

Evaluation of the Research and Other Activities of National Institute of Genetics

1. Overall quality of research activities of the institute

The National Institute of Genetics is focused on scientific excellence, as the institute is committed to hiring highly qualified people and to publishing their research activities in influential journals. Until this day, the NIG has produced more than 900 papers, showing that its working environment is adapted for performing cutting-edge research. The institute actively promotes the participation of its own researchers to International Symposium or the establishment of collaborative research with foreign institutions by managing joint research programs. I confirm that these adapted programs contribute to the high-quality research output of the NIG. The overall assessment of the NIG research activities appears to me as excellent, as the institute shows good-to-outstanding performance in terms of research quality.

In the 70 years of history, the National Institute of Genetics (NIG) has inherited the tradition of being a basic research institute for the genetics of diverse organisms, from microorganisms to plants and animals, and achieved excellent basic research results. During recent 5 years from 2014, NIG published 900 manuscripts, some of which were published in high impact journals. In addition, NIG has developed advanced genomics and bioinformatics platforms, and has published excellent research results on systems analyses of genome functions.

NIG also has supported individual research activities of universities based on its platforms, especially genome analyses and integrated databases. NIG has organized various research international and domestic workshops and symposium for the advancement of genetics, genomics and bioinformatics.

NIG has contributed to human resource development and graduate education. In the Center for Frontier Research, many talented young leaders have been employed to be a professor of NIG to promote new frontiers of genetics. NIG has contributed to graduate education of genetics in SOKENDAI. NIG has educated a small number of graduate students with strong motivation to study in NIG to be research scientists.

NIG has disseminated the achievements from genetics to the society by various outreach activities, including symposium, open day and lectures, which are important for the visibility of NIG in genome research and biotechnology.

NIG conducts high-standard studies in life sciences that are related to genetics, e.g. the studies of the genetics, by the genetics, and for the genetics. The research activities are overall at an international level, with some being world-leading. These activities are conducted in a well-balanced way in four departments (informatics, genomics and evolutionary biology, gene function and phenomics, and chromosome science) and one center for frontier research. They include both theoretical and experimental studies at levels from the molecular to the organismal to the population, most of which meet international standards. Thus, NIG could be regarded as a world-leading institute in genetics research.

It is extremely difficult to evaluate the overall quality of research activities of NIG solely from the self-evaluation report (It was necessary to access NIG's website and refer to papers available there in addition to reading the report). NIG's activities cover all relevant basic research fields including genome science, genetics, evolutionary biology, molecular biology, cell biology, and developmental biology, and the directionality of research is left to each laboratory. As far I can see, NIG's research activities in the fields nearest to my specialty (molecular biology, cell biology, and developmental biology) are vigorous and at an international level.

While NIG's basic policy on research in general is made relatively clear, NIG is required to constantly review its general research policy considering the significant advances and rapid development of genome science in recent years (that does not necessarily mean NIG should only keep pace with this rapid development; it is equally important for NIG to generate such development, as well as to utilize its unique position that allows it to avoid being buffeted by rapidly changing trends in research fields). In my opinion, NIG needs organizational initiatives in this area.

Normally, turnover of staff presents a great opportunity for adjusting or expanding the directionality of research. Regarding laboratories led by staff that reach retirement age, I believe it is crucial for NIG to determine its policy taking a long-term view spanning a 10-20 year time frame, and give to consideration to future human resources and directionality at an early stage.

NIG's research activities are at a sufficiently high level internationally (and domestically as well of course), and have produced results accordingly..

Since the establishment by the Japanese Ministry of Education in 1949, the National Institute of Genetics (NIG) has been keeping central position, where many excellent researchers have made remarkable contribution for comprehensive studies of genetics. Responding to technological advancements for research, such as gene manipulation technology and bioinformatics, NIG was reorganized into an Inter-University Research Institute in 1984, and it is currently providing three services: DNA Databank of Japan (DDBJ), Advanced Genomics Services, and Bioresource Services, in addition to collaborative research. Since then, in fact, this service has been continuing to play a central role in the advance of basic and molecular biology, including medicine. While NIG chose to belong to Research Organization of Information and Systems in 2004, consists of the National Institutes of Polar Research (NIPR), Statistical Mathematics (ISM), Informatics (NII), it appears to me that the balance, so to speak between "wet and dry", remains essentially unaltered in the research infrastructures of NIG.

The genetics particularly focuses genetic mechanisms, which are the most universal and basic phenomena in biology. Recent genetics, covering cell biology, neuroscience, biological evolution, and even anthropology, requires the understanding of genetic behavior from the wide range of viewpoints from molecules to living organisms. On the other hand, recent rapid developments of gene technology have been innovating applied sciences, such as medicine and agriculture. At the moment, thus, it appears difficult and risky for NIG to concentrate its research fields upon some particular and fashionable ones. Instead, this evaluator feels that the NIG researchers should pursue original and unique subjects inspired by individual scientists. It is well known that NIG is the traditional and superior institute, which produced many leading geneticists in the past. In comparison with the most successful period, the number of papers, published into top journals with high IF values, seem to be becoming less. However, this situation is not a critical point in my evaluation, which certainly appreciates high potentiality in the future. In particular, the career and research activities of four young group leaders in the "Center for Frontier Research" section appear to be promising, convincing that the creation of this section is successful. If allowed, I would like to mention that NIG may be able to hold one or two research groups, which will work on methodological developments focusing on genetic manipulation. For instance, the CRISPR/Cas9 system was initially discovered as the immune system acquired in prokaryotes. Presumably, this type of research would not require big research funding. In addition, NIG has only one group, which is working on problems related to symbiosis. I personally and humbly suppose that basic studies about symbiosis at the molecular level will increasingly become important subjects in the future, because of relevance to environmental problems.

