Case Study Report on Genome Synthesis Technology

Forum on Genome Ethics

March 2024

*This is a translation of the original (https://www.jst.go.jp/ristex/internal_research/files/casestudyref.pdf).
In the event of any discrepancy or inconsistency, the original will prevail.

Contents

1. Preface

With R&D on genome-related technologies advancing rapidly, we have entered a new era of artificial designing and synthesizing of genome sequences at our will, including the decoding of human genome sequences and the emergence of CRISPR-Cas9 genome editing technology. While such technical advances could benefit many focus areas significantly, they could also negatively impact life, species, and even ecosystems because genomes are the Blueprint for Life. Under such circumstances, promoting R&D on new technologies related to genomic information requires the consideration of ELSI/RRI perspectives and the establishment of the underlying norms and values.

In this context, the Research Institute of Science and Technology for Society (RISTEX) of the Japan Science and Technology Agency (JST) established and operates the Forum on Genome Ethics (hereinafter "the Forum") to solve envisioned ethical, legal, and social issues/implications (ELSI) associated with the R&D and social implementation of emerging technologies. Also, RISTEX set up the Forum as part of the initiative to contribute to responsible research and innovation (RRI) through approaches to ELSI. Through the Forum, RISTEX discusses ethics-related considerations for genome-related technologies and social ethics and implements survey/research activities.

The Forum is engaged in activities to examine and experiment with what ELSI/RRI should be from the upstream of R&D through online seminars and joint workshops (hereinafter "WS") in collaboration with Large-Scale Genome Synthesis and Cell Programming, a focus area of the JST Strategic Basic Research Programs CREST/PRESTO) (hereinafter "Genome Synthesis Area"). The Program aims to create essential technologies for cell utilization based on interpreting the principle of genome operation and the knowledge thereof.

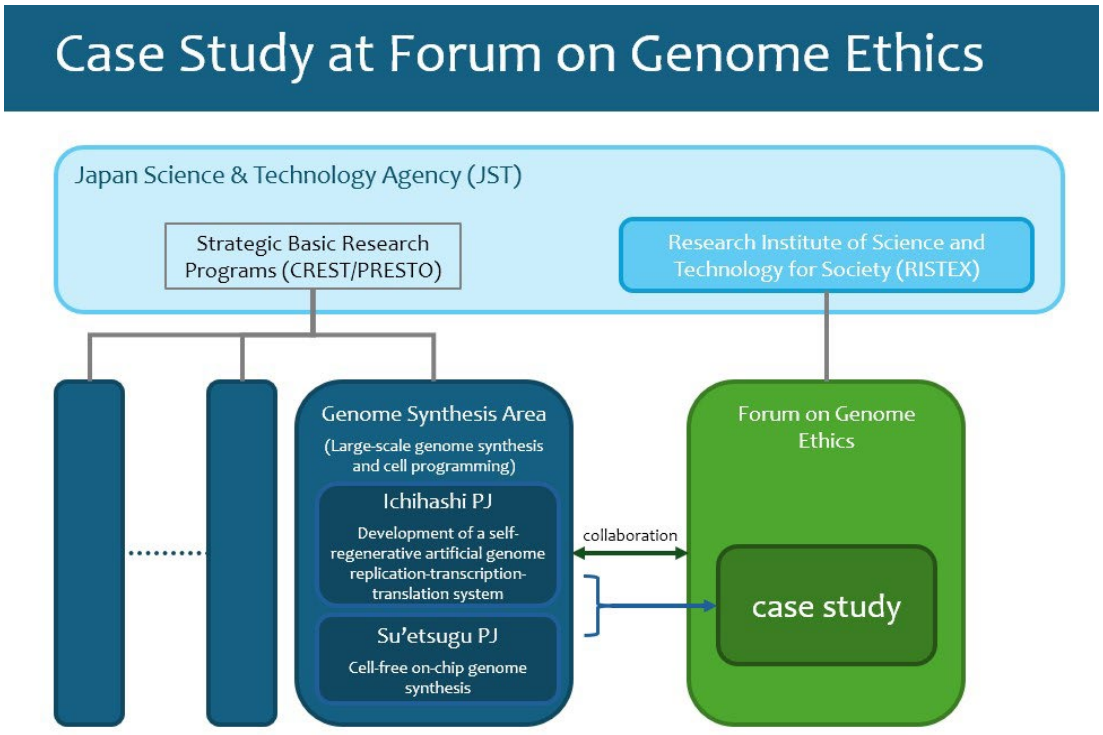

Figure 1 Case study at Forum on Genome Ethics

(Source: Prepared by the Secretariat of Forum on Genome Ethics)

This fiscal year, the Forum held individual WS and group interviews to sample public awareness as a case study (Figure 1) aimed to discuss ELSI issues and critical perspectives for two projects (PJs) in JST-CREST's Genome Synthesis Area. In addition, based on the above results, the Forum held a joint PJ WS to overview the case study. This report summarizes the case study, including the entire process, discussion results, insights gained from the results, and participant feedback.

2. Process and Results

To promote our discussions in the Forum up to FY2022, we used the ELSI Perspective Map 2022 (Figure 2) for the case study in this fiscal year. This map was created based on common and different responses from questionnaires sent out to researchers in the CREST/PRESTO Genome Synthesis Area and the members of the Forum on Genome Ethics regarding their awareness of ELSI perspectives.

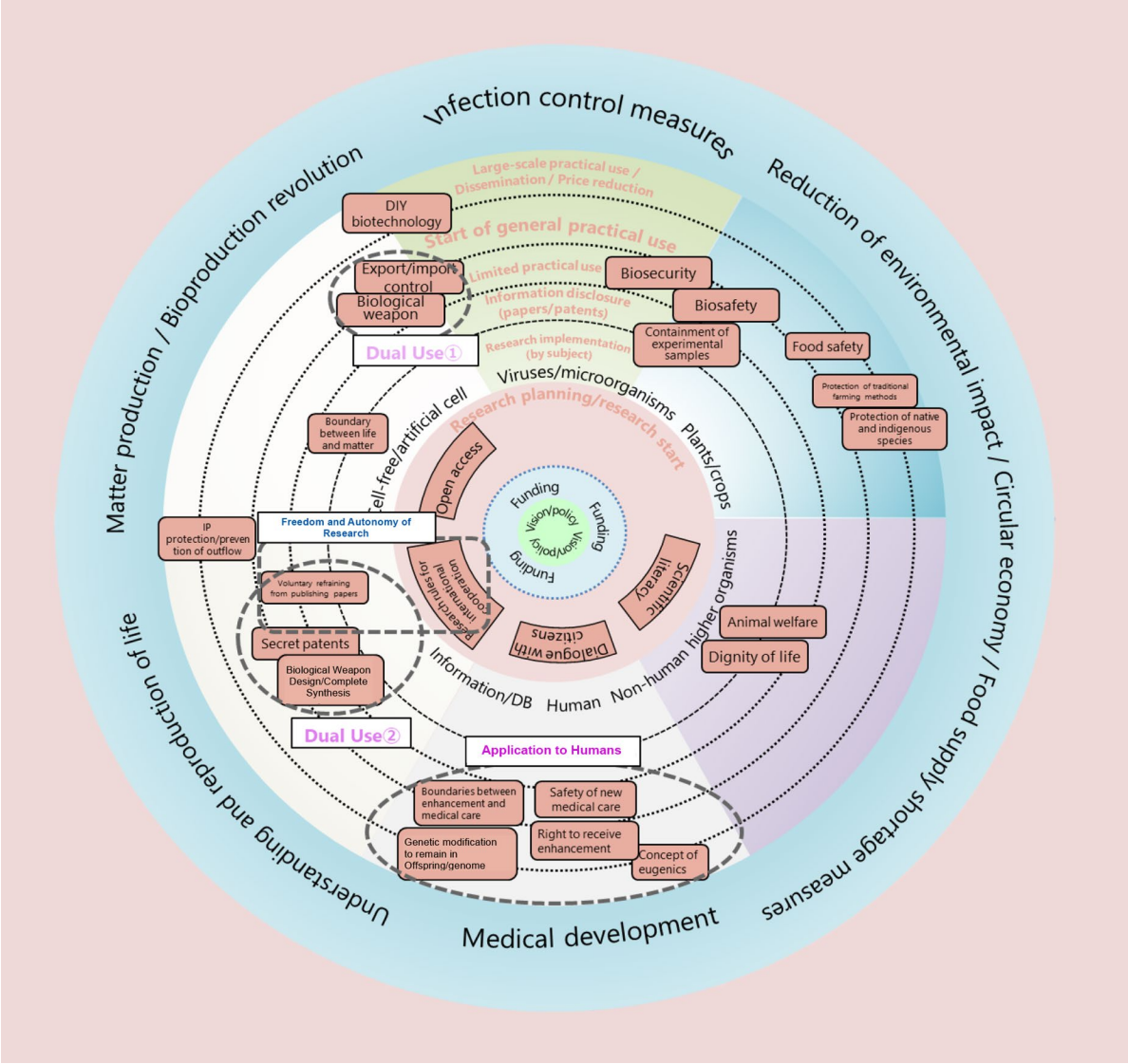

Figure 2 ELSI Perspective Map 2022 (Relationship between ELSI perspectives and research targets)

(Source: https://www.jst.go.jp/ristex/internal_research/elsi/genome/genome_map.html)

In this case study, three types of events were conducted: [1] two individual WS for each target PJ, [2] citizen group interviews (hereinafter "Citizen GI") for each target PJ, and [3] a joint PJ WS to summarize the former two).

2.1 Ichihashi PJ

The Ichihashi PJ refers to the CREST Development of a Self-Regenerative Artificial Genome Replication-Transcription-Translation System project, for which Dr. Norikazu Ichihashi (Professor, Graduate School of Arts and Sciences, University of Tokyo) serves as Principal Investigator. The PJ is to develop a DNA replication, transcription, and translation system that self-reproduces all genes (36) required for the replication, transcription, and translation of artificial genomic DNA, excluding ribosomes. To ensure the feasibility of this goal, the PJ employs a DNA sequence optimization method based on a proprietary, simplified DNA replication system and the mechanism of evolution.

2.1.1 The first Individual WS

(1) Process

On July 3, 2023, Dr. Ichihashi and core Forum members held a kickoff meeting to discuss the details of the WS and how to proceed. At the meeting, the Forum members offered some proposals, including Dr. Ichihashi's introduction of his research area for liberal arts college students and a presentation on a roadmap for how technology would be utilized in future society. In response to those proposals, Dr. Ichihashi said he wanted to speak about the Dignity of Life listed on the ELSI Perspective Map. On the other hand, he expressed his concern that touting the benefits of something that does not yet exist might be taken as megalomania since the social implementation of such research is 10 to 20 years away. It was also proposed that the WS discuss in depth which ELSI perspectives must be determined today and which must be examined over future generations, such as the pros and cons of genetic recombination of germ cells. In any case, it was confirmed that instead of the WS coming up with the solutions, it should output additional ELSI perspectives and what research is needed to tackle them. In light of the above discussion, the Secretariat envisioned the ELSI perspectives listed in Table 1.

Table 1 ELSI perspectives envisioned for the Ichihashi PJ

Dual use [top left on the map]

- Concerning issues such as “gene-edited twins”, it is essential to determine at which stage of the technology dissemination regulations should be introduced.
- In Japan, once a technology is authorized, the use of that technology may continue to spread endlessly. Applying this technology to humans also influences the timing of such regulations.

IP Protection and Prevention of Outflow / Open Access [center left on the map]

- If a technology is over-protected, the users of the technology are not comfortable using it. Dr. Ichihashi tries to make his accomplishments open resources. However, patents on mycoplasma strains that other labs create stay active even when new strains are created.

Scientific Literacy [bottom right on the map]

- There are research workers who do not know the Cartagena Act (regulations on genetic recombination).

Dignity of Life [bottom right on the map]

- The question is whether to consider artificial life as an organism or not. Some believe that if it is regarded as an organism, regulations on living organisms apply. Which should we put more emphasis on, apparent creatureliness or structural creatureliness? Are the amino acids that nourish the increased molecules derived from life? In the end, does anything non-killing exist in the food we eat?

（Source: Prepared by the Secretariat of Forum on Genome Ethics）

The first individual WS of the Ichihashi PJ was held from 13:00 to 17:00 on August 31, 2023, in a hybrid meeting between the Ichihashi Lab at the University of Tokyo and online. This WS was organized by the Forum and operated/facilitated by the Secretariat. Dr. Ichihashi introduced his research details in this WS, followed by a lab tour. We then discussed the points and

direction of the ELSI perspectives of the Ichihashi PJ in depth while looking at the ELSI Perspective Map. The Secretariat then reported on how to proceed with the Citizen GI, which the participants discussed.

(2) Results

According to Dr. Ichihashi's explanation, his research field encompasses a variety of studies, generally called Artificial Cells. Among various studies, his interest is in bottom-up approaches that reorganize living organisms using their components. To this end, he is pursuing his research with two objectives: (1) to understand their origins, and how biological functions are created from molecules, and (2) to extract the functions of creatures in a form that is handy for humans. Specifically, he is creating artificial cells that are automatically reproduced once the first one is made, just like Doraemon's secret tool "Baibain (Multiplication Liquid)." He is now pursuing efforts to move the central dogma, the core part of this mechanism.

Dr. Ichihashi says he does not become attached to the artificial cells that can be revived at any time, feeling that they are much different from multicellular organisms. In response to this comment, a Forum member (Dr. Tagawa) commented that the concept of Life used when saying "Life is important" (living organisms such as multicellular organisms) and the concept of Life including microorganisms and plants may be different. Another Forum member (Dr. Iwasaki) commented that the context in which independence is found is critical because while *E. coli* isolated in labs does not have many emotional mutual interactions, pathogens project their independence as the attacker on their opponents. Based on these discussions, while Dr. Ichihashi wanted to distinguish between multicellular and unicellular organisms, he said, "The latter are living in biology but many non-specialist think they have no life. I am sure what I am making now has no life. At least, I think so." He also expressed his intention to conduct his research in a manner that would not be subject to biological regulations, if possible, and his belief that the existing regulations for DNA synthesis are sufficient. After that, regarding laws and regulations, Dr. Nakamura asked about the possibility of constructing logical boundaries between creatures. However, there are biological aspects that are incompatible with the definition of living organisms in law in the first place. Conversely, there is a point of view that this condition indicates the difficulty of defining living organisms in a unified way (Dr. Iwasaki). There is also an opinion that humanities knowledge should be better used to develop successful stories, putting them into social acceptance and law (Dr. Nakamura). With these views, the Forum intended to implement positive ideas about ethics and ELSI perspectives.

Points and perspectives we wanted to discuss in depth for the second individual WS and the Citizen GI included awareness of the designation Artificial Cell and how Dr. Ichihashi presents his research. Some proposed that as an introduction to the discussion in the Citizen GI, producing alternative food would be an easy-to-understand narrative.

2.1.2 Citizen GI

(1) Process

The Citizen GI is conducted to collect the opinions of non-WS participants so that we can discuss a wide range of viewpoints in the second individual WS. The Citizen GI also aims to pick up opinions about topics, characteristic of the Ichihashi PJ's research activities and in which Dr. Ichihashi is very interested, among the ELSI perspectives listed in Table 1, whose discussions are expected to come in the second individual WS.

