial team of *Circulation Reports (Circ Rep)* looks forward to receiving a wide range of manuscripts from all over the world.

Best wishes,

Masataka Sata, MD, PhD
Editor-in-Chief
*Circulation Reports*
Preparation for First Issue
— Clinical Field —

Motoaki Sano, MD, PhD

*Circulation Reports* accepts papers related to medical care, research, education, and innovation in the cardiovascular field, in addition to the topics dealt with in the *Circulation Journal*, such as epidemiology, pathogenesis, diagnosis, pathology and treatment of heart diseases (heart failure, coronary artery disease, valvular heart diseases, cardiomyopathy, arrhythmia) and major vascular diseases (aortic dissection and peripheral artery disease).

- Risk factors (hypertension, dyslipidemia, abnormalities of glucose metabolism, obesity, renal dysfunction, aging, cancer, cardiotoxic drugs, macromolecular abnormalities) and improvement of lifestyle (physical exercise, diet, quitting smoking, sleep quality, happiness).
- Cardiovascular surgery; diagnostic and therapeutic radiology; anesthesia; cardiopulmonary resuscitation; shock; congenital and acquired heart disease in infants, children, and adolescents; maternal heart disease; public health.
- Multi-occupational collaborations; heart teams; patient education; nursing care; cardiac rehabilitation; palliative and end of life care; liaison psychiatry; home medical care.
- Medical engineering, such as methods of measurement and diagnosis; medical robotics; biological devices; biomaterials; organ fabrication; artificial intelligence; internet of bodies; virtual reality; computer simulations.
- Recommendations on medical policy, medical economy, medical system, such as social security system; optimization of medical expenses; hospital management; health improvement plans; long-term care insurance systems; regional medical collaborations between hospitals and clinics; home care.
- Protocol papers for clinical trial.
- Pilot studies because of small sample sizes or shorter follow-up periods, but only if the study is new.
- Voluntary submission of reviews, new hypotheses about mechanisms of action, timely commentary on research papers, large-scale clinical trials, and statements and guidelines are welcomed.
Launching *Circulation Reports* — A New Era for the Big Challenges in Cardiovascular Science —

Yoshikazu Yonemitsu, MD, PhD

Congratulations on the launch of a new cutting-edge online journal, *Circulation Reports*!  *Circulation Reports* is a sister journal of *Circulation Journal*, an official journal of the Japanese Circulation Society, and led by the strong leadership of Professor Masataka Sata at Tokushima University as Editor-in-Chief. *Circulation Reports* covers extensive fields of cardiovascular medicine, related not only to basic and clinical science, but also surgery, engineering, nursing, clinical trials, politics, and economics.

On behalf of the editorial members of *Circulation Reports*, I would like to describe the general scope of the journal, particularly focusing on basic cardiovascular research.

*Circulation Reports* Strongly Encourages Submission of Papers Related to Basic and Experimental Cardiovascular Science

According to the statistics, submitted manuscripts in the category of ‘experimental’ for the *Circulation Journal* in 2015 comprised only 10.1%, whereas those in ‘clinical’ were 67.3% (*Figure*). The editorial team at *Circulation Reports* would like to increase the numbers of submitted papers related to experimental and basic cardiovascular medicine, particularly those that cannot be published in the *Circulation Journal*.

Publishing high-quality papers on essential clinical practice and establishing new evidence for cardiovascular medicine has been a top priority of the *Circulation Journal* since its launch. However, the editorial teams of both the *Circulation Journal* and *Circulation Reports* consider good papers in clinical medicine and basic cardiovascular science are ‘two sides of the coin’ for these Journals. *Circulation Reports* opens the submission window worldwide, whereas the *Circulation Journal* pays particular attention to productive activity by Japanese scientists because it is an official publication of the Japanese Circulation Society. Unfortunately, as the former Editor-in-Chief of *Circulation Journal*, Professor Hiroaki Shimokawa at Tohoku University, has recently pointed out, various published indexes indicate that activity in basic cardiovascular...
research in Japan has been shrinking, in clear contrast to that in China and South Korea.\textsuperscript{2,3}

Multiple factors (i.e., less funding for research as well as difficulties in publishing papers) have led to the imbalance in the clinical and basic sciences seen in the Journal, and in scientific activity in Japan particularly. The limitless publishing space of \textit{Circulation Reports} and seamless exchange of manuscripts with \textit{Circulation Journal} will help researchers keep their motivation for basic cardiovascular science. This editorial policy applies to cardiovascular scientists all over the world.