Finally, when considering the recent remarkable developments of information science, NIG may be required to have deep insights into theoretical and philosophical aspects about the boundary between living and inanimate.

Over the past five years, 901 research papers have been published, many of which appeared in high-profile

journals with impact factors of more than ten or in top journals in the fields of genetics. Even considering its mission of promoting collaborative researches at universities in Japan, the scientific productivity of the institute with only 64 faculty members is quite good. In addition, the institute recruited promising young researchers at the Center for Frontier Research, some of whom already have gained significant results at the institute. Therefore, the overall quality of research activities is satisfactory and convinces me of good future prospects of the institute as a research organization.

At NIG, many research groups promote a wide spectrum of research on various organisms ranging from microbes through plants to higher animals including human beings at molecular, individual and organism group levels. NIG's outstanding characteristic that sets it apart from other life science research institutes is that almost all researchers establish a theory based on genetics and scientifically demonstrate it through repeated experiments. NIG is the mecca of genetics in Japan. In fact, NIG has produced internationally distinguished researchers like Dr. Motoo Kimura who put forward the neutral theory of molecular evolution and Dr. Tomoko Ohta who proposed the nearly neutral theory of molecular evolution. Even now, at NIG, inheriting such a great tradition of genetics, many researchers are promoting a variety of genetics studies. These can be divided into the fields of information research, genome and evolution research, inherited character research, and inheritance mechanism research, and excellent research activities are being conducted at NIG. In this research period (2014-2018), as shown in the list of literature in the report, NIG has published as many as 180 academic papers per year presenting cutting-edge research on genetics, which plainly exemplifies NIG's energetic research activities. However, considering that as many as one million academic papers are published per year worldwide, what is important is not the quantity of published papers but their quality, and improving the quality of research is an essential task for NIG to continue and expand its activities. Although publishing many papers with high impact factor (IF) is one basis for evaluation, more important than that is the promotion of original and creative research and the production of world-leading results. NIG has many research groups and their performance considerably varies from group to group, but still its research activities in general can be highly appraised. However, when observed from the higher viewpoint of whether NIG is leading the world in proposing notable theories and hypotheses, NIG's research outcome is underwhelming. Meanwhile, for its special characteristics of being able to freely utilize the latest information and documents on genetics and supporting many genetics researchers, NIG has been actively promoting joint studies with organizations inside and outside of Japan and has published high quality papers in leading journals. Genome studies have developed unprecedentedly and there are currently high expectations for its expansion and utility in medical research, and for innovations in information science. However, NIG will struggle to work on a wide range of basic studies without also adhering to "useful research." As an inter-university research institute with an established foundation of abundant knowledge in genetics, NIG is required to actively utilize that expertise and to show its additive and synergistic effects in the further development of related research fields.

Research activities of individual groups are of high quality as the publication list shows. However, I feel some uneasiness on what is the challenge or aim of NIG as a whole institute in research field. Although it is well appreciated that genes and their functions underlie most biological phenomena, and that genetics is a common basis of life sciences, current research groups in NIG, which are within the scope of "genetics and related fields", are too diverse from outside view. History may be responsible for this: NIG continually expanded and reorganized its Departments, Centers, and Divisions or Laboratories for research. The current organization of 5 research Departments including altogether 34 Laboratories started just this year. Reexamination of the group structure may help.

Judging from the publications of individual researchers, overall research activities of the institute are high, with some outstanding achievements in various area of the research especially in the genetics-genomics field. At the same time, the institute serves as an important base for the infra-structure of the genetics-genomics and of the

bio-resources within Japan and for the world.

I noticed a significant number of PIs who made outstanding achievements were about to retire or already left the institute. The smooth transition to the next generation of PIs is quite important for maintaining and enhancing the high activities of the institute. This is particularly important, because we are now in the era of the transformation of genetics. Genetics is becoming a “big data” science and its research focus is shifting from model organism to “wild” organism including human. With the strong tradition of theoretical genetics and with the presence of DDBJ, super-computer center and bio-resource group, it is a chance for the institute to establish its uniqueness and to gain more visibility among other centers in the world.

National Institute of Genetics (NIG) was originally established in 1949 as one of the national institutes to pursue and develop genetic research using a wide range of organisms as experimental models. In 1984, the institute underwent reorganization process and became one of inter-university research institutes in Japan: Since then, NIG strives to not only pursue their own genetic and related research but also facilitate collaborations with external researchers by providing (1) biological sequence datasets through the DNA Databank of Japan (DDBJ), (2) advanced genomic information through Advanced Genomics Services, and (3) bioresource through Bioresource Services. NIG also serves as the Department of Genetics of SOKENDAI (the Graduate School of Advanced Studies) to educate PhD students and award them PhD degrees upon evaluation. NIG also promotes alliance with industry and academia to contribute socially.