The theme the Secretariat proposed in the first individual WS on August 31 was "What is life? How do you think about creating life?" Since it would be difficult to answer such a question from the outset, we decided to start by asking their impressions of our research without overly narrowing down the list of themes. We envisioned that the target citizens were liberal arts college students, who usually had little contact with the Ichihashi PJ and were interested in the above-proposed themes. However, their knowledge

of the research did not matter. In addition, we tried to align the attributes of members of each group to some extent, considering the ease of their response. We asked the participants to read the ELSI Perspective Map in advance and think about points of concern/interest as preparation from their side. The Citizen GI was conducted online for 90 minutes. The participants introduced themselves, and then Dr. Ichihashi presented his research in a video message. The participants then discussed their impressions and concerns and which points of the ELSI Perspective Map they were concerned about. At this point, we shared the contents of our discussion in the first individual WS with them, asking their reactions and own thoughts. We also proposed that Dr. Ichihashi or a student in the Doctor's Course participate in the Citizen GI to respond to questions from the participants.

On September 7, we prepared a draft plan for the Citizens GI, proposing the following guidelines.

- Each Citizen GI will be conducted using an online conference system for 90 minutes on a weekday evening during the last week of September 2023. For the convenience of facilitation and discussion and due to the need to carefully listen to citizens' opinions, we will not allow multiple groups to discuss simultaneously in one event by setting up breakout rooms.
- Due to time and other constraints, it will be most feasible to hold the Citizen GI with one or two groups per PJ, with each group consisting of five to six members.
- To avoid group think, we will not employ the method of comprising groups by attribute unless otherwise specified. Conversely, we will be conscious of the diversity of the participants to acquire emergent dialogue and awareness. In exceptional cases, such as DIY communities, where community members with the same attributes and a weak sense of belonging can be secured in a group and where they know each other, they could be separated by attribute.
- Although the number of participants in each event is small, we will make use of a chat system characteristic of online events. In this setting, the participants will fill in the chat section, which allows them to reflect on their thoughts, just like writing on a sticky note, present their position fairly, and leave the notes in a written record.
- We will be able to learn about changes in the participants' awareness by asking about points of concern at the beginning and end of the event, making the outcomes of the Citizen GI explicit. At the same time, picking up the final perspectives will provide the questionnaire items particularly noteworthy in a citizen awareness survey and their response alternatives.
- To create an atmosphere where the participants can speak in a free, self-centered manner, PJ-related personnel and the Forum members will refrain from joining the event, with the Secretariat limiting its participation to a minimum.
- The ELSI Perspective Map will be sent to the participants in advance to get them to think over their points of concern or interest. The Secretariat will prepare a minimum-level explanatory note for each ELSI perspective.

On September 11, Dr. Ichihashi, core members of the Forum, and the Secretariat met to determine how to proceed with the Citizen GI based on the above guidelines and draft program plan. The Citizen GI is intended (1) to provide new perspectives and viewpoints unique to citizens for the second individual WS and (2) to find the perspectives to which citizens should pay attention based on the opinions and thoughts of individual participants. During the Citizen GI, the participants introduced themselves and identified the perspectives picked from the ELSI Perspective Map as concerns they had identified in advance. Dr. Ichihashi [1] introduced his research PJs and [2] raised issues about the social impact and challenges of his research via a 5-minute video message for each topic. The participants then discussed and responded to each topic. Lastly, the participants were asked to discuss broader ELSI perspectives. Two separate video messages were prepared to promote scientific understanding and interest among the participants and stimulate societal debate, or to proceed with the event by explicitly separating the objective fact-finding and subjective opinion-expression phases. The frame reflection method was employed to discuss broader ELSI perspectives at the end of this event. This process was implemented in a 90-minute WS for iGEM program participants and Dutch high school

students to encourage comprehensive reflection on how people perceive the genome synthesis field. The first half of the WS developed the so-called First-Place Argument on the values and assumptions that underlie the analysis of issues in the development of genome synthesis. It is possible to express awareness of the issues that citizens have at the root of their lives by the answers to questions such as what is the role of genome synthesis technology in future society in the first place and what the relationship between humans and technology should be like in the first place [1]. The following perspectives were envisioned for this Citizen GI to show the participants.

- The role of genome synthesis technology in future society
- What scientists and researchers should be
- The relationship between humans and technology
- Others

Of the above perspectives, "What scientists and researchers should be" was the reflection of what had been discussed in the first individual WS of the Su'etsugu PJ, which was aimed to get the participants to envision the workstyle of being a researcher and entrepreneur, just like Dr. Su'etsugu, and the changing future image of professional scientists.

After completing the Citizen GI, we solicited questions and messages for Dr. Ichihashi from the participants. We delivered these questions and messages to Dr. Ichihashi in the second individual WS for feedback. The participants in the Citizen GI received Dr. Ichihashi's comments through this report, realizing dialogue between researchers and citizens indirectly.

(2) Results

We held the Citizen GI of the Ichihashi PJ twice online for 90 minutes each, one on September 27 and the other on September 29. A member of the Secretariat staff recruited participants using the snowball sampling method, constituting a group based on preliminary discussions mainly from liberal arts college students who had little contact with the Ichihashi PJ. We asked the participants to join the event with the video kept ON to the extent possible. However, since this event's results would be opened on the web as an event report, we advised that their faces and names might appear on the capture screen. We then arranged an appropriate measure for those who did not want to have their faces and real names appear on the screen. The Secretariat served as facilitator and recorder, and some Forum members attended with the video/microphone kept OFF. After completing the Citizen GI, we sent an honorarium to the participants.

The first Citizen GI (September 27)

We conducted a group interview with three student friends majoring in humanities. The three said they were learning about the interactions between society and humans (A), law (B), and conservation of world heritage sites (C). The following summarizes the main discussions with them.

A: I thought that genome synthesis technology could solve the problem of food shortages. However, I am not sure if I can eat artificial food served in front of me. As candy gummies are not natural but artificially produced, eating artificial food may not feel so strange if it becomes more popular.

B: There is doubt about the safety of food tampered with by humans. It also makes me wonder if artificial food tastes good in the

[1] van der Meij M.G. et al. (2018) Frame reflection lab: a playful method for frame reflection on synthetic biology. *Nanoethics* 12, 155-172.

first place. The safety of artificial food may cause problems later.

C: I believe this is groundbreaking research. This would be very good for vegetarians. On the other hand, while children today can understand culture through food education, there will be no way of providing food education to children in the future with such artifacts. This concern may lead to a loss of opportunities for cultural education.

B: We have a severe waste problem today, so it would be good to see production efficiency increase. On the other hand, inedible parts of animals and plants are effectively used for different purposes even today. I feel it could be a problem if it is related to culture.

C: I think that no ethical issues exist in the first place. I believe creatures are beings that move and use their brains like animals and humans. On the contrary, I do not feel plants and the like are life. In the same way, I believe what is created by research is not life.

A: I think about the Boundary between Life and Matter with humans at the center. For example, people want to avoid food shortages. However, food is matter and life simultaneously, so I thought it necessary to consider being at the boundary. This is the importance of thinking from the food side.

B: Concerning what researchers should be, I think that even if some act is regulated by law, what is important is not only to comply with the law but also to keep thinking about right and wrong. Specifically, it is essential to create an opportunity for researchers to exchange and compare their ethical views.

A: Concerning the role of genome synthesis technology, I think it can contribute to helping solve existing problems (such as global warming and food shortages). On the other hand, I think it questionable to tamper with something that is not a problem today.

The second Citizen GI (September 29)

Four members were invited to the group interview from a network to which liberal arts college students belong. A student learning economics and political science (D), a graduate student researching rocket engines (E), a liberal arts student learning public policy (F), and a medical student interested in intestinal bacteria and Legionella bacteria (G). The following summarizes the main discussions with them.

G: I have a simple question. If it takes decades to realize a self-propagating artificial biochemical system, it may take much longer before it can contribute to food supply. Is it possible technically?

E: The video message [1] emphasized the benefits of genome synthesis technology, but the issues not presented there are: (1) there is something weird about it; (2) it is questionable to jump from what has been continuing in the framework of nature to something novel or incomplete.

D: If eating artificial food is inexpensive and efficient, I want to try it, but (1) is it a good thing not to kill animals? Just as not eliminating deer would destroy farmland, would eating artificial food not disrupt the total ecological system?(2) Since eating food will remain a recreational activity rather than a source of nutrition, we will probably not consider eating natural products to be barbaric in the long run.

F: Eating artificial food will spread where it can, such as in Japan with a low food self-sufficiency ratio, and will not spread where it cannot. I think the appearance of artificial food matters a lot.

E: The indicated definition of Life is algorithmic. However, I do not see it that way or consider something without its own will to be a living organism.

F: Even if the artificial food is not a living organism intuitively, it might provoke controversy. Unlike other issues, the issues of Life are more human and vary depending on an individual's thoughts and beliefs and how the individual interacts with living organisms, which may make discussing such issues complex. Some people are grateful for eating, and some are not.

D: As the object becomes closer to humans, it will generate a beneficiary relationship with humans, and may become something for us to be wary of.

G: I think it depends on whether or not there is a feeling of strangeness arising from fundamental human values. It depends on

whether the object appears to have subjective consciousness when viewed from the outside. Plants are generally believed to be unconscious, so humans do not have a sense of resistance against creating new plants.

E: I think the items forming a watershed between people's acceptance and rejection are cost, environmental benefits, or branding. Because of the risk of a complete transition to artificial food, another important point would be whether turning back half way through is possible. Also, this is not a comparison between nature and humans because humans are part of nature.

In the Citizen GI, we asked each participant to write in the respective chat sections the ELSI perspectives in which they became interested after reading the ELSI Perspective Map (hereinafter "Pre-Citizen GI"), and write the ELSI perspectives they thought important after viewing and discussing the video message (hereinafter "Post-Citizen GI"). Concerning the chat sections for Post-Citizen GI, we told the participants that they did not necessarily have to write strictly according to the ELSI Perspectives Map. Table 2 shows the results.

Table 2 ELSI perspectives in which Citizen GI participants are interested (Ichihashi PJ)

	Pre-Citizen GI	Post-Citizen GI
A	Dignity of Life, Food Safety	Boundary between Life and Matter
B	Concept of Eugenics, Genetic Recombination to Remain in Offspring	Protection and Prevention of Outflow
C	Protection of Traditional Farming Methods	Food Safety, Secret Patents, IP Protection/Prevention of Outflow
D	Safety of New Medical Care, Concept of Eugenics	Protection of Native and Indigenous Species, Boundary between Life and Matter
E	Genetic Modification/Genome Editing, Safety of New Medical Care, Concept of Eugenics	Cost, Environmental Benefits, Branding, Possibility to Turn Back Half-way Through
F	Biosecurity, Biosafety, Containment of Experimental Samples, Protection of Native and Indigenous Species, Concept of Eugenics	Dignity of Life, Concept of Eugenics, Biological Weapons, Protection of Native Species
G	Containment of Experimental Samples, Biosafety, Biological Weapons, Concept of Eugenics	Dignity of Life, Food Safety, Biological Weapons

2.1.3 The second individual WS

(1) Process

On October 3, Dr. Ichihashi, core members of the Forum, and the Secretariat held a preliminary meeting to discuss the details of the second individual WS and how to proceed. In the meeting, they agreed that having a diagram that ties each ELSI perspective together and a list of ELSI perspectives in clear language would be better. Based on the agreement, the Secretariat revised the presentation materials for the second individual WS accordingly. The following three are the ELSI perspectives we envisioned in advance.

1. Non-algorithmic Views of Life

The Darwinian Evolution-Enabled Autonomous Chemical System is an algorithmic definition of life. However, several Citizen GI participants did not view life with such a definition but had instead views relying on consciousness and mobility. Just as appearance and texture are important for food, and just like those who are grateful for eating and those who are not do not depend necessarily on their thoughts and beliefs, attitudes toward life and artifacts are in no small part based on previous contact with the objects (ontological relationship). However, attitude formation based solely on sensations such as "weirdness" can easily lead to discrimination and the concept of eugenics. Therefore, fostering a balanced view of life between logic and sensation may be necessary, including what branding should be.

2. Anthropocentrism and the Anthropocene

The above view of life needs to be supplemented with "for humans." Humans arbitrarily determine what to eat, what not to eat, what to keep alive, and what to kill. We can say that due to such anthropocentrism, no real nature now exists for humankind, which has altered the Earth's nature and left its mark even on the geological scale. To what extent are highly human solutions we call technological advancement effective in addressing global-scale issues like climate change and food shortages? Is there a risk that the evolution of artificial species will cause a loss of species diversity? Are there any contradictions or risk trade-offs against the proposition of a sustainable society? What does the whole concept of anti-anthropocentric R&D look like?

3. Irreversibility

The discussion so far has covered little of how to respond to the irreversible effects of research and innovation advancement on society. In Japan, little progress has been made in examining risks to the survival of humankind. Is this because assuming unexpected risks is a risk to social reputation, or is it simply because of the unacceptably high social costs required to discuss and prepare for events that can hardly be predicted and whose impacts are enormous? In this respect, to what extent should the government and society allow research on genome-related gain-of-function (GOF), for example?

Meanwhile, What Communication with Citizens Should be was added as a reference to the critical perspectives presented during the preliminary meeting, albeit the meta-related perspectives related to what the citizen participation process should be, instead of ELSI perspectives related to the Ichihashi PJ.

4. What Communication with Citizens Should be

Some Forum members wanted to continue communicating with citizen participants through the Citizen GI. How can such Forum members discuss with the citizen participants who have understood and acquired the knowledge of their research? How can we know if those citizens expressed their opinions only relating to the Ichihashi PJ or if they expressed their views with some knowledge of gene drives? What actions should we take to continue communicating with citizens on our research? When, in an attempt such as this Citizen GI, some perspectives were selected based on a misunderstanding, should we provide a more detailed technical explanation to avoid such misunderstandings when we present them to citizen participants?

Based on the above perspectives, we created an ELSI Perspective Map for the Ichihashi PJ as shown in Figure 3. Unlike previous ELSI Perspective Maps, this map shows arrow-connected relationships between the main ELSI perspectives: 1) Non-Algorithmic View of Life, 2) Anthropocentrism, and 3) Irreversibility, and their derivative perspectives, with the three perspectives laid horizontally. However, this map was created to help understand the connections between the perspectives in a panoramic view, and the size and position of each circle do not have any particular meaning.