\textbf{Circulation Reports Seeks High-Quality Papers Directly Assessing the Molecular Mechanisms of Cardiovascular Diseases and Their Molecular Targets}

To maintain the similar high standard of the \textit{Circulation Journal}, \textit{Circulation Reports} strongly encourages authors to submit papers directly assessing molecular mechanisms and targets related to cardiovascular diseases, because some recent examples in clinical trials in different fields have revealed a common molecular pathway directly correlated to multiple diseases.

For instance, sustained inflammatory reaction in atherosclerosis in both experimental and human materials has been shown for nearly 30 years to involve various inflammatory cytokines (i.e., interleukin-1 (IL-1), as well as C-reactive protein (CRP));\textsuperscript{4-6} however, subsequent clinical and experimental studies have not been able to demonstrate ‘the main actor’ in inflammation in human atherosclerosis, even though a mouse model suggested the critical role of IL-1 receptor signaling in plaque destabilization.\textsuperscript{7} A recent phase 3 clinical study using canakinumab, a therapeutic monoclonal antibody targeting IL-1\(\beta\), involving 10,061 patients with previous myocardial infarction and a high-sensitivity CRP level of \(\geq 2\) mg/L, demonstrated that inhibition of IL-1\(\beta\) not only resulted in decreased CRP but also reduced recurrent cardiovascular events, irrespective of lipid-lowering.\textsuperscript{8,9} Therefore, this trial was the first to show that the IL-1\(\beta\)-related innate immune response, rather than CRP, may be at least ‘one of the main actors’, in other words an ‘upstream player’, in the human atherosclerosis theater.

The IL-1\(\beta\) story has continued. Amazingly, subsequent analysis of CANTOS trial revealed that anti-inflammatory treatment using canakinumab significantly reduced the incidence and mortality of lung cancers,\textsuperscript{10} suggesting that the IL-1\(\beta\) signal transduction pathway is common to the completely different diseases of atherothrombosis and lung cancer. A prospective study assessing the role of IL-1\(\beta\) in lung cancer will be initiated in the near future.

This IL-1\(\beta\) and other examples strongly imply that continuous and steady progress in basic research is required for producing epoch-making new treatments.

\textbf{Closing Remarks}

Clinical/basic studies, as well as translational/ reverse translational researches, are ‘two sides of the coin’ and should be developed in tandem.

Welcome to \textit{Circulation Reports}!

All editorial members welcome authors, especially young scientists, who are interested in basic and clinical cardiovascular medicine.
Launching Circulation Reports

References


Yoshikazu Yonemitsu, MD, PhD
Associate Editor
Circulation Reports
Medical Engineering
— Pushing Innovations in Evaluation Methods Forward for the Benefit of Patients and Society —

Kiyotaka Iwasaki, PhD

On behalf of the Editorial Team of *Circulation Reports*, a new open-access rapid publication journal of the Japanese Circulation Society, I am delighted to inform colleagues that *Circulation Reports* features original research from medical engineering that contributes to gaining knowledge and insight into facilitating novel medical device development, investigating more effective and/or safer interventional and surgical treatment, expediting clinical translation of new findings, investigating underlying mechanisms of clinical questions, seeking solutions for clinical demands, and improving clinical outcomes.

Expediting patients’ access to innovative medical devices and interventional and surgical treatments while reducing risks is craved globally to improve clinical outcomes, quality of life, patient satisfaction, and usability, and to prevent progression of diseases.

When developing medical therapies, the identification, evaluation, and reduction of individual risks are indispensable, in conjunction with evaluation of probable benefits. Medical doctors, staff, biomedical scientists, and engineers are strongly encouraged to collaborate on the common goal of improving patient outcomes and satisfaction.