Structurally, NIG belongs to the Research Organization of Information and Systems along with the National Institute of Polar Research (NIPR), the National Institute of Statistical Mathematics (ISM), and the National Institute of Informatics (NII). In this high-structured organization, NIG plays a central role in integrating bioinformatics and systems biology and strengthening research infrastructures including databases with massive genomic information.

Reading through the Report on Research and Other Activities of National Institute of Genetics (During 2014-2018) (the NIG Report), I found that NIG strives sincerely to complete their missions in appropriate ways and the efforts have produced excellent results.

Research Activities: NIG has four departments for research activities, (1) Department of Informatics, (2) Department of Genomics and Evolutionary Biology, (3) Department of Gene Function and Phenomics, and (4) Department of Chromosome Science, which consist of 6, 7, 12, and 6 research groups, respectively. The total number of published papers (including those through collaborative services) was 901 in five years (pages 57-). There are 31 groups (PIs) in total in the departments. This means that one group published in average 5.8 papers per year. Based on this, I consider that the research activities at NIG are very high. Particularly, the numbers of papers published by Profs. Arita and Nakamura at the Department of Informatics, Profs. Ikeo and Toyoda at the Department of Genomics and Evolutionary Biology, Profs. Kawakami and Saga at the Department of Gene Function and Phenomics, and Prof. Shiroishi at the Department of Chromosome Science are remarkable and worth to praise. Of course, the numbers of publications depend on when individual PIs started their research at NIG, although the NIG Report however failed to provide such information. It would be highly appreciated if NIG provides such information in the NIG Report for evaluation. It would also be appreciated if NIG provides information to tell us which PIs are full professors or associate professors. How about funding situations of individual PIs in the fiscal years of 2014-2018? This type of items should also be helpful for evaluation.

Four PIs at NIG are female, accounting for 13.0 %, which is not high, I must say. To increase the number of female PIs, what efforts were carried out at NIG? Among four PIs, two seem full professors while two others are associate professors. I went through their publications in the NIG Report and found that the associate professors have no papers in the last five years. I have no idea when they started to run their own groups at NIG but I expect that NIG will support them to publish for extending their carrier. Recruiting foreign PIs is also an important issue.

The Center for Frontier Research: It seems that the tenure-track system has undergone nicely considering the fact that four members become tenured professors in the past five years (what was the percentile in total, though?). According to the publication list (page 57-), all those tenured professors seem very active in trendy fields; namely, systems neuroscience, chromosome biochemistry, cell dynamics and organization, and quantitative mechanobiology. I will look forward to their further progress. According to the NIG Report, each tenured professor obtains 36 million

JPY for five years, a postdoctoral fellow, and a technician which is indeed generous. It would be nicer if their brief CV and individual publication lists were provided in the Report. Do they have mentor(s)? If the answer is yes, how often and to what extent do they have chance to interact with the mentors?

Regarding the research results in the past 5 years, my assessment is that NIG has tackled frontline issues of life science and generated remarkable outcomes both qualitatively and quantitatively, while fully understanding the flow of genetics by Dr. Kihara and Dr. Kimura, the wellsprings of NIG so to speak, and the flow of genomics, the major tide of life science that started at the end of the 20th century. The research style of NIG, where researchers working on leading-edge life science tasks dealing with a variety of organisms from microbes through model flora and fauna to human beings gather in one place, is precious for today's life science that calls for multi-faceted comprehension of life, and I expect a new tidal current of life science to be developed from NIG. In the future, I would like to see NIG also utilizing its strength in taking on the new tide in life science, that may be called design biology or creative biology, primarily genome editing and synthetic biology that have rapidly developed in the last several years.

2. Contribution of the institute to development and reinforcement of infrastructures, such as databases and bioresources for life science

- 1) DDBJ is put to good use internationally as a core genome database in Asia. Its activities can be rated highly.
 - 2) In the National Bioresource Project, NIG is engaged in basic activities such as lineage preservation (including creation in some cases) and distribution, centering on *E. coli*, rice, *Drosophila*, zebra fish and mouse. In particular, NIG is playing an international role in lineage creation and distribution of *Drosophila* and zebra fish, which can be highly rated.
 - 3) For *Drosophila*, it appears generational change has progressed successfully and NIG's activities are continuing smoothly. Meanwhile, as a base of the National Bioresource Project concerning mouse, seeing that the professor in charge has left, NIG should carefully consider how to develop this area in the future taking into account sharing/splitting of the role and cooperation with Riken's BRC. NIG has to build a strategy that enables it to acquire a budget for a long period of time..
-

My assessment is that NIG has established a steadfast intellectual infrastructure for life science in Japan as a joint research institute, and is greatly contributing to the development of life science in Japan.

Specifically, having forecast the rise of genome science about 30 years ago, NIG launched DDBJ and played a leading role toward today's big data era. Based on that, NIG has not only enhanced DDBJ but also promoted the development and provision of super computers, and as such NIG is providing a solid infrastructure for life science of Japan in this big data era. Furthermore, NIG has established the Advanced Genomics Center to provide domestic researchers, young researchers in particular, with cutting-edge DNA sequence analysis services and is playing a propelling role in Japan's life science, especially in genome science.