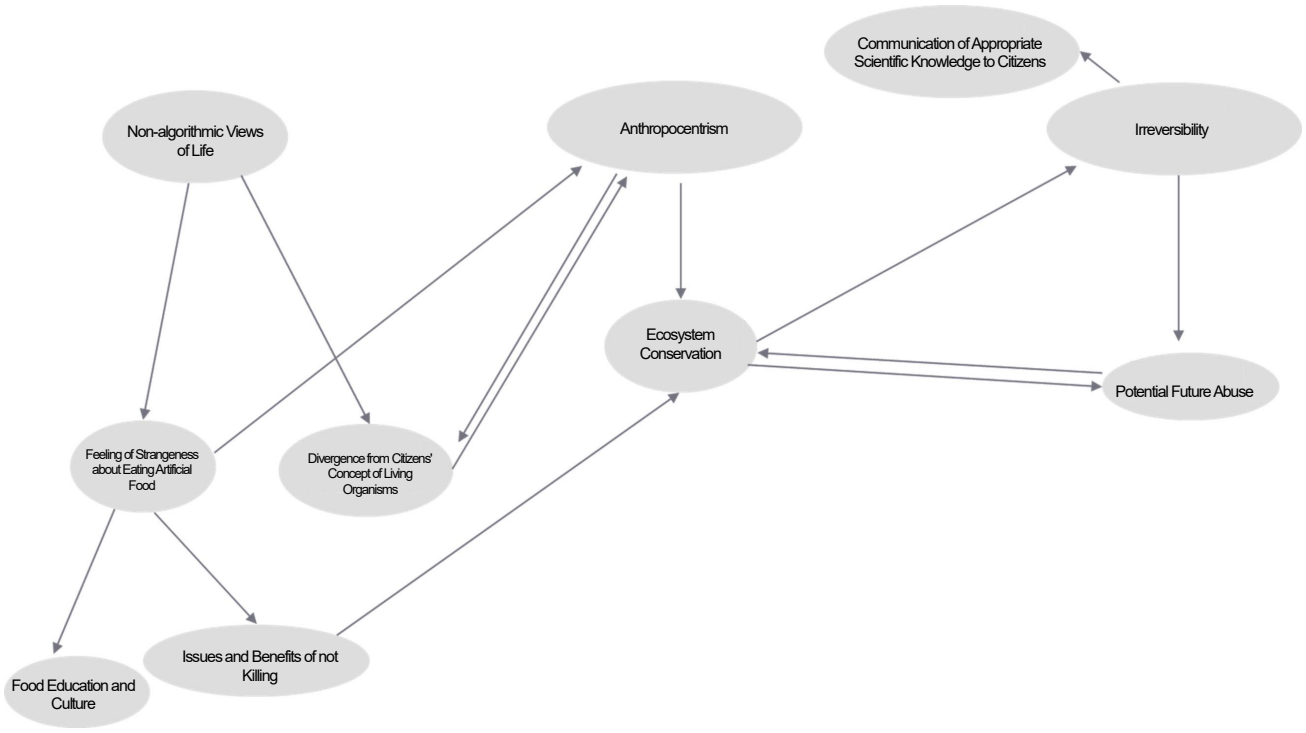

Figure 3 ELSI Perspective Map for the Ichihashi PJ

（Source: Prepared by the Secretariat of Forum on Genome Ethics）

The second individual WS of the Ichihashi PJ was held from 13:00 to 16:00 on October 20, 2023, in a hybrid meeting between the Ichihashi Lab at the University of Tokyo and online. This WS was organized by the Forum and operated/facilitated by the Secretariat. In the first half of the WS, we shared the results of the Citizen GI summarized by the Secretariat, presented the ELSI perspectives and ELSI Perspective Map (Figure 3) based on the first WS and Citizen GI, and then exchanged opinions. In the latter half of the WS, the core Forum members facilitated a deep discussion of the ELSI perspectives.

(2) Results

First, the Secretariat reported the summary of the Citizen GI discussions. Then, the Secretariat read messages and questions from the Citizen GI participants, and Dr. Ichihashi responded orally to each question. Table 3 shows the results.

Table 3 Messages and questions from Citizen GI participants and responses to them (Ichihashi PJ)

Messages and questions from Citizen GI participants	**Responses from Dr. Ichihashi (excerpt from the minutes)**
When I heard the word genome, I used to get negative images in my mind, such as designer babies. However, after viewing Dr. Ichihashi's video message, I realized many possibilities and benefits. Responding to the question of "what is essential in the interaction between researchers and genomes," I thought the answer would be the researchers' sense of ethics. However, I wondered how Dr. Ichihashi would respond to this question as an incumbent researcher. Lastly, I	I agree with you. A sense of ethics is essential. A law-abiding spirit is equally important. I will conduct my research within the law.

greatly appreciated Dr. Ichihashi's valuable talk.	
Dr. Ichihashi's research details were fascinating. This technology would benefit Japan, where the agricultural population continues to decline. I wanted to ask Dr. Ichihashi through this interview who will be allowed to access this technology when it becomes a reality. I wondered if this technology would be commercialized or managed for use only by researchers.	This technology will find its way into commercialization without a doubt. I am not happy that only researchers can use this technology.
Dr. Ichihashi's research is fascinating because of its novelty and potential. Amid growing anxiety about the future due to many social issues being brought to the surface, Dr. Ichihashi's research can provide a clue to relieving such concerns. In Dr. Ichihashi's presentation, I was impressed by the question of whether something produced through research can be called life. I personally thought in vain about whether there were differences between life and matter other than the Presence/Absence of Evolution, which led me to think deeply about what life is in the first place. Lastly, I sincerely wish Dr. Ichihashi success and progress in his research. I am grateful for this opportunity.	
When ethically gray research such as genome synthesis is possible or when starting such research, is there a phase or practice in research to verify the ethics?	I am not involved in such a phase or practice as an individual researcher. However, I get such verification done by JST and the Forum, so I believe such steps are already in place.
Dr. Ichihashi mentioned that it would take ten years before the production of sugars and proteins is commercialized using in vitro autonomous systems. What are the bottlenecks to overcome in the commercial production process?	There are two bottlenecks. One is the lack of ribosome synthesis. The other bottleneck is entirely a problem with yield. The existing in vitro autonomous systems can produce polynucleotides and proteins to some extent, but the yield is as low as 10%. It must be improved to 100% to enable multiplication. This is where we will need a relatively large amount of work by trial and error.
I appreciated that you gave me a precious opportunity to deepen my understanding of genomes, a topic unfamiliar to me as a student majoring in humanities despite its great importance for future society. Dr. Ichihashi explained a future society where genomes are widely used, and it was very interesting and persuasive. I am curious about the following two points: [1] how would the ecosystem be affected if humans stopped killing plants and animals by using genomes to produce food, and [2] what do humans expect from dining in the first place, and would the expectation be fully satisfied using genomes? I want to know Dr. Ichihashi's thoughts on these two points. I would appreciate your comments.	[1] It is probably like returning to the state before there were any humans. So, there should be apparent impacts, but I feel such a world would be OK. [2] Humans expect taste, quantity, and nutrition from food, and they do not care much about whether the food is derived from creatures or not. Thus, humans' expectations of food will be completely satisfied.

In the Q&A session following the report on the results of the Citizen GI, there was a question about whether or not any participants considered eating from the perspective of culture or sustainability. We responded that there were participants who did not necessarily consider food based on whether it was natural or artificial, including student C on September 27, who researched World Heritage sites at college and touched on topics such as agriculture and nutrition education. Concerning the statement of a Citizen GI participant that the definition of life was "algorithmic," we confirmed that Dr. Ichihashi defined life as the Darwinian Evolution-Enabled Autonomous Chemical System in his video message, about which that person expressed it as algorithmic. In

Dr. Ichihashi's video message, only Darwinian Evolution was algorithmic, and Autonomy and Chemical Systems are not usually referred to as algorithmic. A Forum member (Dr. Tanaka) interpreted that there might be a difference in generational culture behind that statement due to the influence of programming education since elementary school days.

We then explained the presented draft of ELSI perspectives and maps, summarized the Citizen GI, and discussed the ELSI perspectives for the upcoming joint WS. As to the Citizen GI, the scientific understanding around the Ichihashi PJ and what life should be were not treated as major discussion themes. We reflected on the fact that comments from Citizen GI participants had been centered on the food we envisioned as application research targets. As exemplified by Dr. Ichihashi's comment, "The participants did not empathize much with my point that we will not have to kill as many creatures as today," the results of the Citizen GI showed that Dr. Ichihashi and the participants were not necessarily on the same page in awareness of the issues. Dr.Matsuo said that the response that awareness of food and sustainability seemed relatively low might be unique to Japan. In Europe, for example, concepts and values such as planetary health, which link to diet, the environment, sustainability, and even the global environment, have gained a certain degree of public support and are also under political discussion. Dr.Matsuo inferred that there might be differences in awareness between countries and regions.

Citing the case of the accident at the nuclear power station in Fukushima, Dr. Tanaka expressed his view that while citizens were asking for "controllability" in the wake of the accident as a safeguard and policy compensation for the system, the citizen GI participants did not make similar arguments as if their sense of societal involvement was low. However, Dr. Tanaka also expressed his concerns that while cultured meat, insect food, and genome-edited food products were pressing ELSI perspectives, the accompanying problems with widening disparity and fairness remained distant issues.

There were unexpected discussions about the significance of the Citizen GI that would not be encountered in experts' public forums, including a debate on global-scale issues, such as climate change, and topics with extended time frames, such as world heritage sites, despite the main theme being genome synthesis. Dr. Shinomiya analyzed this situation as "just like agreeing to the general principle but disagreeing about the details, the participants' responses might be divided into macroscopic and microscopic views, such as environmental issues and food self-selection, respectively." We exchanged our opinions to link the two divided views, including that a simple scientific or solution-oriented view that "since humans have changed the world this much, we can change the world through science" might be gaining power among the young generation, which sees the Anthropocene as the possibility of global-scale manipulation by individuals.

We then discussed how to proceed with future joint WS, including presenting the perspectives of the Ichihashi PJ and Su'etsugu PJ and that it is preferable to put these perspectives into specific actions, which Dr. Nakamura had pointed out in the previous WS.

In the latter half of the WS, we looked for those perspectives that we should discuss in depth in the following joint WS. We raised several issues, such as the responsibility and faith of scientists and the procurement of raw materials for basic research. However, the most intensive discussions were made on the view of life and its related issue: the designation of research targets in the Ichihashi PJ. Concerning the Artificial Biochemical System advocated by Dr. Ichihashi, he was unsure that calling it a living organism was appropriate. He was concerned that some people might perceive the term "living organism" as dangerous. No living organisms are without cell membranes, and the term Cell-Free originated from microorganisms with membranes. For this reason, Dr. Ichihashi believed it would be more appropriate to call what he was developing "artificial biochemical systems." As his development did not have cells, unlike microorganisms, it could be seen as a simplified microorganism system or a complicated chemical reaction system. There were several opinions about the conflict over such wording. In response to this conflict, Ms. Hibino proposed that instead of deciding whether it is a chemical system or microorganism-like, we instead send out the message that it is a gray area in the first place. Also, Dr. Nobuhara emphasized the necessity and significance of indicating that *it is gray* as the result of thorough discussions by the parties concerned from the upstream R&D stages without placing the burden only on Dr. Ichihashi.

Dr.Matsuo commented that so-called bio-manufacturing activities might also involve this conflict over wording. In response, Dr. Nobuhara questioned whether the word "bio" might be derived from being a living creature. On the other hand, there were other exchanges of views, including the inference that the term "bio" might refer to the existence of the systems that microorganisms possess rather than the existence of the microorganisms themselves (Dr. Mikami and Dr. Shinomiya) and the opinion that using bio-based materials might also be a contributing factor (Dr.Matsuo). Furthermore, "bio" could be rhetoric that evokes nature-friendly and sustainable products that differ from what is produced industrially. According to Dr. Kamisato, these questions can be classified into three groups: [1] What is the fundamental technology?; [2] How does society understand the technology?; [3] How is the technology branded in the design phase before budgeting, industrialization, and commercialization?

Regarding future ELSI perspectives that the Ichihashi PJ can envision, Dr. Tagawa foresaw that those perspectives would be OK at the stages where our research is called chemical synthesis systems. However, a whole different set of possibilities might emerge in the stages where evolutional forms of research become available, including a risk of abuse. Dr. Tagawa also commented that researchers may have to consider this risk thoroughly.

2.2 Su'etsugu PJ

The Su'etsugu PJ refers to the CREST Cell-Free On-Chip Genome Synthesis project, for which Dr. Masayuki Su'etsugu (Professor, College of Science, Rikkyo University) serves as Principal Investigator. The PJ is to develop Cell-Free On-Chip Genome Synthesis using in vitro genetic reorganization technology and microfabrication/manipulation technology. In addition, the PJ is aimed to implement the Make, Activate, and Evaluate cycle at high speed and low cost by evaluating the process from transplanting synthetic genomes into cells up to their activation.

2.2.1 The first Individual WS

(1) Process

On June 26, 2023, Dr. Su'etsugu and core Forum members held a kickoff meeting to discuss the details of the WS and how to proceed. In the meeting, Dr. Siomi, who oversees the Genome Synthesis Area, said he hoped to see new biology, new species, and the process of species differentiation with the help of genome synthesis technology. However, he added that he wanted to communicate this approach carefully to avoid causing misunderstanding among the general public as if we were creating a monster. Dr. Su'etsugu advised the Forum members that he wanted to deepen their discussions on two points: [1] How to market handy genome synthesis kits for very-long-chain DNA appropriately; [2] The need for additional ethical issues when designing new species using genomes. Furthermore, Dr. Su'etsugu raised questions about at what point of time the "artificial" or "synthetic" would be removed from artificial cells and synthetic cells, and at which stage of the technology development the Cartagena Act would be introduced, and applications for genetic recombination would be accepted. Dr. Su'etsugu also expressed his belief that research on advanced technology, among other things, would require adjustments in the legal system and people's concept of values. In light of the above discussion, the Secretariat envisioned the ELSI perspectives listed in Table 4.

Table 4 ELSI perspectives envisioned for the Su'etsugu PJ

Biosafety / Biosecurity [top right on the map]

- Dr. Su'etsugu developed a technology to synthesize long-chain DNA by combining DNA oligos around 100 bases long. At present, DNA oligos are difficult to handle. DNA oligos can be stored in a stable condition in a cell.
- Even viruses can be manufactured using DNA oligos. DNA oligos enable anyone to recombine genes (DIY biotechnology).

IP Protection and Prevention of Outflow [center left on the map]

- DNA synthesis kits could be misused. Large companies have the advantage of investing huge money instantly to accelerate their research.

Scientific Literacy [bottom right on the map]

- It is necessary to use IP according to the Cartagena Act (regulations on genetic recombination). Understanding of this rule must be promoted.
- This concerns literacy-related issues that arise when explaining the safety of gene-recombined agricultural products (during general discussions).

（Source: Prepared by the Secretariat of Forum on Genome Ethics）

The first individual WS of the Su'etsugu PJ was held from 14:00 to 18:00 on August 24, 2023, in a hybrid meeting between the Su'etsugu Lab at Rikkyo University and online. This WS was organized by the Forum and operated/facilitated by the Secretariat. Dr. Su'etsugu introduced his research details in this WS, followed by a lab tour. We then discussed the points and direction of the ELSI perspectives of the Su'etsugu PJ in depth while looking at the ELSI Perspective Map. The Secretariat then reported on how to proceed with the Citizen GI, which the participants confirmed.

(2) Results

Dr. Su'etsugu initially researched bacteria and genomics in molecular biology and then came to research cellular organization and cell replication reorganization after moving to Rikkyo University. He started a new company named OriCiro based on the technology he developed in this project. In January 2023, the company was sold to Moderna and became Moderna Enzymatics. Motivated by his desire to explore what life is, Dr. Su'etsugu is pursuing his research focusing on the central dogma to understand self-replication and evolution, which are the definitions of life. Dr. Su'etsugu is interested in something like Doraemon's secret tool "Genesis Set," in which living organisms evolve independently to create a second Earth. Specifically, he tried to increase the amount of ring-shaped genomic DNA in *E. coli* using 26 kinds of proteins. At OriCiro, he packaged all the necessary materials and methods and sold them as genome synthesis kits.

In the discussion with the Forum members, Dr. Su'etsugu received several questions, including the need for genome synthesis kit sales, users' applications, and the reason for having withdrawn from the kit sales as a corporate strategy. Dr. Su'etsugu explained that he first thought it would be good to sell genome synthesis kits so that anyone could use them, which would help spread the technology worldwide. However, the reagent market was not large enough for his business to continue for long. Thus, he shifted his focus to creating a drug discovery platform. In the discussion surrounding the definition of life, Dr. Nobuhara questioned whether Dr. Su'etsugu would call memes in digital space and things that increase and evolve in a material-only world living organisms. Dr. Su'etsugu said that his senses would consent to it, but added that life would still require a metabolic system. Looking back on the discussions so far, Dr. Siomi confirmed that although the Genome Synthesis Area is considered application- or exit-oriented, it is basic research aiming to reorganize the behavior and actions of living organisms appropriately. Dr. Siomi also expressed the view that since ordinary people only see the final accomplishments, it is essential to get them to understand the discussions that bridge applied research and basic research, the mechanisms that support basic research, and the diverse applied research produced as accomplishments, when they do not know about the 20 years of achievements from the preceding basic research.

