Executive summary

Breakthrough discoveries and cutting-edge technologies in life science and clinical research area are driving our lives healthier and more sustainable.

Cross-interactions between various disciplines, such as clinical medicine, biology, chemistry, physics, informatics, and engineering are the key to deliver rapid advances in analytical methods, tools, and technologies, which are vital for attempts to decipher the rules of life. In addition, it is noteworthy that data science is becoming more and more important in the field of life science and clinical research, as researchers in this field are dealing with big data in various aspects. Multi-disciplinarity is crucial also in the process, where the outcomes of fundamental research turn into game changing innovations as a series of social applications; not only the technological robustness, understanding of various social aspects, such as social demands, market trend, legal requirements, economic viability, start-up company ecosystem, social acceptance of advanced technologies have to be assessed. An iterative interaction can be observed during the process in which social implementation of advanced technologies; application of new technologies derived from fundamental research often present new subjects that have to be addressed by further fundamental research.

Here we report the latest trends and topics in life science and clinical research area, ranging from basic to applied research activities, moreover, the social issues, such as science/technology policies, social demands, market trend, legal requirements, economic viability, start-up company ecosystem, social acceptance of advanced technologies are also assessed. The report mainly covers the recent topics in Japan with comprehensive comparison to global trends. During our analyses on the social aspects, we have identified that truly effective technologies/ solutions are much sought after, and more importantly, such solutions also have to be concurrently sustainable in various aspects. The word "sustainability" doesn't only mean to ensure the earth's natural systems which can support humanity's safe operation, but also includes the adequate/just use of medical/human/economic resources, which are also finite. The concept that combines the sustainability of earth's natural systems and human health is known as "Planetary Health" which was originally proposed by Horton et al., in the Lancet journal in 2014.

In many cases, the best efficacy and sustainability are contradicting each other; for example, using biomass fuels could reduce CO_2 emission from fossil resources, but at the same time it could squeeze the farmland for food production, possibly resulting in the destruction of natural forest with high biodiversity. In the case of medical treatment, cutting edge medications derived from advanced bioscience could provide cures for incurable disease, but the costs are often so high that only world's richest can afford them, widening the health inequalities by wealth. In many cases, several factors are so closely interrelated that it is almost impossible to have an intuitive solution that resolves the conflicting interests of best efficacy and sustainability. Thus, what we have to pursue is not the ultimate efficacy, but the better-balanced solution over the conflicting various interests. In order to see better- balanced solution, an objective evaluation of the solution

from various aspects, including social impacts, needs to be made numerically. Here we would like to propose that advanced data science with universal data availability and accessibility is essential to solve such multivariable challenges (Fig. S1).