Additionally, NIG's Genetic Resource Center holds valuable bio resources that have been accumulated at NIG as well as plays a part in the national bio resource project, and is thereby firmly supporting the foundation of Japan's life science.

NIG has the Intellectual Infrastructure Center subsectioned to (1) DDBJ Center, (2) Advanced Genomics Center, and (3) Genetic Resource Center.

The DDBJ Center: This center provides supercomputing services to domestic researchers who analyze biological sequences. According to the NIG Report, they had 600 users from 130 institutions per year, which,

I found, is numerous. Papers published by the users were ~100 per year. I wonder if this number was reasonable or the center expected to have a higher number. The center also develops software tools, updates computing environment, and outreaches to educate researchers, all of which are very important tasks to stimulate life science research in Japan. DDBJ shares datasets with NCBI and EBI for integrating global coordination. This type of efforts is highly appreciated. According to the NIG Report (Table 2), the majority of data submission was domestic while only ~10% was from overseas. Is this expected situation? Or, does the center expect a higher number of international submissions? It seems that the supercomputer congestion is a problem to be solved. For this, the center now offers paid services. I wonder if the problem was solved expectedly by them. The staff organization (and gender balance) at the DDBJ center seems to be adequate.

The Advanced Genomics Center: This center has five missions: (1) Development of advanced genomics technologies, (2) Development of bioinformatic technologies, (3) Promotion of collaborative research, (4) Promotion of open science and open data, and (5) Education on advanced genomics. Research projects that this center runs are selected from applications to the NIG-AGC Joint Program. Besides, the center runs four research projects: National BioResource Project (supported by AMED, 2011-), Platform for Advanced Genome Science (MEXT, 2016-), Human Microbiome Project (AMED, 2017-), and Promotion of Microbiome Research (ROIS, 2018-). I wonder how the National BioResource Project (launched in 2011) has gone. It would be highly appreciated if the progress was provided in the NIG Report. Other projects were just started: I expect that all the projects will be fruitful at the end. The center has various next generation sequencing machines including ABI 3730x1 and HiSeq 2500. How often are they used by the external users? Such important information was lacking in the NIG Report. How about the staff organization?

The Genomic Resource Center: The first paragraph in the overview (page 32) noted that this center consists of two divisions, (1) Bioresources Division and (2) Database Division. However, just below it (on the same page), it is noted that the center has (1) Bioresource Management Division, (2) Plant Resource Development Division, (3) Division for Development of Genetic-Engineering Mouse Resources, and (4) Bioresource Database Division. This is very confusing. According to the upper table (page 33), the center has 65,067 *E. coli* and *B. subtilis* stocks (as of Sep 2018). The lower one shows the numbers of orders and strains. For instance, in 2017, the center received 404 orders and the strain number was 155,318. Does this mean that one order was for 384 strains? The Zebrafish Resource section published more than 100 collaborative papers (page 36). This type of information should be provided from other sections. The whole NIG organization is complicated: Can Bioresource Database Division be integrated, for instance, in Database Division at Bioinformation and DDBJ Center?

As one of the three members of the International Nucleotide Sequence Database Collaboration (INSDC), DDBJ has been contributing to the accumulation and dissemination of DNA data. The supercomputing capability provided for researchers by the center is also important. In the genome age, the availability of such infrastructure is essential for biological research. Even on a limited budget, the equipment and tools in the center have been updated in a timely manner to meet the needs of users. The Advanced Genomics Center also contributed to research in the genome era by providing the latest equipment for sequencing. Another important resource for biological research is the collection of genetic strains of model species. The importance of genetic diversity is well recognized, and the Center is Japan's headquarters for activities that maintain and provide these resources to a broad community of biodiversity research.

I think highly of both the DDBJ and bioresources operations at NIG, having seen sufficient results (having made contributions to other research institutions) and having become a domestically-indispensable intellectual infrastructure.

NIG provides the scientific community with a wide variety of research infrastructures through the activities of three intellectual infrastructure centers, Bioinformation and DDBJ Center, Advanced Genomics Center, and

Genetic Resource Center. Their activities are well organized, with each being at a very high level. They support the scientific community and the support is welcomed by the scientific community. Thus, NIG makes an enormous contribution to the scientific community, and therefore should be regarded as a world-leading institute not only in research but also in support in research infrastructure.

NIG has established platforms of the latest genome research, bioinformatics, databases and bioresources. These are DNA Databank of Japan (DDBJ), Advanced Genomics Services (Advanced Genomics Center, AGC) and Bioresource Services (Genetic Resource Center, GRC). These platforms have been productive not only in the analysis of genetic systems but also in active support of individual research activities of universities. These platforms are important visible activities in NIG in the foundation of life science through basic research activities such as diverse genome analysis, integrated database and biological resources. NIG has taken leadership in these research platforms.

The DDBJ has provided web interfaces to analyze genome sequences from its web browsers. Major research tasks of AGC are funded on 4 major projects supported by AMED, MEXT and ROIS. From 2014, there were 80 publications on genome analysis in AGC. These services are useful for university researchers on genome research. BRC has contributed to National Bioresource Project (NBRP) as the leading institute and a national center of bioresource information.