Regarding the areas and perspectives to be discussed in depth in the second individual WS and the Citizen GI, some suggested that we clearly define the significance of citizens participating in the Citizen GI. This is probably due to a motivation to discover what professional researchers could not see. There were several other proposals, such as requesting opinions about stopping the genome synthesis kit sales from the DIY community, what scientists think about returning their accomplishments from government-funded scientific research to society, and asking the citizens whether they would want to know that.

2.2.2 Citizen GI

(1) Process

The Citizen GI is conducted to collect the opinions of non-WS participants so that we can discuss a wide range of viewpoints in the second individual WS. The Citizen GI also aims to pick up opinions about topics, characteristic of the Su'etsugu PJ's research activities and in which Dr. Ichihashi is very interested, among the ELSI perspectives listed in Table 4, which are expected to be discussed in the second individual WS.

The draft theme the Secretariat proposed in the first WS on August 24 was: "How should we consider the balance between IP protection and open access in government-funded projects, with case examples of activities toward the development of research accomplishments, such as those from the acquisition of IP based on JST research accomplishments to venture startup and the sale of the venture to US-based Moderna?" The target citizens we envisioned included the DIY community, IP and legal professionals, and students of science and biotechnology. We asked the participants to read the ELSI Perspective Map in advance and think about their points of concern and interest. In addition, we shared basic information related to IP with the participants in advance, such as the policy flow of the Bayh-Dole Act and one selected case whose IP handling was in the news, such as blue LEDs.

On September 13, Dr. Su'etsugu, core members of the Forum, and the Secretariat met to determine how to proceed with the

Citizen GI based on the draft plan of September 7 shown in Section 2.1.2 above. The objectives and method of proceeding with the Citizen GI are similar to those for the Ichihashi PJ.

(2) Results

We held the Citizen GI for the Su'etsugu PJ three times online for 90 minutes each, on September 25 and 28 and October 5. A member of the Secretariat staff recruited participants using the snowball sampling method. We also asked Dr. Iwasaki to recruit participants from the DIY community. He is a core member of the Forum and has longstanding connections with that community.

The first Citizen GI (September 25)

We conducted a group interview with three science students/researchers: A graduate school student of bioscience who studies insects coming to buckwheat flowers (A), a university teacher of theoretical physics (B), and a medical student (C). The following summarizes the main discussions with them.

A: The term "genome synthesis" sounds so magical that some may think it would cause major ethical issues. This technology is excellent. Ethical issues have been discussed for years, so we only need to continue the discussions.

B: Many researchers do not think about how to return their research accomplishments to society. On the other hand, the general public who feel a sense of distrust may sometimes consider the adverse effects of research. The general public needs people to translate the significance of research for them.

B: Personally, the most important thing is that excellent technologies will spread quickly. On the other hand, I would feel it questionable if the research receives funds from Japan over the research period but does not return its accomplishments to the country.(Concerning how much of its accomplishments should be returned to Japan) the system requires research to satisfy its performance target. In the case of research grants, for example, that performance target is the submission of its research report. If research accomplishments are not returned to Japan and are outside the system, we can only escalate public sentiment by changing the majority voice through political action.

C: I am not sensitive to ethical issues in the technology itself. No ethical issues are involved in figuring something out and exploring it. Since ethical issues arise when applying research accomplishments, it seems better to proceed with this discussion by separating research from application. On the other hand, since there are cases where the name of the technology may evoke its application, the necessary regulations should be considered early on.

A: From a scientist's viewpoint, the acquisition of Japanese businesses by US-based companies does not matter. However, if we want Japan to remain a developed country, and in the context of Japanese pride, I cannot necessarily say it does not matter. It is sad, but there are no other options.

C: I am curious about the comparison with PCR. I am intrigued by the superiority of this technology to the existing technology.

A: The diversity of scientists is called for as what researchers are supposed to be. On the other hand, looking at the researchers around, the number of sharp researchers is decreasing because society appears to expect everything from them.

C: There are limits to regulations, so sharing a sense of ethical rights and wrongs is critical. It is also essential to create such an environment. Currently, we see the images of right and wrong fixed, leading to few debates among scientists.

The second Citizen GI (September 28)

Thanks to the call by Dr. Iwasaki, seven members of the DIY community participated in the Citizen GI. The seven members

consisted of the operator of BioClub[2] from Austria specializing in media art and biological art (D), the founder and operator of Japan's first community bio-lab at the Yamaguchi Center for Arts and Media (YCAM), who is concurrently working as a university teacher (E), a musician interested in bioinformatics, who is a system engineer by profession and a regular BioClub member (F), a Ph.D. student belonging to the Faculty of Art and Design at their university, who creates artworks using luminescent bacteria (G), a regular BioClub member who is a systems engineer but also researches miso (H), a contemporary artist in the UK who is interested in the theme of genome editing (I), and a science communicator/writer and medical book editor who has covered DIY biotechnology in their career (J). The following summarizes the main discussions with them.

H: I am concerned about how the boundary of living organisms is defined. If something is capable of autonomous reproduction, it may be considered a living organism.

G: There are many reasons why legislation is needed. I can understand it is better not to conduct research that might cause irreversible situations. On the other hand, there are things that we can only understand by actually going out to take a look. This point is also crucial when we create artwork.

F: Unlike IT and the like, the scope of consequences of biotechnology violating the law could be much greater, and the resulting adverse effects cannot be figured out immediately. Since the Earth cannot be restored once destroyed, synthetic biology research activities must be conducted outside the planet (or in an environment where complete physical containment is ensured).

E: Because synthetic biology has a negative image, researchers must take the initiative to learn and practice bioethics.

I: Not only technology but also human resources have moved overseas. This situation highlights the importance of funding. The future of Japan hinges on how research institutions can generate funding.

F: Japan is losing power. One reason is the lack of education to make people prouder of being Japanese.

E: (As a method of allowing amateur researchers who do not belong to research institutions or companies to use genome synthesis kits) introducing a licensing system might make sense.

G: (Concerning the topic of technology and human resources moving overseas) the situation is attributed to the fact that many technologies cannot be completed within Japan due to budgetary constraints and the slow approval speed. Instead, it would be better to have research that finds its significance in being conducted slowly.

E: If I think of experts working together then it is possible they can wear two hats. However, just like citizen science, I want to consider hats that everyone can wear together.

J: In Japan, there seems to be no way for those who used to conduct experiments at university to be able to do the same again after going out into the world. The theme of expanding the base of science has been around for some time. To make it happen, increasing the opportunities for "reskilling" is essential.

The third Citizen GI (October 5)

We conducted the third Citizen GI by inviting five people, including attorneys and a patent attorney recruited using the snowball sampling method, and students and DIY biotechnology professionals assigned to this third-round event due to scheduling conflicts. The five were a corporate attorney (K), a student studying fetishism in anthropology (L), a patent attorney working on data science for a pharmaceutical company (M), a corporate attorney (N), and a DIY biotechnology professional involved in woodworking, electronics, and other mobile device manufacturing (O). The following summarizes the main discussions with them.

[2] A community bio-lab operated on the 2F of FabCafe in Shibuya, Tokyo, which is one of the DIY biotechnology bases in Japan.

O: I am interested in animal welfare from the standpoint of living in this world without knowing about the ethics of non-human living organisms and their benefits.

L: Genome synthesis for whom? Whom will genome synthesis make happy? I am interested in human life and death but wonder if living a long life is good.

N: I do not know the basics of genome synthesis, so I do not understand its technical side. I can expect much from artificially produced substances but feel fearful at the same time. Probably, my fear comes from not knowing or having any idea what is happening.

M: This is a difficult subject even for me, who has studied molecular biology, but can find it amazing in some vague way.

L: The word "synthetic biology" has a strong impact. It feels like something beyond human knowledge and untouchable. Creating artificial viruses depends on the conscience of scientists. What are the standards for research ethics or boundaries between other technologies?

O: While the benefits of genome editing, for example, can be identified quickly, verifying how the technology will work in the long term or different environments seems complicated. Is designing from scratch based on the assumption that "there is nothing that humans cannot know?"

M: If only Moderna had approached the startup genome synthesis kit business instead of Japanese companies, how should we judge it?

K: It appears contradictory to prevent misuse by having a letter of approval signed and be acquired by foreign capital. It must be challenging to balance these two options.

O: Although not a scientist, I am involved in DIY biotechnology and want to become more familiar with DNA and deepen my understanding even if only a little.

L: How is the mental health of scientists and researchers protected? Efforts for leading-edge research that the public cannot understand may put a heavy burden on scientists and researchers.

In the Citizen GI, we asked each participant to write in the respective chat sections the ELSI perspectives in which they became interested after reading the ELSI Perspective Map (hereinafter "Pre-Citizen GI"), and write the ELSI perspectives they thought important after viewing and discussing the video message (hereinafter "Post-Citizen GI"). Concerning the chat sections for Post-Citizen GI, we told the participants that they did not necessarily have to write strictly according to the ELSI Perspectives Map. Table 5 shows the results.

Table 5 ELSI perspectives in which Citizen GI participants are interested (Su'etsugu PJ)

	Pre-Citizen GI	**Post-Citizen GI**
A	Reduction of Environmental Impact	Dialogue with Citizens on Ethical Issues Specific to Genome Synthesis
B	Dialogue with Citizens	Open Access
C	Application to Humans, Safety, Infection Control Measures	Application to Humans, Comparison with PCR
D	Legal Status of Modified Life	
E	DIY Biotechnology, Scientific Literacy, Dialogue with Citizens, Reduction of Environmental Impact, Circular Economy	
F	Reduction of Environmental Impact, Genetic Recombination to Remain in Offspring and Genome Editing	
G	DIY Biotechnology, Biosafety, Biological Weapons (design/complete synthesis)	

H	Boundary between Life and Matter, DIY Biotechnology, Application to Humans
I	Application to Humans, Safety, Impact on Offspring, Concept of Eugenics, Legislation on Ethical Aspects
J	Open Access, DIY Biotechnology, Biosecurity
K	Impacts on Human Body and Health, Ownership of Technology and IP
L	Impact of Technology and others (Information Disclosure, View of Life, etc.)
M	Medical Development
N	Medical Development
O	Application to Humans (Concept of Eugenics, Boundaries between Enhancement and Medical Care), Animal Welfare (concerning setting boundaries between applying/not applying ethics to living organisms other than humans simultaneously)

* Due to the relatively large number of participants in the second and third Citizen GIs and their fulfilling discussions, we judged that we needed more time after the events to confirm the ELSI perspectives in which they had become interested. For this reason, unlike the first Citizen GI, we did not ask them for feedback.

2.2.3 The second individual WS

(1) Process

On October 2, Dr. Su'etsugu, core Forum members, and the Secretariat held a preliminary meeting to discuss the details of the second individual WS and how to proceed. The following three were the ELSI perspectives the Secretariat envisioned in advance.

1. Versatility of the Term Genome

Japanese people's awareness of Genome expressed in katakana is lower than that of the words Gene and DNA. According to a survey, whereas 55% of people know the term, no more than 15% know its meaning.[3] This fact could be turned into research and industry strategies. As far as food products are concerned, genome editing is more limited in ownership than genetic recombination at this stage, and analysis shows that such strategies have successfully established a neutral image because of positive framing in news report coverage and lower social risk awareness.[4] The unfamiliarity of the word Genome could lead to the spreading of a sense of universalism and a positive image. On the other hand, there is a possibility that some social event related to Genome could trigger fear among people.

2. Significance of Japan in Research

Why is Japan investing in genome synthesis research? Not limited to genome synthesis, Japan's science, technology, and innovation policies appear to have only general and vague exit strategies, such as promoting basic research and creating social value. Furthermore, we recently saw genome synthesis research subjected to strong technological sovereignty and economic

[3] Ishiyama, I. et al. (2008) Relationship between public attitudes toward genomic studies related to medicine and their level of genomic literacy in Japan. *American Journal of Medical Genetics Part A* 146A, 1696-1706.

[4] Masanari FURUHASHI (2022) "A Study on the Social Amplification of Risk in the Introduction and Diffusion of Innovations: Textual analysis of genetically modified foods and genome-edited foods as a case study," The Journal of Science Policy and Research Management, 37(4), 418-431.

security pressures. This is why many citizens must be ambivalent about Moderna's acquisition of the genome synthesis kit business. In the end, this situation may be attributed to the significance of Japan in promoting research "As Japan" remaining vague about whether it is positioned in the hegemony of strengthening basic research capabilities and national security or whether it is positioned in the cooperation of contributing to the international market and society by ensuring the diversity of resources and output.

3. What hats that everyone can wear together should be

We are concerned that a society that requires researchers to wear two hats and act both as researchers and entrepreneurs also demands excessive competence from those researchers and places a heavy burden on them. In today's research environment, researchers must already be versatile in research and education, industry-academia collaboration, councils, science communication, and many other areas. We may have to change the size of the hats instead of increasing their number. In this sense, we wonder what type of hats there will be for citizen science like DIY biotechnology. In addition, diverse stakeholders will inevitably make the same journey on industrialization, security, and communication in the genome synthesis area where integration occurs between biotechnology, which has a sizeable spatial-temporal impact, and digital technology, which provides high accessibility and speed. We wonder if traditional sectors are ready to cope with such changes. There may be a problem that those who wear the hat first continue to wear it without taking it off (or being able to take it off), deforming its shape to the extent that other persons can no longer wear it.

We also added the Difficulty of Public Discussions as a reference, not to the ELSI perspectives related to the Su'etsugu PJ, but to other perspectives raised in the Citizen GI.

4. Difficulty of Public Discussions Concerning Ethics

As with Germany, there is no national forum for bioethics deliberations in Japan, and the government's Experts Panel on Bioethics of the Council for Science, Technology and Innovation (CSTI) has long been a forum for technical discussions on specific individual topics. On the other hand, we do not know of any instances of scientists compiling guidelines through bottom-up discussions, as is the case with the Asilomar Conference. The limited availability of Japanese-language journals that publish scholarly debates among researchers explains the difficulty of publicly displaying principles or opinions in a culture where assertion and personality are inseparable. How can we have more open discussions beyond individual issues and projects, including the Forum on Genome Ethics?

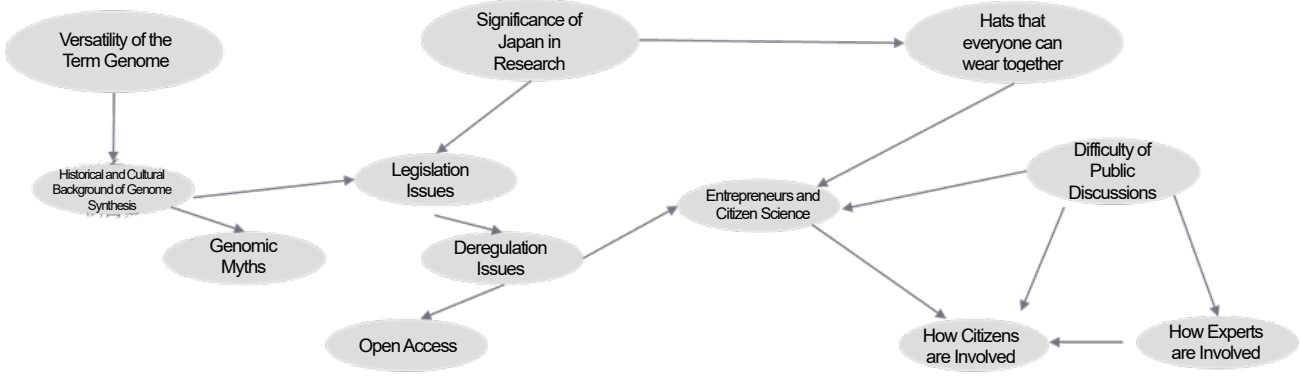

Figure 4 ELSI Perspective Map for the Su'etsugu PJ

（Source: Prepared by the Secretariat of Forum on Genome Ethics）

Figure 4 shows the ELSI Perspective Map for the Su'etsugu PJ. As described earlier, the Figure shows the derivative perspectives from the main ELSI perspectives, such as Versatility of the Term Genome, Significance of Japan in Research, and Hats that Everyone Can Wear Together, and the schematic relationship among these perspectives. The Figure was created to facilitate the discussions in the second individual WS.