One good example of medical device development is the implantable left ventricular assist device (LVAD), “EVAHEART”, which was invented by a cardiac surgeon Dr. Kenji Yamazaki.1 In Japan, patients supported by LVAD have longer waiting times for heart transplantation than patients in the USA and EU, which has been clearly elucidated by data from the Japanese registry for Mechanically Assisted Circulatory Support.2 Especially for implantable medical devices such as LVADs, follow-up periods in clinical trials are limited by the time constraints for market approval. A recent, sophisticated bench study showed that the durability of EVAHEART was maintained for 8 years.3 Such data may be crucial for expanding the indication of devices as destination therapy in countries with severe donor shortages.

Another example of the development of a surgical treatment option is a novel stentless mitral valve (NORMO valve),4 invented by Dr. Hitoshi Kasegawa (Figure 1). The valve is constructed by suturing anterior and posterior leaflets which are prepared using

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**Figure 1.** Stentless mitral valve invented by cardiac surgeon Dr. Hitoshi Kasegawa.

Cooperative Major in Advanced Biomedical Sciences, Joint Graduate School of Tokyo Women’s Medical University and Waseda University, Waseda University, Tokyo (K.I.); Department of Integrative Bioscience and Biomedical Engineering, Graduate School of Advanced Science and Engineering, Waseda University, Tokyo (K.I.); and Department of Modern Mechanical Engineering, School of Creative Science and Engineering, Waseda University, Tokyo (K.I.), Japan

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autologous pericardium along an annuloplasty ring. Leg-like parts of the leaflets connected to the papillary muscles partially have the function of the chordae tendineae. The limited durability of bioprosthesis, and the need for life-long anticoagulant therapy with mechanical prostheses, make the choice for young patients, including women who wish to have a child, difficult and unsatisfactory. Thus, there is a strong demand for other treatment options. As a result of ongoing collaboration between cardiac surgeons and biomedical scientists, the design of the valve has been improved using various types of newly developed test systems. A team from the Committee of the Japanese Society of Stentless Mitral Valve elucidated excellent in vivo performance. More than 20 cases of implantation have been conducted in accordance with the Japanese Advanced Medical Care B program. Development of innovative patient-oriented testing methodologies is anticipated for both evaluating and increasing the safety and probable efficacy of new treatments, accelerating patients’ access, and supporting evidence-based clinical translation.

Once medical devices are approved, how to achieve better real-world clinical outcomes is of great concern. Clinical outcome can be affected by both interventional procedures and patient characteristics.

One good example is “Three-times balloon inflation for coronary stent deployment”, an interventional procedure that is popular in Japan and widespread around the world. The “Three-times inflation” method for achieving larger coronary artery cross-sectional area was invented by a biomedical scientist based on data from a patient-oriented stenotic coronary artery model, and has been proven in real-world clinical practice through extensive collaboration with interventional cardiologists. The method has also shown promise in coronary artery bifurcation stenting.

How to tackle more severe cases has clinical interest with regard to improving the quality of life for patients. New hypotheses and insights to improve clinical outcomes and to understand underlying mechanisms may arise when dealing directly with patients.

One example is an investigation of the mechanism of paravalvular leak after transcatheter aortic valve replacement (Figure 2). Anatomically and mechanically matched patient-specific models and a clinically relevant pulsatile flow system may provide valuable insights into technical procedures for challenging cases. Sophisticated models based on patient-specific computed tomography data may become powerful tools for investigating the potential causes of a need for pacemaker implantation and of transcatheter heart valve thrombosis. Advanced medical engineering will contribute to knowledge about more effective and safer applications of medical devices and treatments for individual patients, and to the development of next-generation devices.

Creating consensus documents and guidelines for preclinical evaluation of medical devices and their proper use for challenging subsets is another significant issue in medical engineering research. A major focus in improving clinical outcomes is stent treatment of coronary artery bifurcation lesions. The European Bifurcation Club works
extensively to develop consensus documents for bench testing and computer simulation, in collaboration with
the world’s leading researchers.\textsuperscript{11,12}

In Japan, under a program of the Ministry of Health, Labour, and Welfare, guidance on sophisticated bench
testing has been developed and published in mutual collaboration with medical doctors, biomedical scientists,
officers of the Pharmaceuticals and Medical Devices Agency, and industry representatives.\textsuperscript{13,14} Some examples
are the durability test method for coronary stents, the durability test method for vascular stents intended for the
superficial femoral-popliteal artery, and the method for in vitro thrombogenicity testing for the inflow cannula
of LVADs. Clinically relevant test data based on understanding real-world situations and deep discussion among
clinicians, biomedical scientists, regulatory agencies, and industry representatives will aid in constructing fruitful
consensus documents and guidelines.