Because of the presence of DDBJ, super-computer center and bio-resource group, the institute is contributing considerably for the development and reinforcement of infrastructures for life science, especially for non-medical field, within Japan and for the world. These activities should be maintained and enhanced.

I wish to point out the importance of the institute as the base of infrastructure for the non-medical life science within Japan. For the medical field, there are several centers that can substitute the activity of the Institute of Genetics, such as Human Genome Center in the University of Tokyo or as Tohoku Megabank in Tohoku University. But, for non-medical life sciences, the institute is the only one to support the infrastructure, especially for informatics and sequence data production. The importance of informatics and big data production will continue to grow in the future.

Achievements of Intellectual Infrastructure Center are highly evaluated.

Not to mention, DDBJ has played an internationally important role as an official database center of Japan to participate in INSDC. Advanced genomics and Genetic Resource Centers have contributed to research development throughout Japan. They are literary infrastructure for life sciences and support the broad range of research communities. Since informatics training in universities is normally behind, education and outreach programs by Bioinformation and DDBJ Center are greatly welcome. Matters of concern will be the confliction between financial shortage and extent of desired services. This always happens. Practical solutions like user fees, choice of efficient and effective software or tools need to be earnestly considered. Also, it is hoped that proper (intimate but not overlapped) collaborations with other related centers or organization as DBCLS and AMED are maintained.

This evaluator is not an expert of database analysis, and has no experience of using databases hosted by DDBJ. Thus, the following descriptions are noted as a summary of some users' comments around himself.

The DDBJ is continuously collecting and releasing sequence data as an active member of INSDC, and also hosting the Genomic Expression Archive (GEA) and the Japanese Genotype-Phenotype Archive (JGA) as the original databases. The DDBJ activities appear to be steady and satisfactory in progress, including the handling for the large-scale data produced from NGS (Next Generation Sequencing) studies. The DDBJ also appropriately takes measures toward the data from human genome cohorts, which require the rigorous confidence of data. The computing nodes and data storage have been up-dated timely and satisfactorily. It is continuously offering its computational resources to public users, including the Group Cloud service (DGC)

users, who are handling the confidential data. About 90% (106/921 as login user-base) of the resource is supposedly used for the public users, and the number of users has been increasing gradually. The staffs in DDBJ have been making efforts for education and outreach activities, such as DDBJing and D-STEP, for promoting the DDBJ resources. Based on these facts and statistics, it should be concluded that the role of DDBJ is satisfactory as the joint-use research center.

It should be nevertheless noted that the DDBJ is required to promote its uniqueness among the INSDC members. The DDBJ is currently offering MiGAP and DDBJ-pipeline as the original on-line applications, which can be highly appreciated. It should continue to develop original and useful applications, which might be accessed from worldwide users. In this respect, the collaboration with DBCLS (Database Center for Life Science) that started from 2014 is important. According to the descriptions in the report, however, the status and scope of the collaboration with DBCLS are not so clear. The collaboration between DBCLS and DDBJ would be quite effective in developing original applications and databases.

It should be also noted that some users wonder whether the human resource of DDBJ is properly managed in terms of a balance between efforts for database maintenance and scientific research. Presumably, the databases have been maintained with ~10 curators by using ~10% of total computational resources. The most of the curators are doctoral degree holders, and this is understandable because the data curation for DDBJ requires sophisticated expertise. Therefore, a special and kind attention should be paid for their career path. It may be desirable that the DDBJ stands at the proper position for the role of “data curating by professional curators”. Unfortunately, such important and indispensable role for scientific activities is not widely accepted. Thus, I expect more intensive efforts for promoting and visualizing their activities toward both scientific and public societies.

In my point of view, the research institute is very well supplied with resources in terms of infrastructure and equipment. The DNA Data Bank of Japan (DDBJ) has been efficiently operated with a constant data submission to the system over the years, and also shows a noteworthy adaptation to the technological advances of the sequencers, as well as to the various trends appearing continuously in the life science field. Moreover, the institute is increasing the visibility of the DDBJ by arranging lecture and training courses that are essential to promote its extensive outreach, on both domestic and international levels. The Genetic Resource center that directs the maintenance and distribution of various organisms takes also an important place at the national level, well-illustrated by the increase in user demand over the past 5 years. To meet the different needs and requests of the research users, the institute has increased the number of the stocked bioresources and has also strategically reinforced the development of prominent resources.

In conclusion, the NIG, with the DDBJ ahead, excels in terms of infrastructure, database, and resources, dedicated for life science research.