The second individual WS of the Su'etsugu PJ was held from 09:00 to 12:00 on October 16, 2023, in a hybrid meeting between JST Tokyo Headquarters and online. This WS was organized by the Forum and operated/facilitated by the Secretariat. In the first half of the WS, we shared the results of the Citizen GI summarized by the Secretariat, presented the ELSI perspectives and ELSI Perspective Map (Figure 4) based on the first WS and Citizen GI, and then exchanged opinions. In the latter half of the WS, the core Forum members facilitated a deep discussion of the ELSI perspectives.

(2) Results

First, the Secretariat reported the summary of the Citizen GI discussions. Then, the Secretariat read messages and questions from the Citizen GI participants, and Dr. Su'etsugu responded orally to each question. Table 6 shows the results.

Table 6 Messages and questions from Citizen GI participants and responses to them (Su'etsugu PJ)

Messages and questions from Citizen GI participants	**Responses from Dr. Su'etsugu (excerpt from the minutes)**
The research challenging the boundaries between living organisms and matter is super exciting! I have many questions to ask, including whether the genome of non-circular eukaryotic organisms will be synthesized, what kinds of materials will be needed at minimum for the cells to fulfill their functions, and what kind of problems will occur if the unnecessary portions of the genome are removed. Please keep up the excellent work with your research!	
I am very intrigued by Dr. Su'etsugu's research details. While understanding that solving social issues is a critical viewpoint, I want you to pursue research that will excite many people. (It may sound intrusive for an outsider to say something about research details conducted by other scientists ...)	
I would be happy to get more details of the genome synthesis kit, such as the differences from PCR.	PCR is short, and even a single gene can amplify. You also need a device to raise and lower the temperature. The technology I am developing can increase circular DNA with the ring shape maintained. This process can amplify a genome with roughly several million base pairs through only heating. The accuracy is also high.
Thank you for the lecture. I learned a lot from Dr. Su'etsugu's straightforward presentation of research details, which was easy-to-understand even for an outsider like myself. The most interesting point was that all ATGC databanks have become full, making conducting gene synthesis based on such databases	

theoretically possible. The research combined with its ethical aspect made it a deeply interesting topic.	
[1] I am sure this research will go down in history. I respect what you have done. [2] What made you look at synthetic genomes? [3] Have you felt any backlash from the public?	[2] It is just how things turned out. I encountered a new technology that hinted at the possibility of genome synthesis. In addition, there were trends for synthetic genomes around the world. [3] No, I have not perceived any significant backlash. I heard some fears expressed, but it wasn't really a backlash.
I wanted to ask what your ultimate goals are.	I want to understand life.
What do you think about making rules for genome synthesis technology?	The situation has made little progress, and my technology is only useful with genome synthesis kits. For this reason, restrictions on such kits may be necessary.
I remember Dr. Su'etsugu saying at the beginning of his speech that he wanted to know what life is as the starting point of his research. I am curious to know what impressed him during his research, such as the wonder and elaborateness of life.	So many things impressed me. While some are unexpectedly simple or appropriate, others have a great deal of diversification.
(Although you don't need to answer this question) did any Japanese companies approach you about acquiring the company? If the answer is yes, what was the offered price?	As we have been interacting with several Japanese companies for a long period, Moderna was not the only company that approached us.

In the subsequent Q&A session on the report of the Citizen GI results, questions centered on the way the citizens developed their discussions. Although the participants communicated in a way seemingly caught up in the event's atmosphere, many from the DIY community appeared to have solid opinions. On the other hand, the corporate and patent attorneys, who were also familiar with bioscience IP, commented that understanding research details and studying social issues was challenging. This condition is likely attributable to their familiarity with IP and research to some extent, highlighting what they could not understand. Separately, Dr. Nobuhara expressed his impression that the participants' opinions did not appear conflicting. The Secretariat analyzed his impression and responded that the situation might be attributable to the event's objective: intended to identify diverse perspectives and not designed to try to converge opinions. Concerning rulemaking for genome synthesis technology, Dr.Matsuo said that the viewpoint of safety seemed dominant in the Citizen GI. She also raised a concern that we need to take care of standardization in data collection, processing, standards, reproducibility, and other items. However, Dr. Su'etsugu pointed out that few researchers were now studying genome synthesis and related technologies practically, so it was no use standardizing those items for the sake of such a limited number of researchers.

We then explained the presented draft of ELSI perspectives and maps, summarized the Citizen GI, and discussed the ELSI perspectives for the upcoming joint WS. Dr. Su'etsugu said he learned through the Citizen GI for the first time that the general public was more receptive to the term Genome Editing than Genome Synthesis. Dr. Su'etsugu also noted that when he explained the technology used in his research, the Citizen GI participants needed help understanding it due to their lack of knowledge of DNA, so he requested that they learn about the central dogma and proteins. Concerning the acquisition by Moderna, Dr. Iwasaki

pointed out that the Citizen GI participants were concerned about losing Japan's presence. He also pointed out that Dr. Su'etsugu contended that the distinction of countries was unnecessary. Thus, he proposed that the difference in their positions be another ELSI perspective. There was an opinion (Dr. Minari) that from the scientific viewpoint of the sell-off to Moderna, it would be useful to consider two elements: the moment Dr. Su'etsugu's research drew attention and the moment the importance of technology was switched to different directions. There was an additional comment (Ms. Yokono) that the amount of private funding was an order of magnitude smaller in Japan than in the US.

Concerning the discrepancy with the sense of citizenship, there was a thought (Dr. Mikami) that the general public might want to see the technology returned to the Japanese economy since it was born from research funded by Japanese taxpayers' money. There was a counter-comment (Dr. Su'etsugu) that the money Moderna paid to acquire his technology eventually flowed into Japan as a return. In support of the latter comment, Dr. Siomi pointed out that since "Japanese Pride" was useless in science, it was far more critical that the government was supporting science in the face of fierce international competition. However, entering the competitive market is only possible by turning the ecosystems in our favor. In this sense, a suggestion was made (Dr. Nakamura) about the possibility of promoting the Japanese brand by linking our favorites to the characteristic of Japan's earnestness. On the other hand, wariness of increasing discourses of conducting research for national interest and other conservative elements was also expressed (Dr. Tanaka). In pursuing who gains benefits like this, we should remove the sense that conflicts of interest are bad. Policymakers, scientists, and corporations work independently with their own objectives and interests. There was a comment (Dr. Mikami) that we must discuss how to fix situations where conflicts of interest exist under normal conditions.

2.3 Joint WS

(1) Process

After completing the second individual WS (Su'etsugu PJ, October 16; Ichihashi PJ, October 20), we held a preliminary meeting for the joint WS at the Secretariat office on November 10. In the meeting, we agreed on how to proceed with the WS, including two specific points: (a) two Forum members would provide topics for discussion, and (b) several citizens would also participate in the joint WS. Points (a) and (b) were both chosen based on the opinions and comments obtained from the participants before, during, and after the second individual WS. The former point (a) aimed to (1) provide continuity between research, which is the Forum members' primary business, and their activities related to the Forum, (2) create synergy between the two sets of activities, and (3) strengthen the members' commitment to the Forum. Aiming to delve into the core perspectives of each of the Ichihashi PJ and Su'etsugu PJ, the Ichihashi PJ side sounded out Dr. Iwasaki, who has a bioscience background, to speak about the scientific significance of Artificial Biochemical Systems and communication with society. On the other hand, the Su'etsugu PJ side asked Dr.Matsuo to speak about how international standardization around synthetic biology should look like, on which other Forum members had seldom touched as a focused discussion.

The latter point (b) aimed to respond to the comments that the Citizen GI participants needed deeper scientific understanding and the impression expressed by the participants that they also wanted to have a dialogue with scientists. The latter point (b) also aimed to open the activities of the Forum more to society by making it a grassroots event, albeit indirectly. Furthermore, we planned to employ graphic recording for the joint WS, encouraging the experts to make the discussions more understandable for ordinary people.

On November 29, the core members of the Forum and the Secretariat held another preliminary meeting. In parallel, the Secretariat discussed with the two speakers for the joint WS to check the contents of their presentation. The Secretariat also met with Ms. Kubomi (Ms. Mami Kubota), who was going to serve as the graphic recorder. Based on these discussions, we made changes to the programs for the day, preliminary materials, and presentation materials.

The following three were the finalized objectives of the joint WS.

1. Share the results of individual discussions for the two PJ cases and identify case-specific differences and similarities in ELSI perspectives
2. Based on those ELSI perspectives common to the two PJ cases, extract those perspectives considered important to Genome Synthesis Area and society.
3. Based on the important ELSI perspectives obtained, each stakeholder considers what kind of challenge it can take on, namely Next Step Forward, on a commitment basis.

The joint WS was held from 09:00 to 12:00 on December 22, 2023, in a hybrid meeting between the JST Tokyo Headquarters Annex 2F Conference Room and online. The WS was organized, operated, and facilitated by the Secretariat. In the first half of the WS, the Secretariat presented a summary of the past discussions and perspectives. Then, Dr. Iwasaki and Dr.Matsuo provided their topics and summarized the discussion for 30 minutes each. In the latter half of the WS, the citizen participants raised questions about the discussions up to that point, to which the Secretariat responded. Then, group work was conducted to consider the Next Step Forward, followed by general sharing, summary, and review using graphic recording. The joint WS was concluded with a greeting from the Director-General.

The theme of the group work was Next Step Forward. This group work was designed based on the opinions obtained from the Forum members in previous individual WS, including the advice that we should come up with specific ideas to be put into each WS (Dr. Minari) and the need for time-frame consciousness of the perspectives and response to them (Dr. Nakamura).In the group

work, each member of the group first thought about Next Step Forward items to figure out how that member could promote efforts related to ELSI of genome synthesis in their position or on behalf of the Forum on Genome Ethics or CREST. Then, we got the members to write down those items that can probably be implemented in the next fiscal year as Own Business on a yellow sticky note. In the same way, the members wrote down those that can be implemented in several years, those with low feasibility, and those requiring other stakeholders' cooperation on a green sticky note. After completing the above procedure, the group was asked to share their ideas and summarize possible measures to be taken in an Actor x Feasibility matrix (Figure 5).

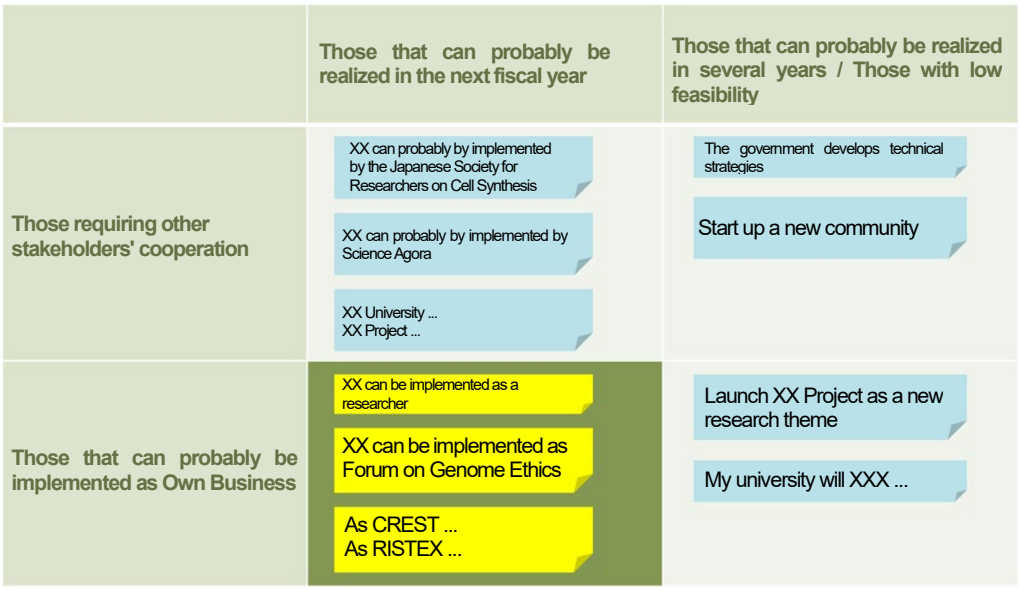

Figure 5 Image of a matrix used for group work

(Source: Prepared by the Secretariat of Forum on Genome Ethics)

There were 20 on-site participants, with Citizen GI participants excluded. So, the group work was configured in four groups of five participants. The four groups were divided into two groups focusing on the Su'etsugu PJ and the other two on the Ichihashi PJ. Dr. Su'etsugu and Dr. Ichihashi were asked to join one of the former and latter pairs, respectively. The citizen GI participants were asked to discuss their expectations of researchers, the government, and others as they wished.

(2) Results

At the beginning of the WS, the Secretariat explained the framework of the Forum and case studies for citizen participants. After that, the Secretariat showed them a summary of the discussions and ELSI perspectives in the first and second individual WS and Citizen GIs for each of the Ichihashi PJ and Su'etsugu PJ.