I am honored to have the privilege to serve as Editor in the field of Medical Engineering Specialty. Innovative
medical devices and treatments are often produced at the interface between disciplines. We encourage authors
to submit manuscripts on a variety of original investigations that contribute to improving patient care, clinical
scenarios, and clinical outcomes. We sincerely welcome your input to \textit{Circulation Reports}.

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Increasing Concerns With Medical Economics

Medical economics is an area of study encompassing medical science and economics that deals with a wide variety of topics and issues related to the medical and healthcare field. The primary objective of medical economics is to analyze diverse phenomena (e.g., technology, management, policy) occurring in relation to medical systems and clinical practice using methodologies of economics, including econometrics, value evaluation, decision making, and behavioral science, as well as medical statistics, to contribute to the advancement of both medical systems and public health and welfare. As part of efforts to achieve these objectives, medical economics research, from the standpoint of a group of personnel involved in the medical field, particularly focuses on discussing approaches to optimizing cost effectiveness and maximizing the happiness (i.e., quality of life) of patients, their families, and the general public as a whole. Separately, from the standpoint of ensuring social equity, medical economics research is expected to present academic concepts and supporting rationales based on discussions of the rational allocation of medical resources (e.g., public expenditure on universal healthcare).¹

Medical economics is steadily raising concerns among both the general citizenry and medical personnel engaged in clinical practice, and an increasing number of reports, including clinical studies, are emerging from this area of study. In the background of such a move lies the fact that medical costs are growing at substantially high rates globally, because of sharply increasing rates of morbidity, multiple stratification of diseases, and advancements in medical technology. Innovation in medical technology is costly, and effective implementation of innovations depends on larger budgets and infrastructure of research and development (R&D) systems amid the complicating and diversifying effects of discovery (or component) technologies. This in turn indicates the increasing emphasis placed on economic themes among the main issues in the medical and healthcare field.

One example of this increasing concern in medical economics is the year-by-year increase in the number of articles on medical economics in the circulatory field accessed on PubMed, which is operated by the National Center for Biotechnology Information: compared with only 3 reports published in 1985, this number had grown to 90 by 2016. When the number of medical economics articles in the circulatory field is expressed as a ratio of the total number of the articles in the same field, the annual increase in publication in the 2010‒2014 and 2015‒2017 periods was 4.7- and 6.4-fold the number in the 1985‒1989 period, respectively (Figure 1).²

There are diverse backgrounds to the increase in medical economics articles. Regarding financial burden, annual national health expenditures showed a 1.3-fold increase in the ratio to gross domestic product (GDP) over the 3-year period from 2015 to 2017 compared with the ratio over the 1985‒1989 period in both the OECD and G20 countries (Figure 1).³ A comparison of the ratio of national health expenditures with the number of

medical economics articles indicates that the number of articles increased as the ratio of the expenditure increased and vice versa with a slight time lag (Spearman’s rank correlation coefficient: $r^2=0.964$, $P<0.01$). This trend shows that an increase in financial burden makes medical economics issues apparent, leading to increases in concern about and research into medical economics-related subjects.

**Concept of Medical Economics and Recent Subjects of Economic Research**

The following is an additional discussion of the concept of medical economics as briefly described above. Medical economics articles in the circulatory field may be roughly classified into macro and micro subjects (Figure 2).

Macro subjects include social security-related issues that are concerned with financial resources for medical insurance systems; health policy-related issues covering medical services; and, although less frequently studied, medical industry-related issues, including systems for new drug development, systems for medical device supply, and model development of genetic diagnosis. Micro subjects include human resources management, which is essential for administration of medical institutions; safety management; and medical economics research, including economic evaluation of team-based care and inter-institutional collaboration. The number of articles is also increasing in the areas of economic evaluation (including cost-effectiveness assessment) of medicines, medical devices, and medical-care information systems. In addition, there are sporadic instances of research in which behavior modifications in patients, their families, and medical personnel are examined from a medical economics viewpoint by taking into account desired forms of decision making and support measures.