One of its characteristics as an inter-university research institute is that NIG serves as a world-leading research base that manages and operates gene and genome information. Such data are currently soaring in quantity, as represented by terms like big data and data science, and the DNA Data Bank of Japan (DDBJ) can be credited for fulfilling its heavy responsibilities with an international perspective, achieved by integrating Japan’s DNA databases, establishing close collaboration with the US NCBI and European EBI, and participating in the International Nucleotide Sequence Database Collaboration (INSDC). In fact, DNA information on humans and other organisms is essential in today’s genetics studies and disease research, and DDBJ has made remarkable contributions including the sharing and integration of a massive amount of data in Japan and the development of new analysis methods. However, currently, it is slightly concerning that a large majority of users registered at DDBJ are researchers in Japan. That is, NIG may have to work on initiatives to expand the area of genome information gathering by encouraging registration in Asian countries that have been left out. There are common diseases and race- or region-specific diseases in the world, and the necessity of gathering and sharing DNA information is expected to increase from the point of view of deepening medical research. Meanwhile, related

to that, NIG has introduced large-scale large-capacity leading-edge super computers and offered them free of charge to researchers in Japan, contributing to effective information processing in life science and medical studies. In addition, as part of its inter-university joint research activities, NIG has established the Advanced Genomics Center and conducted metagenome analysis for organisms such as animals, plants and microbes, humans and the environment, making huge contributions in assisting genomics research in Japan. Further, NIG has built the Genetic Resource Center to establish a system for gathering, storing and providing bioresources (biological genetic resources) for *E. coli*/*B. subtilis*, rice, *Drosophila*, zebrafish, mouse, etc. These resources contribute to life science and the Genetic Resource Center actively promotes the distribution of experimental organism systems, which can be considered as a major contribution to the academic community.

3. General management and administration: Is overall organization and administration of the institute appropriate as an inter-university research institute?

Again, because of DDBJ, super-computer center and bio-resource group, the institute is contributing considerably for the research of other universities within Japan, thus, the institute is functioning as an inter-university research institute excellently.

Only problem may be the branding of the activity as the activity of the institute. The presence of the institute is somewhat attenuated because of the high visibility of each group such as DDBJ or bio-resource group. Joint Research program is also received as the collection of individual collaborative research of the PI of the institute rather than the program of the institute. A strategy for the branding may have to be considered.

The Research Department is divided into Department of Informatics, Department of Genomics and Evolutionary, Department of Gene Function and Phenomics, Department of Chromosome Science. Genetics is the basic science, covering entire biological phenomena, and thus apparently large spread of subjects would be natural. Nevertheless, the facilitation of joint researches between departments may be desirable in the future. The Center for Frontier Research appears to be impressively successful. There is overall no negative aspect in the balance between Research Department and Intellectual Infrastructure Center. In respect with personnel composition in the DDBJ, however, intensive administrative efforts may be required to increase the number of professional curators.

The main frame of organization looks sound. As to how cautiously and effectively each division works is difficult to read from the report. As mentioned above, diversity of research groups seems to lack order, and need reconsideration to shape up the Institute's exclusivity or uniqueness, because "Cutting-edge" researches are encouraged in any institutes or universities. However, considering that the current system was established less than a year ago, big changes would be inappropriate in short time but small modifications such as relocation of Laboratories among Departments and proper choice of new groups in the Center for Frontier Research would be less difficult. I would like to expect the Council for Strategy Planning to consider NIG's mission and future development in longer time span more intensely.

Currently NIG is managing the balance of research and business well, but it may be advisable for NIG to examine what its organization and administration should be and clarify their directionality considering the possible reduction of the budget in the future.

As an inter-university research institute, NIG conducts many joint studies every year. It is noteworthy that, regarding zebra fish in particular, NIG has engaged in numerous international joint research projects and produced outstanding results.

My assessment is that NIG has conducted a number of joint studies with domestic and overseas researchers and produced outstanding results. Lately, the research environment surrounding Japan's (national) universities has become more severe, and regional universities and private universities especially are having a very tough time. Amid such a situation, joint research offered by NIG may provide precious opportunities for financially struggling regional universities and young researchers. As an inter-university research institute, NIG has not only engaged in cutting-edge R&D but has also made steady and patient efforts without abandoning the outskirts of Japan's research infrastructure. NIG's staff may be facing challenges on a daily basis to conduct cutting-edge research as well as to establish the infrastructure and bolster the outskirts. I would like to praise the contribution of NIG's staff for steadily producing results as an inter-university research institute under these conditions.

It catches my eye that NIG has established quite a few various committees and meeting bodies as part of its management system, while it is experiencing hardships in the overall management. I understand that each meeting body has its own purpose to establish external involvement including MEXT, but it is easy to imagine that even a small committee requires a certain amount of time and effort. I would like for NIG to consider whether it can simplify its operation system a little bit more so that it can fully utilize its limited staff and funnel their time and effort into its original mission.

A recent regrouping of laboratories into four departments made the organizational structure of the institute simpler and is expected to improve flexibility in hiring faculty members and to promote exchanges of ideas within a department. Under this new organization, some members also participate in the center activities. Therefore, determining how efforts are allocated to each of research and center activities is important for the members and the administration. Another important issue is communication between the departments. The NIG Colloquia open to all members of the institute is one such mechanism to exchange ideas and is expected to be useful for the cohesion of the researchers of the institute. Simplicity of the organization and the atmosphere of free exchanges of ideas among researchers provide good environments for those participating in inter-university collaborations. The addition of the Collaborative Research (A2) category and support for an international symposium to the joint research program promotes international collaboration in the genetic research community.

Since 1984, NIG was reorganized as an inter-university research institute for the promotion of collaboration with universities based on research projects and research platforms. The NIG leaders recognize this important mission to promote various types of collaboration with individual researchers in universities. The genomics and bioinformatics researchers have contributed to university researchers to promote genetics in Japan based on collaboration. From 2019, new organization of departments and research centers started to carry out more efficient research in genetics. For the activation of this new organization, efficient management of these departments and research centers are important for the advancement of research and development of NIG.