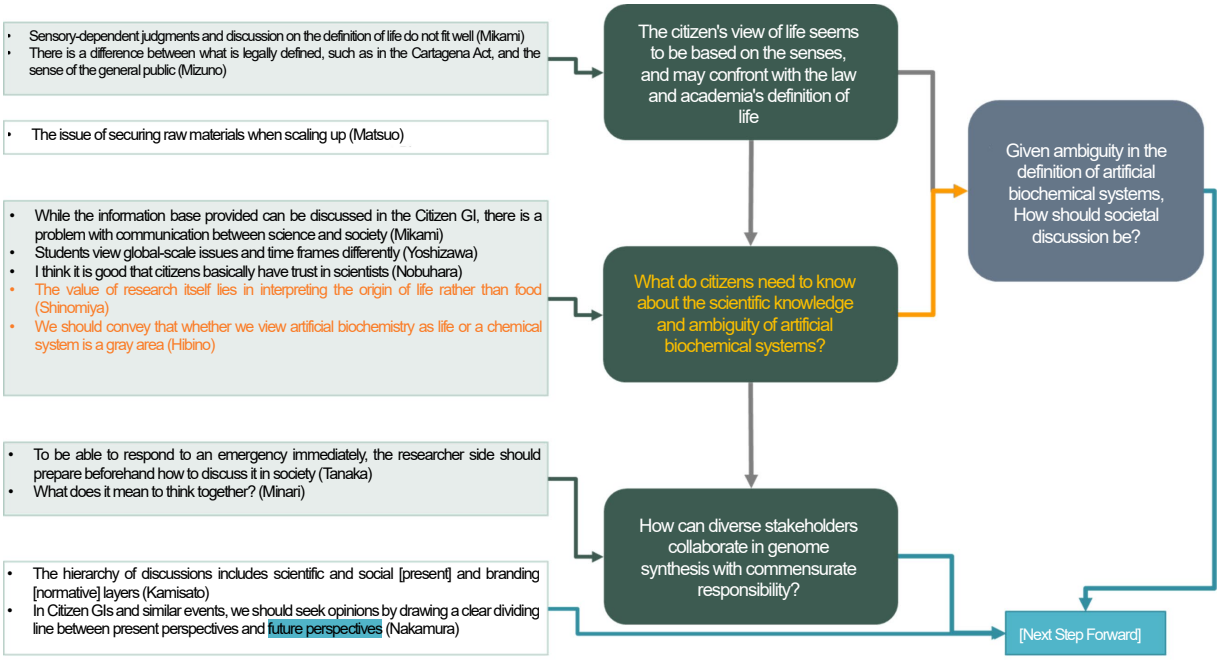

Figure 6 Changes in perspectives (Ichihashi PJ)

(Source: Prepared by the Secretariat of Forum on Genome Ethics)

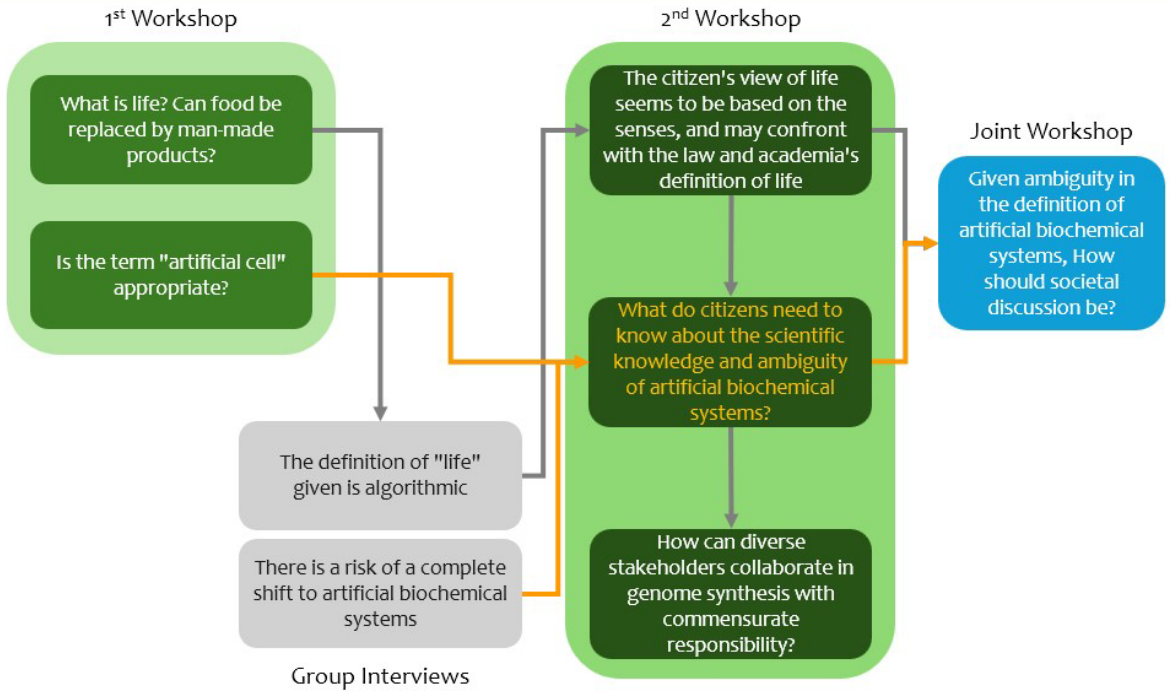

Figure 7 Perspectives obtained from the second individual WS (Ichihashi PJ)

(Source: Prepared by the Secretariat of Forum on Genome Ethics)

Of the participants, Dr. Su'etsugu was the only expert who was listening to the history of the Ichihashi PJ discussions (Figure 6, Figure 7) for the first time, so we asked him to comment on the history. Dr. Su'etsugu commented, "The term Artificial Cell may not appear easy for citizens to understand. However, when put into "Eating" for the output, this helps convey the results to citizens. So, it is an excellent branding tool." Meanwhile, the orange lines and text in the Figure show genome-synthesis-specific ELSI perspectives. This setting is based on Mr. Shimura's point in the individual WS: We should develop unique, meaningful discussions in this case study by avoiding duplication with other technologies and case studies.

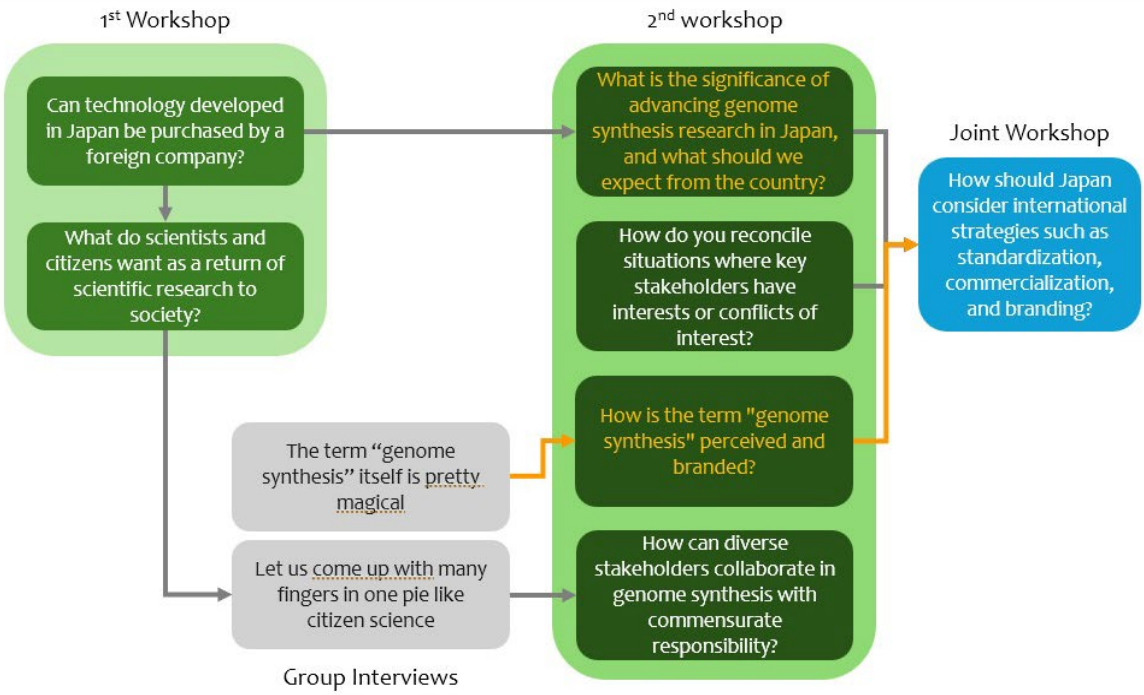

Figure 8 Changes in perspectives (Su'etsugu PJ)

(Source: Prepared by the Secretariat of Forum on Genome Ethics)

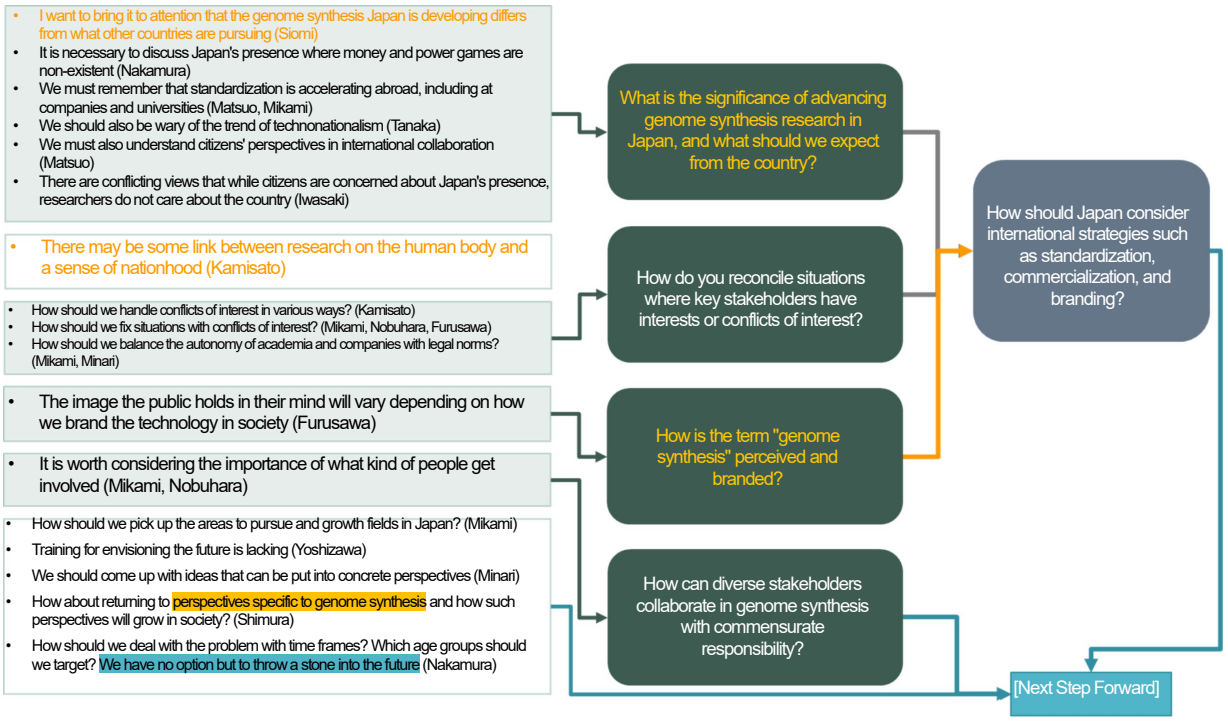

Figure 9　Perspectives obtained from the second individual WS (Su'etsugu PJ)

（Source: Prepared by the Secretariat of Forum on Genome Ethics）

In response to the history of discussions in the Su'etsugu PJ (Figure 8, Figure 9), Dr. Ichihashi said, "This is a down-to-earth piece of research." Then, he opened up and said, "As a researcher, I want to conduct my research with an open mind using overseas resources. However, doing it would be difficult because my research is funded by the Japanese government, which requires me to conduct research for the benefit of Japan."

Then, Dr. Iwasaki provided the following topic related to communication with society.

At KENPOKU ART 2016 in Ibaraki, we erected a burial mound of artificial cells. We asked the synthetic biologists invited there, including Dr. Ichihashi, to donate the remains of their artificial cells and bury them under a stone monument. We asked those biologists to talk about the death of their artificial cells, and recorded the comments. At that time, many researchers thought artificial cells would die when their reaction stopped. However, Dr. Ichihashi responded by saying that artificial cells would not die because they could be remade again. His response was very interesting. In other words, he meant that while we can make a living artificial life, we cannot make artificial cells deemed to die. On the other hand, the big question remains whether we can say something not deemed to die is alive.

Based on the above, I was asked to talk about a topic themed on how society will discuss artificial biochemical systems despite the ambiguity in its definition. In the first place, I have barely heard of the term artificial biochemical system. Biochemistry is a concept that falls somewhere between artificial and non-artificial. For example, biochemistry has a classic image of reorganization, such as the purification of enzymes. This is precisely the same as the in vitro reorganization of the events occurring inside a cell. Furthermore, biochemistry also has the image of biochemical reaction networks and metabolic maps, which could be applied to material production through hacking. Another representative image of biochemistry is that it grinds everything up, which many make fun of. There is a well-known classic criticism against biochemistry: "To understand chickens better, start after grinding them all down and making them into a juice, but the question is whether it helps understand the creature better?"

Biochemistry has the image of a complex phenomenon occurring inside a cell, and the image of artificially simplifying that complex phenomenon to perform some operation in a test tube. Furthermore, adding the prefix "artificial" to biochemistry has some impact.

Although this is just my supposition, Dr. Ichihashi used the term artificial biochemical system probably because of his reluctance to term something that is different from typical living organisms as life or living organisms. Artificial biochemical systems are different from typical living organisms in that they will not die. There may be other reasons, including an aversion to killing life, getting around cumbersome rules, and avoiding social backlash.

When looking back at changes in terminologies, the term synthetic biology was initially avoided in Japan. It used to be called constitutive biology or a constitutive approach. It was only around 2011 that we began to see the translated term of synthetic biology. Today, however, few people feel uncomfortable with the term synthetic biology, which makes us believe the acceptance of the term has changed significantly over the past ten years.

When it comes to artificial cells, there are two types of approach: One is the Craig Venter approach, in which minimal cells are created by large-scale genome modification, and the other is the scratch-and-build, bottom-up approach, which Dr. Ichihashi and Dr. Su'etsugu have employed. However, in the former approach, the question is whether the artificial cells can be said to be pure artifacts. In the latter approach, on the other hand, the artificial cells are undeniably artifacts, but the question is whether they are alive. Identifying which parts are questionable in the two approaches is an exciting part of our research.

In response to Dr. Iwasaki's topic, Dr. Ichihashi commented that Dr. Iwasaki was almost correct in his points. However, Dr. Ichihashi added that he did not use the term artificial cell because his research did not require cell membranes and that using the term would feel strange. Dr. Ichihashi added that the term Living Organism Reorganization would mean the creation of living organisms, so he wanted to make it look artificial to make it sound better and easier to use. As a result, he picked up the term biochemistry to express his intent. At that point, Dr. Su'etsugu expressed that adding the prefix Artificial to provide an engineering nuance was an excellent idea. He also thanked Dr. Iwasaki for his presentation looking back on these 10 to 20 years which had impressed him so much.

After that, there was a discussion (Mikami) that the term Artificial Biochemical System should be interpreted as the Artificial System of Biochemistry rather than the System of Artificial Biochemistry, to emphasize that natural systems can be realized artificially. There were also discussions about the history around the translation of "synthetic biology" and the comparison with its synonyms.

Following Dr. Iwasaki's talk, Dr.Matsuo provided the topic shown below, entitled "Rule and norm formation is also part of ELSI/RRI – Everyone must keep this in mind."

I am engaged in research on science, technology, and innovation. One of my research areas is transition management research. The concept of Transition management is based on the notion that technology will be formed in mutual interaction with society. The research offers three levels of analysis: the niche level for technological development, the meso level for policies, culture, and markets, and the macro level, which acts as a variety of trends that exist at upper levels. The concept indicates technology will sometimes change the whole society by individual activities at the lower level mutually interacting with regulations, culture, and social institutions at the meso level, or the even higher landscape level, and conversely, technology and social institutions will change mutually under the influence of the whole society.

The question here is how we should shape technology under such mutual interactions. This is where the so-called Collingridge Dilemma arises - at the initial stage of developing technology, we do not know how to control the technology due to its unclear prospects, however, it would be too late to control it when the impact of the technology becomes known. This is why we need to consider social impact in advance by conducting Technology Assessment. In controlling the social impact of technology, it is necessary to consider governance taking into account the implications of ELSI. It is my belief that such activities are the basis of

Responsible Innovation.

Next, I will introduce biotechnology-related government policies. In the US, the Office of Science and Technology Policy (OSTP) and the Department of Defense issued their policy documents in response to the 2022 Executive Order on Biomanufacturing. The UK veered toward promoting innovation after BREXIT, issuing a national vision policy document on engineering biology at the end of 2023. Likewise, Japan's political momentum is growing, with the Cabinet Office actively making moves, including a bio-strategy review.