In recent years, it has become fairly common for macro subjects to be cross-sectionally discussed with micro subjects, as seen in the education of medical personnel and the health literacy of patients. There are also cases in
which the economic value of aspects of the healthcare system, such as treatment modalities, is analyzed from a new methodological point of view by applying the parameters of not only patient outcomes but also the values to the public. In the not-too-distant future, it will become more common to see, even in the circulatory field, the more active pursuit of socioeconomic research using, for example, practice models of therapy based on new strategies made feasible by progress in medical information and communication technologies, and improvement in other infrastructure environments (Figure 2).

Circulatory Field and Medical Economics: Vision and Values of Circulation Reports

_Circulation Reports_ will explore the subjects related to the economics of health and medical in the circulatory field in depth, with due consideration of the aforementioned backgrounds. Research topics are anticipated to include the following.

As future research areas, not only adverse economic effects and determinants of morbidity of circulatory diseases but also the social significance of economic investment in health behaviors of therapeutic and preventive interventions are expected to be extensively discussed topics. It is also critical to analyze regional medical systems and welfare systems, which relate to the aforementioned economic effects and significance of economic investment, from the perspective of medical economics. Furthermore, it is highly likely that particular attention will be paid to research on the management of medical institutions that support the healthcare system and to research on behavior modifications (not only of patients but also healthcare providers).

Other highly interesting topics include economic evaluation of innovative medical technologies in the circulatory field through clinical trials and distribution of medical resources based on other cost-effectiveness assessments with modeling estimates. In relation to these topics, it is also important to determine the effectiveness (or restrictions) of medical treatment, including the measurement of therapeutic and preventive efficacy, from broader and deeper perspectives than before. These topics require the development of a range of methodologies for the calculation of utility value of patients and patient-reported outcomes (including patient’s quality of life, functional status, and satisfaction with provided medical treatment), which are closely related to the evaluation

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_Figure 2._ Structure of the main subjects in health economics (medical economics in the broad sense). (Modified with permission from original reported (Figure 2) by Takura T.) ICT, Information and Communication Technology.
of medical economics.

The healthcare system, per se, involves public aspects to a greater or lesser extent in any region of the world, so significant progress in medical treatment in the circulatory field could be achieved through theory development, empirical studies, and associated investigations of welfare economics verifying the validity of health policy. In particular, there is a need for efficacy evaluation of various health policies and medical services, as well as medical economic verification of the quality of medical services, against the background of discussions concerning the supply and demand of medical services.

Lively and in-depth future-oriented discussions of these topics will facilitate the construction of valuable evidence that helps all personnel engaged in medical economics research (including members of the Japanese Circulation Society) in not only gaining new insight into medical economics and but also enhancing their explanatory power in propagating the significance of medical economics in the circulatory field. These approaches will reinforce the foundation of medical economics research by economically supporting the advancement of circulatory science. Circulation Reports welcomes and encourages contributions from researchers in the circulatory field who are studying medical economics with new discussion points, theories, and findings.

References

Recent accelerated progress in the development of a dramatically increasing number of therapeutic medicines, devices and techniques is strongly leading to advanced medical markets, which in turn give physicians a wide variety of effective therapeutic options in daily medical practice. However, it is also leading towards more cross-sectional techniques, as well as comprehensive or integrative medicines and devices, which are often beyond the existing regulatory systems.

To deal with this overwhelming and inevitable global trend, prompt, effective and generally accepted regulations are continuously needed to not only make all such developments effective and safe in every instance, but also to ensure rapid access for each patient eagerly awaiting more effective and personalized therapies. A promising movement to expedite the marketing process is inter-regional harmonization of the process for pharmaceutical approval, known as ICH (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use), which aims to create globally standardized uniform regulation to facilitate rapid and simultaneous global access to novel qualified therapeutic technologies.

Meanwhile, the Japanese government has established a variety of unique and specific medical policies and regulations to keep facilitating innovation of therapeutic technologies.