The NIG is greatly involved in educating and promoting young scientists, as shown by the organization of various events for students and young researchers to interact with each other. In particular, the NIG INTERN program is proving to be a success with the host of about 30 students from all over the world, selected among 400 applicants. These efforts that the NIG make to promote international exchanges are highly appreciated.

In conclusion, the working conditions in the NIG are perceived as excellent, offering an attractive environment as an inter-university research institute for researchers that are able to withstand competition with international

research units.

The activities of Joint Research and Research Meeting (NIG-JOINT) and International Symposium were summarized on page 41. However, the amount of information was too small that it is difficult for me to evaluate and make comments on the activities. For instance, the number of collaborative joint research meetings held in 2018 was 19, which, I found, was pretty good. It would be highly appreciated if the title, the organizers, the number of participants, the date and so on were provided for each meeting. How many papers were published through NIG-JOINT? Which universities were involved in NIG-JOINT as collaborators? These types of information should also be provided in the NIG Report.

The organization and administration of NIG are quite appropriate and well-organized under the strong leadership of Director-General. NIG welcomes external advices and suggestions, and incorporates them in its management policy. Thus, NIG's organization and administration are improving constantly.

All the three centers engaged in inter-university joint research projects (Bioinformation and DDBJ Center, Advanced Genomics Center, Genetic Resource Center) have well-experienced researchers and support staff and operate under well-considered organizational systems and management. Today, the quantity of biological information is increasing at a phenomenal rate, and gathering and managing information data and bioresources of various organisms is extremely important. At the same time, facilitating access for researchers in Japan who desires to utilize such information is an important mission for an inter-university research institute. Considering that maintenance and management of the three centers calls for plenty of experience and knowledge, I expect that NIG will continue to develop human resources and master new technologies and to innovate in these areas. These knowledge base-establishing projects will contribute to the development of life science research in Japan.

4. Others (ex. Educational activities for graduate students, publicity activities and intellectual right-related activities)

The Office for Research Development (ORD) was established in 2014 and carried out enhancing research activities, institutional research and public relations. ORD has contributed to various activities of NIG. Among them, public relations are important for the visibility of NIG to society. ORD members are all former and current faculty members to start ORD. In the next step, more interaction and communication with University Research Administrators (URA) in ROIS and other universities are necessary to improve the ORD activities.

The NIG Innovation started in 2013 to promote technology transfer management. The income for FY2018 has increased more than 3 times of the FY2013 income. The NIG Innovation activities have advanced collaboration with companies and local government, which will contribute to financial improvement in the future

It appears that educational activities are not necessarily NIG's main focus. There may be room to reconsider allocation of resources and efforts to educational activities amid the anticipated reduction in the budget and personnel. NIG's publicity activities and intellectual rights-related business have borne some fruit.

My assessment is that NIG has broadly conducted activities for the benefit of society and produced excellent results.

The reviewer wishes to emphasize the success of the establishment of the Center for Frontier Research, which successfully recruits leading new talents. This system greatly contributes to the future of life science research.

The NIG has a graduate school program, and the educational activities for graduate students are of high quality. Public relations are appropriately promoted as mentioned above.

Development of highly-skilled human resources based on genetics requires specialized educational activities, and NIG is actively working in this area. However, the number of postgraduate students at NIG does not feel large enough for the scale of its research organization; NIG should actively work on projects that enable participation by many postgraduate students. While NIG is vigorously engaged in campaigns to improve the awareness and understanding of genetics by holding international workshops and conferences, enhancement of its website is essential as a societal publicity activity and that requires updating its webpages (at least updating the performance section) about once a year. Regarding the content of its research, initiatives like preparing materials designed for the general public in addition to those for experts, and publishing them on its website will be required. A TLO has been established, and the intellectual rights-related activities seem to be functioning well. Also, NIG has created the Center for Frontier Research as part of its bid to establish a system envisaging the future. This Center assists promising young researchers in cultivating new research fields, and is a program I think highly of.

NIG's educational activities as the Graduate University for Advanced Studies have much higher importance than I thought. However, the number of postgraduate students NIG has acquired doesn't seem to match the efforts it has put in. Acquiring a certain number of postgraduate students and promoting research while educating them are important in Japan at the present time, and from my personal experience, are a major element to vitalize a laboratory. From that aspect, it is regrettable that the activities at the Graduate University for Advanced Studies have made little contribution to it. As a result of its effort in recruiting overseas postgraduate students, NIG has secured a certain number of overseas postgraduate students but that is largely thanks to endeavors by individual staff as it depends on forming a close relationship with research institutions in relevant regions. Further organization of these initiatives may be warranted. Additionally, though I don't know if regulations allow NIG to conclude cooperation agreements with nearby universities and other institutions, if that is possible then NIG should promote such activities to recruit more postgraduate students.

All research institutions consider publicity activities to be of great importance as they are directly involved with various aspects of their operations, such as research activities and acquisition of postgraduate students. I sometimes see advertisements for research seminars hosted by NIG, but they seem to be held almost always in and around Tokyo, possibly for the sake of efficiency. It would be advisable for NIG to steadily expand its activities at places where regional universities are located through collaboration with such regional universities (it may also be wise for NIG to seek cooperation from partners in joint research, taking advantage of its status as an inter-university research institute).