Now, I will talk about the impact of regulations and standardization. In Japan, the regulatory requirements for genome-edited products were clarified in 2019, with six notifications having already been submitted so far (as of December 2023), including tomatoes and fish. Before we knew it, Japan was positioned as a global leader in the market introduction of genome-edited notified products. We understand that this accomplishment is attributable not only to the regulatory requirements being clarified expeditiously but also to how it was clarified. In other words, the accomplishment can be explained by the Notification System allowing public disclosure of notified products and the product labeling system, which worked well.

Lastly, Dr.Matsuo referred to a case of handling digital sequence information (DSI) in the Convention on Biological Diversity (CBD) as a recent topic related to the rules for biotechnology. The CBD stipulates that when moving genetic resources transboundary between two countries, the user that accesses the genetic resource shall obtain prior informed consent from the provider country, and both user and provider shall mutually agree with the sharing of benefits arising from using such resources (the mechanism is called Access Benefit Sharing or ABS). While the objects subject to ABS up to now have been materials, a discussion is now underway about extending the objects to include digital information. (This is because product manufacturing using digital information became possible in recent years.) This discussion is now underway, which significantly impacts researchers and companies that use digital information to promote manufacturing.

In response to Dr.Matsuo's topic, Dr. Shinomiya said that while the regulatory requirements could be divided by genetic modification (GM) and genome editing, such division seemed complicated in the minds of the public. He asked Dr.Matsuo for her comment. Dr.Matsuo recalled that some genome-edited products were exempted from regulations due to the regulatory requirements for such products clarified in 2019. At that time, some (negative) reaction was expected from citizens, but there was not much media coverage of the event. This situation was likely attributable to the introduction of an open Notification System for the products exempted from regulations, with a certain level of transparency ensured. (In other words, those products exempted from the regulations did not enter society unnoticed, and at least which products had been notified was publicly known.) We also reasoned that the products notified had a small market size and low impact on the market. Dr. Kamisato recalled Japan's reaction to genetically modified foods at that time was weak compared to Europe and the US because of its lack of interest arising from other severe problems such as dioxin, BSE, and mislabeled foods. Dr. Kamisato also analyzed that the Frankenstein Complex might be weak in Japan due to its cultural aspects.

After a break and at the start of the second half of the WS, we asked three Citizen GI participants about their reactions to the discussion up to this point. As a student majoring in humanities, A was rather fascinated by the word ethics. A expressed their impression that since the concept of ethics and the language surrounding biochemistry were so fragmented, it was hard to think that the two could not be engaged together. B, a doctoral student in ecology, understood these discussions to some extent and felt less resistance to technology. After saying they were not confident of giving a meaningful opinion as a citizen, B thought that artificial cells that fix carbon and cellular agriculture that does not involve killing livestock were excellent things to do. B encouraged us to keep pushing along these technologies. C, a medical student, expressed appreciation for the opportunity to learn something exciting about things which they were unfamiliar.

In the opinion exchanges between the Citizen GI participants and experts, Dr. Nobuhara questioned whether ecologists might have strange feelings about the initiatives with artificial life. B responded that it might be the case if such initiatives caused a conflict with open air natural ecosystems and the principle of preserving biodiversity. However, B added that they did not perceive any conflicts with synthetic biology at this stage. Additionally, Dr. Siomi spoke about his awareness obtained from these

discussions that some misunderstandings might be eliminated if the term artificial biochemical system was used instead of artificial cell. Dr. Siomi also expressed his view that since the media's reactions would make significant differences in forming social opinions, our approach of starting a discussion at a forum like this and then having appropriate media pick up our points might be critical. In response to Dr. Siomi's view, Dr. Iwasaki said that taking something strange as a "misunderstanding" was problematic and that considering what constitutes life was a matter of cultural and personal feelings that could not be defined academically. Dr. Iwasaki also noted that although Dr. Ichihashi is very much in the minority with his opinion on the death of artificial cells, he said in an interview that it was unsurprising in some ways that many people console artificial cells and consider their death. Citing this story, Dr. Iwasaki called attention to the range and diversity of people's perception of artificial cells and artificial biochemical systems.

In the subsequent group work, Next Step Forward, the four groups spent time discussing individually within each group and shared the outcomes with the other groups. Group A selected regulations and education as topics they would work on together in the coming fiscal year. As for regulations, it was likely that topics like Digital Sequence Information (DSI) introduced by Dr.Matsuo have not been discussed much in JST. As a result, there was a need to fill the gap. The group recognized the need for branding education, including ideas to build ways of disseminating our message nationwide and the creation of Yuru-Chara mascot characters. Topics for the coming year and beyond included reviewing academic disciplines such as bioethics and philosophy and studying the need for banks for stocking *E. coli* and the like. Dr. Su'etsugu expressed his view that while the National BioResource Project (NBRP) now collected, preserved, and provided biogenetic resources, if the project only stored information to create microorganisms from genomes in the future, it would eliminate the need to stock physical resources.

Group B, considering output as still essential, went in the direction of building a foundation that they could think of, through communication with the scientific community in the form of the perspectives and policy reports of the *EMBO*, *Science*, and *Nature* and presenting the future vision of our genome synthesis, including both positive and negative aspects, to a wide range of ordinary people. Group B said it might also be necessary to present to RISTEX what kinds of benefits we wanted to achieve because our activities would only be sustainable by clarifying the benefits of participating in the Forum. As an added comment, Dr. Nakamura presented his idea that we should target younger people rather than the general population and possibly offer not only experience classes and educational materials but also open a non-natural food restaurant in Akihabara and provide sub-cultural activities, such as movies and games.

Group C wanted to do various outreach activities for now and chose to hold public forums and ELSI-related dialogues. Group C also mentioned that since there were people with various professional positions in the Forum, it might be more inspiring if they could express their opinions from top to bottom by taking advantage of their positions. As an added comment, Dr. Iwasaki said it would be a waste if the knowledge gained from the past ELSI-related discussions ended up remaining in individual, one-off events, proposing that such knowledge be accumulated over the long term. Dr. Iwasaki also expressed a desire to improve the situation that, when viewed from the scientists' side, the Forum should be structured in such a way that makes it a little easier to see what kind of academic output the humanities and social sciences researchers involved with ELSI could deliver.

Group D said that the Forum should take some action as science had progressed to the point where mice could be made in a test tube. The dialogue with citizens on these topics was often conducted at the stage where citizens were being persuaded to agree to such actions when the political response was already largely complete. However, there was an idea to engage citizens and reflect them in policies at a more upstream stage. Group D also said the keyword Economic Security could not be removed from genome ethics when the economic security issue became imminent. Lastly, Group D pointed out that although the continuation of activities at public institutions should be supported, including this event, the shortage of human resources remained unsolved regardless of the situation.

After that, Ms. Kubomi reviewed the discussions so far using graphic recording. On the day of the joint WS, Ms. Kubomi summarized graphically the recorded discussions in real time. For accuracy, she asked the Secretariat to correct the summary by cross-checking it with the meeting minutes. She also revised the summary after having it checked and corrected by the topic providers, Dr. Iwasaki and Dr.Matsuo. Figure 10 shows the final graphic recording of the joint WS.

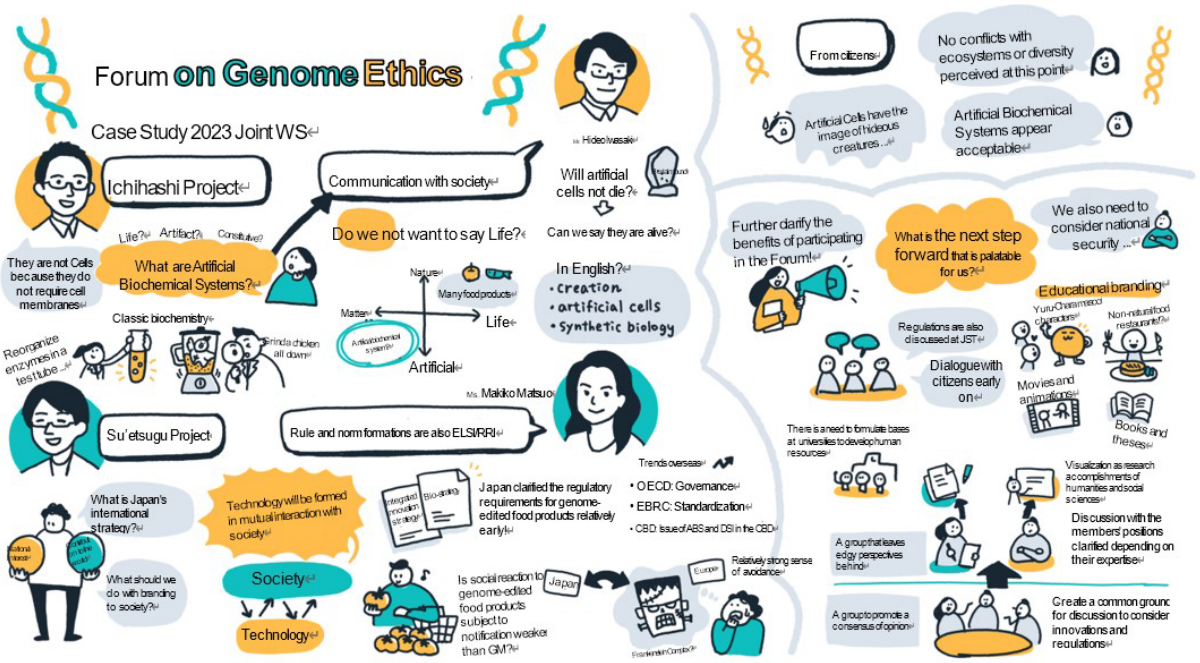

Figure 10 Graphic recording of the joint WS

(Source: Prepared by Kubomi)

2.4 Post-Case Study Questionnaire

After completing the joint WS, the Secretariat conducted a questionnaire for Dr. Ichihashi, Dr. Su'etsugu, and the Forum members to review this case study. First, Dr. Ichihashi and Dr. Su'etsugu positively evaluated the case study initiative for this fiscal year. Dr. Ichihashi clearly stated, "It was a new finding that we probably had better not express artificial biochemical systems as something that resembles life." It was particularly noteworthy that Dr. Ichihashi underlined an outcome from the discussions with the Forum members through this case study. On the other hand, Dr. Su'etsugu expressed his opinion, "Probably because I am accustomed to research of experimental science, which is based on the accumulation of concrete data, I was left wondering whether this discussion was based on the accumulation of previous discussions (such as bioethics, genome editing, and dual use)."As with Dr. Iwasaki's comment at the joint WS, it became apparent that the scientist side were asked to find novelty as compared to past ELSI-related discussions and solid academic achievements in humanities and social sciences presented in the Forum.

On the other hand, the Forum members generally said it was good to conduct the case study. Notably, we heard many appreciating that those involved in CREST, including Dr. Ichihashi and Dr. Su'etsugu, could spend enough time talking with the Forum members. Some responses said that learning these researchers' thoughts and feelings about research first hand, including site visits, was a significant accomplishment. On the other hand, there was an impression right through to the end of the WS that there was no idea what to output. There was also an opinion that accumulating knowledge for generalization was difficult. As a result, some embarrassment was seen about how case studies should be positioned with respect to the overall flow of discussions so far. In addition, some reflected on the failure to conduct thorough discussions on Perspectives of Ethics due to mutual reticence. For example, such discussions should have included the following points: If we believe artificial cells are alive, what ethical perspectives does it involve, and is that something we should consider while conducting our research? What was the real significance of this technology having been acquired by another company? Is it possible to get around regulations on genetic recombination? As regulations on genetic recombination do not protect secrecy in the first place, we wonder if companies and military-related research facilities feel more attracted to artificial life systems so that they will not have to worry about secrecy exposure later.

Regarding the event structure of this case study (individual WS #1 → Citizen GI → individual WS #2 → joint WS), there were comments that the Citizen GI did not function well to help progress the WS and that the Citizen GI might have diverged the discussion in the second WS. There was also an impression that a dialogue specialist's dedication and ingenuity were necessary. In addition, some pointed out that since the joint WS had the vital element of summarizing the discussions up to that point, the efforts to find common ground and breadth of the discussions conducted for the two PJs were lacking. Similarly, some responded that the joint WS only checked superficial perspectives, leaving little time to discuss the lectures. Furthermore, some felt regret that young researchers of the Ichihashi PJ and Su'etsugu PJ were absent from the joint WS.

The researcher and Forum member sides were divided in their opinions about implementing case studies in the coming fiscal year. In addition to the response that it was better to conduct case studies if there were other appropriate research PJs, the following reasons to support case studies were presented: Conducting the case studies would clarify individual perspectives and deepen discussions; it would provide a good reason for involving various stakeholders; there would be a need for long-term accumulation of knowledge and experience; continuing collaboration with scientific researchers daily would be necessary. On the other hand, an opinion suggested that we first clarify our objectives in solving points for improvement by repeatedly considering the future activity plans proposed in the joint WS. A proposal also suggested focusing more on creating outputs applicable to practical use.

Other responses to the questionnaire included an expectation for more participation by young researchers in Science, Technology and Society (STS) and ethics, a suggestion on devising a better approach to outreach, an opinion to suggest creating more opportunities to deepen mutual understanding among Forum members, and a recommendation to consider the necessity to get more commitment from RISTEX as a concerned party. Additionally, several respondents again expressed their gratitude to Dr. Ichihashi and Dr. Su'etsugu for their full cooperation in this case study despite their extremely busy schedules.

3. Consideration

3.1 ELSI Perspectives

Based on the survey results up to this point, the Forum have extracted and analyzed ELSI perspectives specific to the Genome Synthesis Area to prepare ELSI Perspective Maps. With some Forum members requesting the proactive use and expansion of such ELSI Perspective Maps, we tried to apply these maps to this case study for the discussions at the first individual WS and the Citizen GI.

From the beginning, the Ichihashi PJ envisioned Dual Use, IP Protection/Prevention of Outflow, Open Access, Scientific Literacy, and Dignity of Life as their ELSI perspectives (Table 1) In the first individual WS, the discussion centered on what the definition of life should be in a way that is conscious of legal regulations and social acceptance. In the ELSI Perspective Map 2022 (Figure 2), the ELSI perspectives we envisioned were close to Boundary between Life and Matter and Dialogue with Citizens. However, we found that Boundary between Life and Matter was a perspective closely linked to laws and regulations and, in some cases, Biosafety. In the second individual WS, we presented three new perspectives without sticking to the existing ELSI Perspective Map: Non-algorithmic Views of Life, Anthropocentrism and the Anthropocene, and Irreversibility. If we compared these perspectives with the ELSI Perspective Map, the first one was closest to Boundary between Life and Matter, with the remaining two close to Genetic Modification to Remain in Offspring/Genome Editing, if anything. In the discussions at the second individual WS, like a typical case study, Artificial Biochemical Systems and the scientific and social positioning of related terms were highlighted as more specific individual perspectives than the perspective maps. The responses of the Citizen GI participants to the Ichihashi PJ (Table 2) showed Dignity of Life and Boundary between Life and Matter in the ELSI Perspective Map slightly increasing after the discussion of the Ichihashi PJ, directly reflecting their interest in that PJ. On the other hand, the ratio of IP Protection/Prevention of Outflow also increased, probably because the participants had become more interested through discussions on handling genetic information and IP protection issues in technological applications.