As background, all citizens in Japan are primarily covered with official health insurance for pharmaceutically approved treatments operated and prescribed by officially registered health insurance doctors, a system that is known as universal health insurance coverage. Countries other than Japan that use this system are still rare, and even fewer also assure free access by patients to any hospital. On the other hand, to be reimbursed from the official health insurance, health insurance doctors are required to comply with the Rules for Therapeutic Operation and Insurance Coverage attached to the Health Insurance Law, which prohibits the performing of special or novel therapies, prescribing or dosing of agents other than those officially assigned, or performing any clinical tests for research purposes. Eventually, primary health insurance could apply only for treatments that are exclusively products with official approval on efficacy and safety, and because it generally does not allow mixed billing for combined treatments composed of therapies with and without pharmaceutical approval, the end result will be total disqualification from health insurance coverage.

However, there are some exceptions to claiming mixed billing; that is, partial coverage by health insurance of the therapies with pharmaceutical approval combined with total billing of the patient for the treatments without pharmaceutical approval. The Healthcare Services for Assessment is one such program, defined in the Health Insurance Law as applying to advanced or novel therapies that need assessments for efficacy, safety and prevalence to claim coverage by official health insurance. Healthcare Services for Assessment consists of Clinical Trials, the Advanced Medical Care Program and Healthcare Services based on Patients Application. Clinical Trials are
studies complying with the Pharmaceutical Law and progressing towards pharmaceutical approval in the conventional fashion, whereas the Advanced Medical Care Program might be defined as clinical studies that comply with the Official Ethical Guidelines for Medical Studies in Humans, or the new Clinical Research Law. In addition to having a mixed billing system, the Advanced Medical Care Program has another advantage that once the therapies in the program are completed and have successfully appealed their efficacy, they become eligible for the Governmental Review Conference for Fast-track Approval. When products are certified as valuable and accountable enough to get approved without clinical trials, they are directly approved after some documentation. Also, when the benefit of a therapy is not considered as evident but is considered valuable enough to warrant clinical trials, the government urges the companies to develop such therapies for Pharmaceutical Approval.

Another notable unique regulation to accelerate clinical development is the so-called “Conditional Approval with Post-commercialization Evaluation”. This was first launched in 2013 when the Pharmaceutical Law was revised to facilitate pharmaceutical development of regenerative products. Briefly, while conventional pharmaceutical approval needs proof of concept for efficacy and safety, the current law allows for conditional approval of regenerative medical products when the inference for efficacy as well as validation of safety have been achieved. Then, the authority sets a period that allows a product to be released onto the market with further full approval conditional on efficacy and safety studies while commercially available (Figure 1). This idea has been tested in advance in some fields, but appears to be so groundbreaking that some researchers have voiced serious concerns about it, partly because regenerative medicine is a new area and the schemes for evaluating safety and efficacy, as well as consistent quality of the products (mostly from bioengineering processes), have not been established yet, and it might also be difficult to plan double-blind randomized trials in this field.

All these regulations and rules were primarily designed to disseminate good healthcare or to facilitate rapid access to novel advanced medical therapies all across the country. Indeed, we can say that some of them actually brought us historical success; the mean life-span of the Japanese nation has been extended (Figure 2), leaping to the top in the world, and most of us are provided equally with thoroughly well-standardized medication for almost all types of diseases under public insurance coverage. However, it is also true that the regulatory environment has become so unique and diverse that it does not necessarily stand aligned with global trends, and the people in

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**Figure 1.** Introduction of “Conditional Approval with Post-commercialization Evaluation” in regenerative medicine. (Reproduced from public open data issued by the Ministry of Health, Labour and Welfare, Japan.)
other countries often say that they cannot get familiar with specific Japanese regulations. One reason for this diversity might be that our healthcare and pharmaceutical approval systems are unique, and another reason might be that our regulation cannot keep up with the rapid progress in medical science and can only follow with patchy rules, such that they become rigid and inconsistent with each other.

In addition, there might be the field-specific issues. We in the cardiovascular fields are especially encountering the difficult issue of needing huge clinical studies with longer terms and greater numbers of participants to get proof of concept, which makes clinical research and development in this field very challenging, stemming from issues of study design, surrogate markers, and research approaches to testing novel therapeutic principles. Moreover, we also have issues regarding how we develop and warrant access to orphan drugs.

Although there have been some advanced attempts, we obviously need more revolutionary ideas to deal with the many difficulties in regulations, rules and study designs. It is timely that we can now rigorously discuss such issues in this ground-breaking journal, *Circulation Reports*.

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