Although the number of students was small, the graduate school carefully educates students by taking advantage of a high undergraduate / student ratio. The faculty members of other laboratories participated in the student committee to enrich the student's perspective and contributed to the career development of the students as independent researchers. The student support seems better than in other graduate school in Japan. The internationalization of graduate schools is very advanced. In order to recruit excellent students, new recruiting devices EA-MEXT / NIG-GS were introduced. All lectures, counseling and notifications will be provided in English. For evaluation purpose, it might be better to include information of the number of years students took to obtain Ph D and the jobs they got after the graduation in the report. Setting up the NIG INNOVATION and the ORD was successful. It promoted dissemination of knowledge to the community and enhanced research activities, financial status and significance of

the institute.

NIG's education philosophy is splendid and the high ratio of faculty/student should be appreciated by students. Nevertheless, applications in general and international admissions are not plenty and even decreasing. This probably reflects the general difficulty of graduate schools without undergraduate course, and decrease of PhD applicants in general. Taking this tendency in account, NIG's efforts for management and student care are well evaluated as a division of SOKENDAI. Other activities for outreach and intellectual right are also highly appreciated.

I think, the education, publicity activities and intellectual right-related activities might not be in the ideal level, but good enough to be in a satisfactory level.

I wish to point out one other thing: it is The Center for Frontier Research. This center was established to give promising young scientists a chance to conduct their research as principal investigators (under one roof?). This type of organization is urgently needed in order to keep Japanese scientific levels high and all the inter-university research institute should have one.

The important thing for the operation of this type of organization is to avoid becoming too sensitive about the failed cases. Even though the PIs have high expectations, we should accept that a certain percentage of them could not go up to the next step. And this "failure" should not be considered as the failure of the center or this type of system. Obviously, it is good to have some backup plan for the "failed" cases. But, the fear for the luck of such backup should not discourage setting-up and operating this type of organization.

The education and outreach activities of NIG are in general excellent, and this evaluator has no negative comments. However, similarly to other universities and research institutes, NIG is faced with the decreased number of graduate students. In fact, applicants to the general admission have decreased in the past 10 years, because of the overall declining of Japanese young generation. In addition, Japanese young people are particularly urban oriented. In this context, the NIG location at Mishima, considerably far from the Tokyo area, would be one of disadvantageous points. This problem would be overcome by increasing graduate students from abroad. Thus, the intensive efforts of NIG for this purpose should be highly appreciated. In addition to the presently available program, NIG may be able to create a new type of program, which will allow the international exchange of graduate students on the basis of agreements with particular universities.

NIG functions as the Department of Genetics of SOKENDAI (The Graduate University for Advanced Studies) where NIG offers the graduate programs for 5 years and 3 years and awards PhD degrees upon successful completion. The ratio of faculties and students is 1.4:1.0: The NIG Report continues, "*every single student gets the attention of the entire faculty from various disciplines*" (page 42). It would be nicer if the ratio becomes higher (namely, more students per PI). The numbers of applicants for NIG-GS were 22 and 24 in 2016 and 2017, respectively. However, the numbers of enrollments shrank (3 and 2, respectively). In 2017, 6 were admitted for enrollment but 2 actually enrolled. What was the reason for the reduction in the number?

The education program "NIG method" is interesting. Is this type of education available for scientific staff and PIs? The number of students who received PhD degree in 2017 was 12. Where did those young scientists go afterwards? Such information will also be appreciated if provided in the report. According to the NIG Report, NIG has student dormitory but may not be enough to accommodate all the students soon. Will the capacity be expanded in the near future?

I do not think that "NIG Postdoctoral Fellow Program" should be in the "Outreach" activity section (page 47).

The effort to hold the DDBJ lecture courses and BioResourses training courses is highly appreciated. Activities to promote international interaction and cooperation are also fine and I do not see any problem in there. Regarding gender equality; how about the ratio of male vs. female students at NIG? Such information is missing in the report.

I was wondering, however, what you and your colleagues considered to be the outstanding discoveries and exceptional achievements of the past 5 years? I missed a kind of what one might term 'executive summary'. And a sense of changes in emphasis or trajectory...

Sometimes I think people overlook the fact that simply carrying on doing the same thing at a high level consistently for a long period of time - like running a really good restaurant that maintains the highest standards - is overlooked and underestimated. To take the restaurant analogy, there is little or no innovation, but maintaining the service and the standards of cooking and presentation can be very demanding and is highly laudable! I have a suspicion that several of the services you strive to provide fall into this kind of category, and wonder if you would agree?

I regret that there is no opportunity for an actual visit, because this usually gives a much better idea of activities than dusty reports.

Nevertheless, I was generally impressed by the report, and strongly applaud your emphasis on conducting business in English where possible.

Two groups' work particularly intrigued me, next to each other on the same page - the work of the Koide group on the genetics of tameness in mice and the Miyagishima group's researches on the coordination of chloroplast division with the host cell cycle. This is traditional small science of a kind that I appreciate. There is so much DNA sequencing going on these days and not enough physiology, but all the same I see that your researchers are not unaware of this and are making resources available to exploration of the genes of unknown function.