From the beginning, the Su'etsugu PJ envisioned Biosafety and Biosecurity, IP Protection/Prevention of Outflow, and Scientific Literacy as their ELSI perspectives (Table 4). In the first individual WS, the Su'etsugu PJ discussed what corporate strategy should be, the definition of life, and promoting the understanding of science, which could correspond to the Boundary between Life and Matter and Scientific literacy in the ELSI Perspective Map except corporate strategy. In the second individual WS, the Su'etsugu PJ presented three topics: Versatility of the Term Genome, Significance of Japan in Research, and What Hats that Everyone Can

Wear Together Should Be. However, none of them was found in the ELSI Perspective Map. In the WS discussion, various opinions concentrated on the second topic, Significance of Japan in Research, following the Citizen GI discussion that reflected Dr. Su'etsugu's interest. In the responses of Citizen GI participants in the Su'etsugu PJ (Table 5), although little pre- and post-comparison was available, we found it symbolic that some participants chose Dialogue with Citizens on Ethical Issues Specific to Genome Synthesis after the event.

This case study required deeper perspectives than the ELSI Perspective Map to capture the characteristics of each PJ. For this reason, the Secretariat prepared a new list of perspectives and a perspective map showing the relationship between individual perspectives in the second individual WS. Furthermore, the joint WS proposed perspectives based on the list and map and clearly defined perspectives specific to the Genome Synthesis Area. Those perspectives for the Ichihashi PJ were "What do citizens need to know about the scientific knowledge and ambiguities of artificial biochemical systems" (Figure 6). On the other hand, those perspectives for the Su'etsugu PJ included "What is the significance of promoting genome synthesis research as Japan?," "What should the country expect from such research?" and "How is the term Genome Synthesis recognized and branded?" (Figure 8). The scientific definitions and the ambiguity of social recognition surrounding terms such as Artificial Biochemical Systems, Artificial Cells, and Genome Editing would be common agendas to the two PJs. We confirmed that these issues would indirectly lead to discussions on legal regulations, standardization, and social acceptance. Furthermore, the significance of research As Japan was a perspective related to its economic security and technological sovereignty. It was suggested that such an agenda must be considered beyond the two PJs subject to this case study and as part of the Genome Synthesis Area.

3.2 Mapping of Concepts Related to Genome Synthesis

Following the completion of the joint WS, the core members of the Forum and the Secretariat met on January 10, 2024, to review the joint WS and discuss a guideline for preparing this report. In the joint WS, Dr. Iwasaki introduced the historical transition surrounding terms such as synthetic biology and other related terms, which later encouraged discussions on the definitions and concepts of other terms such as Artificial Biochemical Systems and Artificial Cells. As such, the members proposed that organizing these related concepts might be a good idea as one of our accomplishments in this fiscal year. In response to the proposal, the Secretariat created Figure 11 using the dual axis chart of life-matter and nature-artificial that Dr. Iwasaki used as a foothold.

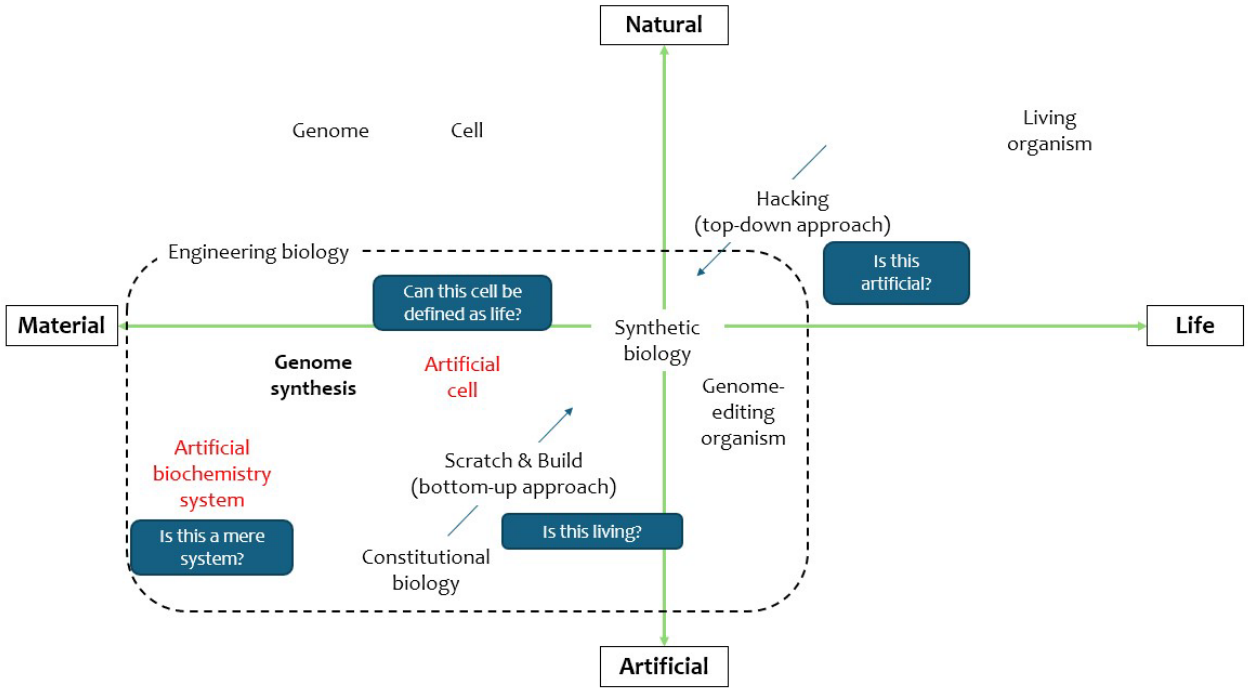

Figure 11 Mapping of concepts related to Genome Synthesis

(Source: Prepared by the Secretariat of Forum on Genome Ethics by adapting Dr. Iwasaki's presentation material)

First, the Living Organism is located at the upper right of the Figure, with the Cell and the Genome positioned on the left at the same height. Living Organisms have life, with plants and animals at the top of the list, and can be regarded as natural objects in the sense that they are not created by human manipulation. Although cells and genomes are natural objects as components of living organisms, they are not as vital as living organisms when viewed as individual elements, and the more they are broken down into separate elements, the more their materiality becomes apparent.

The central theme of the Forum and this case study, Genome Synthesis, has the same materiality as genomes. However, because the Synthesis part implies human manipulation, Genome Synthesis is placed toward the artificial region on the lower side of the vertical axis. Similarly, Artificial Cell is placed at the same height as Genome Synthesis on the vertical axis but closer to Life than Genome Synthesis on the horizontal axis. Genome-Edited Living Organisms can be viewed as more artificial and material than living organisms because genome editing was applied to natural living organisms that have life in the first place.

The difference between Artificial and Synthetic was also discussed in the joint WS. At that time, Dr. Su'etsugu called cellular

systems created bottom-up from matter Artificial Cells and called cells created from natural cells by synthetic genome replacement Synthetic Cells. He considered that Artificial Cells were not subject to the Cartagena Act and that Synthetic Cells are subject to the Act. The Cartagena Act was enacted to prevent adverse effects on biodiversity by establishing regulatory measures for using genetically modified organisms and others. Because Synthetic Cells had a risk of being taken as genetically modified organisms, the term Artificial Cell was considered appropriate to emphasize from the beginning that the objects were unnatural.

In the late 2000s, Synthetic Biology (English) was translated into Synthetic Biology (Japanese equivalent) and Constitutive Biology (Japanese equivalent). The recognition at the time was: "No clear distinction has taken hold between the two terms yet. In some cases, the former is used to construct the basic properties of life and aim at artificial material production. In some cases, the latter is used to understand life through the construction of biological functions. There are also cases where they are used in reverse ways."[5] Our feeling at the time was that there was no recognition that we had changed the object depending on whether it was Synthetic or Constitutive. If anything, Synthetic was said to provide an image of making something that did not exist naturally, which is consistent with "the case of aiming at artificial material production," which was cited above. Note that Constitutive Biology is rarely used today, while Synthetic Biology is used in most cases.

It is said there are two major approaches to this synthetic biology. One is the Craig-Venter type top-down approach, in which minimal cells are created by large-scale genome modification. The other is the bottom-up approach, in which artificial cells are created using scratch-and-build methods, such as the research technique Dr. Ichihashi and Dr. Su'etsugu use. When Venter points to a product obtained through the former top-down approach and says it is the world's first Artificial Life, the ethical/philosophical or scientific/legal question is whether we can call it genuinely Artificial. In other words, the question is how much modification we should add to a living organism before we can regard it as an artifact. On the other hand, products obtained through the bottom-up approach are undeniably artifacts, but whether we can say they are alive could cause a problem.

Now, let's consider the research targets of Dr. Ichihashi and Dr. Su'etsugu, who employ the same bottom-up approach. Dr. Ichihashi's Artificial Biochemical System leaves the question of whether we may consider them simply artificial systems or understand the absence of cell membranes severs ties with biological systems entirely. The Artificial Biochemical System does not follow the two synthetic biology approaches, namely conventional top-down and bottom-up approaches. Instead, it aims at artificial systems independent of biological systems. As such, the Figure shows the Artificial Biochemical System oriented in a direction different from the top-down and bottom-up vectors. Similarly, concerning Dr. Su'etsugu's Artificial Cells, a question can be raised about whether possessing basic building blocks of living organisms, namely cells, may conform to the definition of life. As such, Artificial Cells are placed toward the matter side, outside the conventional frame of synthetic biology.

Europe and the US increasingly call these emerging bioscience technologies, including synthetic biology and genome editing technologies, Engineering Biology. The terms Biotechnology and Bioengineering were already known in the first place. The trend of calling the terms differently is assumed to be attributable to the strong policymaker's intent to enhance new terms' scientific, industrial, and social impacts rather than significant changes in their conceptual frameworks. Conversely, as symbolized by the term bioeconomy, traditional academic terms may have become difficult to use because the economic impact that bioscience technology can bring about has increased remarkably.

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[5] Center for Research and Development Strategy (CRDS) of Japan Science and Technology Agency (JST) (2010), Benchmarking Report on Synthetic Biology, CRDS-FY2009-GR-02, p. 2.

4. Toward the Future

The case study conducted this time was the first attempt by the Forum, and left several issues to address, including communication among the parties involved, the direction of agenda setting, and how to summarize discussions and accomplishments. Despite that, we received generally positive evaluations from Dr. Ichihashi, Dr. Su'etsugu, and Forum members, with several participants sharing their impressions that the initiative was meaningful. As a result, we obtained a variety of perspectives unique to such interdisciplinary activities, which provided ideas that would help our future efforts. As we analyzed in Chapter 3, the achievements that could contribute directly to the Genome Synthesis Area included the more profound analysis of the perspectives specific to the Genome Synthesis Area based on the ELSI Perspective Map and the mapping of concepts related to Genome Synthesis. Regarding concepts related to Genome Synthesis, in particular, we had opportunities in the joint WS to deliberate the background and scientific/social implications of introducing terms such as Artificial Biochemical Systems and Artificial Cells and the historical transition of other related terms. We received a favorable comment from Dr. Siomi, Program Supervisor, stating that he could gain new insights. This particular outcome suggested that obtaining a panoramic view of various aspects by comparing perspectives on both sides was only possible by picking up two PJs in the case study. Thanks to the full cooperation of Dr. Ichihashi and Dr. Su'etsugu and their proactive involvement with the WS, our ambitious attempt to reconcile two objectives in a single joint WS, namely (a) the themes that had been delved in two individual WS and (b) the perspectives of the Ichihashi PJ and Su'etsugu PJ with different targets, achieved a certain level of success. This was an accomplishment noteworthy in this report.

Regarding our future activities, we can think of many possible directions. Conducting new case studies by inviting new CREST researchers might help us explore new perspectives. As proposed in the joint WS, promoting the creation of academic accomplishments from humanities and social sciences by Forum members would also motivate their commitment to continuing their participation. Furthermore, building a cooperation system in science communication activities, such as joint paper writing and dialogue events with citizens, might be possible as part of collaboration between CREST researchers and Forum members. In fact, some Forum members brought the accomplishments back to their labs for their own research activities and tried to find common ground with other projects, communities, or networks they are working with. On the other hand, CREST researchers can receive fresh intellectual stimulation through exchanges with Forum members. At the same time, they can contribute to the project as a more meaningful initiative by reviewing their research activities to develop more socially responsible research and innovation while considering which ELSI perspectives to pay attention to. To this end, the Forum wants to take on new challenges continually and explore what cumulative and sustainable activities should be.

Participants

Program Supervisor of CREST Large-Scale Genome Synthesis and Cell Programming

Haruhiko Siomi	Professor, School of Medicine, Keio University

Ichihashi Project

Norikazu Ichihashi	Professor, Graduate School of Arts and Sciences, University of Tokyo
Hayato Hirata	M1, Graduate School of Arts and Sciences, University of Tokyo

Su'etsugu Project

Masayuki Su'etsugu	Professor, College of Science, Rikkyo University
Kiyoshi Furusawa	Project Associate Professor, College of Science, Rikkyo University / Science Communicator
Takahito Mukai	Assistant Professor, College of Science, Rikkyo University
Yuta Yamagishi	M2, College of Science, Graduate School of Rikkyo University
Umi Ohtake	Sophomore, Musashi High School / Leader of High School Union iGEM Team (Su'etsugu PJ)

Forum on Genome Ethics

Yukihiro Nobuhara	Professor Emeritus, The University of Tokyo
Hideo Iwasaki	Professor, Faculty of Science and Engineering, Waseda University
Takuji Okamoto	Professor, Graduate School of Arts and Sciences, The University of Tokyo
Tatsuhiro Kamisato	Professor, Graduate School of Global and Transdisciplinary Studies, Chiba University
Atsuo Kishimoto	Professor, Osaka University Institute for Datability Science/ Director General ,Research Center on Ethical, Legal, and Social Issues
Nariyoshi Shinomiya	President, National Defense Medical College
Akihiro Shimura	General Manager, Marketing Department No. 7, Dentsu Inc.
Yoh-ichi Tagawa	Associate Professor, School of Life Science and Technology, Tokyo Institute of Technology
Mikihito Tanaka	Professor, Faculty of Political Science and Economics, Waseda University
Takahiro Nakamura	Professor, Faculty of Agriculture, Graduate School of Kyushu University
Aiko Hibino	Professor, Faculty of Humanities and Social Sciences, Hirosaki University
Makiko Matsuo	Project Associate Professor, Graduate School of Public Policy, The University of Tokyo
Koichi Mikami	Associate Professor, Faculty of Science and Technology, Keio University
Tasuku Mizuno	Attorney, CITY LIGHTS LAW/Visiting Professor, Global Innovation Center, Kyushu University*
Jusaku Minari	Project Associate Professor, Uehiro Research Division for iPS Cell of Ethics, Center for iPS Cell Research and Application, Kyoto University
Megumu Yokono	Associate Professor, School of Social Sciences, Waseda University

Japan Science and Technology Agency (JST)

Tadashi Kobayashi	Director General, RISTEX
Takanori Hirao	Director, Department of Planning and Management, RISTEX
Toshiya Otake	Manager, Department of Planning and Management, RISTEX
Izumi Komiya	Deputy Manager, Department of Planning and Management, RISTEX
Yuko Morita	Specialist, Department of Planning and Management, RISTEX
Kazuki Sekimoto	Deputy Manager, Department of Planning and Management, RISTEX
Aya Aoki	Chief, Department of Planning and Management, RISTEX

Etsuko Yamauchi	Researcher, Department of Planning and Management, RISTEX
Namie Shimazaki	Assistant , Department of Planning and Management, RISTEX
Katsura Omachi	Chief, Life Science and Biotechnology, Department of Strategic Basic Research, JST
Hajime Niwa	Senior Researcher, Life Science and Biotechnology, Department of Strategic Basic Research JST

Ernst & Young ShinNihon LLC. (EY)

Go Yoshizawa	Manager, Climate Change and Sustainability Services
Yuki Nanjo	Manager, Climate Change and Sustainability Services
Kota Yamani	Climate Change and Sustainability Services