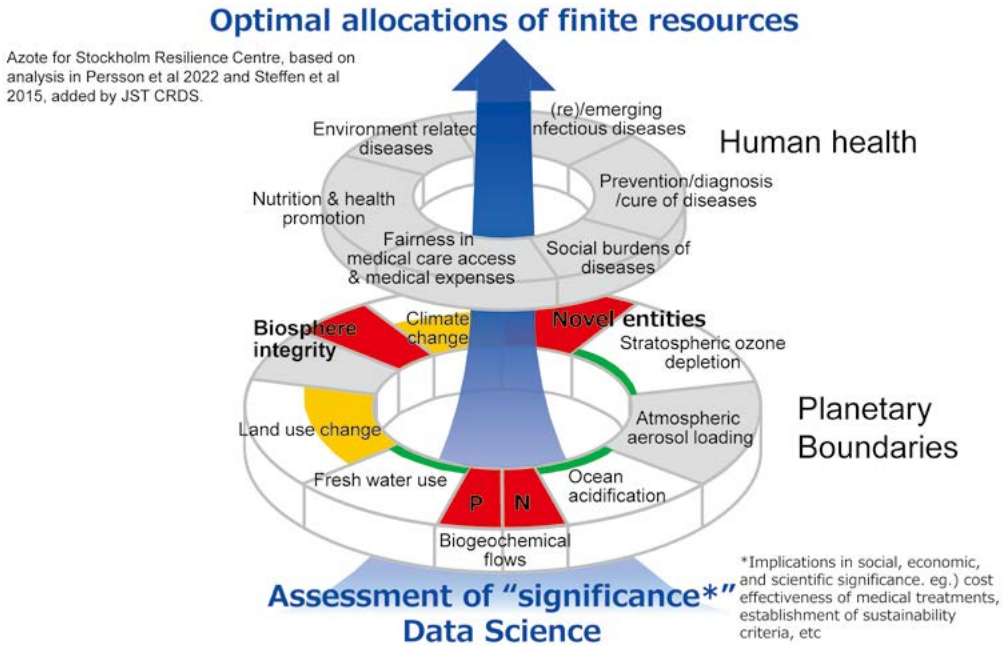

Fig. S1 The Planetary health

In this 2023 edition, recent development in science/technology in each topic are detailed in chapter two; in total 30 topics were categorised into 3 sections. The topics were carefully selected from the aspects of social impact, newly emerging, and fundamental. The "Health and Medical Care" section dedicated for research and development related to human health, sustainable bio-manufacturing related topics are described in the section of "Agriculture and Bioproduction", and emerging technologies serving for the advancement of both human health and bioproduction research area were outlined in the section of "Basic and Fundamental" section.

The revisions from the previous 2021 edition were as follows:

- In order to see the process of technological development from basic and fundamental research to its application in society, "Basic and Fundamental" section was created to emphasize the importance of basic and fundamental research, while the sections of "Health and Medical Care" and "Agriculture and Bioproduction" were expanded to provide applied and basic research topics separately.
- Reflecting the recent trends of utilizing data-driven approaches, intensive descriptions were provided in the sections of "AI-driven drug discovery", "AI-driven diagnosis and prevention", "Agriculture engineering", and "protein design".

The remarkable trends which observed in these couples of years were as follows:

- Low- and mid-molecular drug discovery: the emergence of new concepts in the modalities of drug discovery, including the degradation of target proteins using compounds.
- Long-read NGS: long reads (>20,000 bp) facilitate genome sequencing of a wide variety of biological resources and stimulate useful gene hunting through genome mining of practical plants.
- Genome engineering: clinical trials of gene therapies implementing genome editing and the development of genome manipulation technologies that is not infringing the Cartagena Act have progressed.
- Digital therapeutics (digital medicine): various apps serving as digital therapeutics has been developed to support behaviour modifications in patients with lifestyle-related diseases and addictions.
- Single-cell omics analysis: advances in omics technology that preserves spatial information within tissue and cell populations, accelerating understanding of life and disease at the single-cell level.
- Microbiome: advances in understanding of metabolism and signal transductions in the animal and human gut and soil microbiota. First FDA approval of a therapy utilising gut bacteria in 2022.
- Genetically engineered immune cell therapy (e.g. CAR-T): extensive development has been observed globally including Japan, in particular, enhancing cell function and functional stability, reducing therapeutic toxicity, and expanding the range of diseases to be treated via applying synthetic biology methods.
- *De novo* protein design: technologies related to rational design have been remarkably advanced, delivering the models to design structurally stable novel proteins with novel functions.
- Plant factories: highly efficient production methods have been developed by integrating plant science, agronomy and engineering. A new trend of plant physiology, examining the plant response to non-natural growth conditions, has been emerged. This is thanks to the precisely controlled plant growth conditions in plant factory environment.

With the comparison of global trend, the USA is by far the strongest across all research areas, from basic to applied, while Europe also has an overall presence, particularly in the UK (mainly in health and medicine) and Germany (basic fundamental technologies).

In basic research, Japan has strengths in 'cancer', 'immunology/inflammation', 'biological clock/sleep', 'organ systems', 'agricultural engineering', 'plant reproduction', 'plant nutrition', 'extracellular particles/extracellular vesicles', 'microbiome', 'structural analysis (biopolymers and metabolites)', 'optical imaging' and ' Strengths in 'optobiology'. In applied research, the company has strengths in 'small- and medium-molecule drug discovery' and 'agricultural engineering'.

In the US and Europe, basic and applied research progress almost simultaneously, and in China there are cases where applied research takes the lead, while Japan has 13 R&D areas where it has strengths in basic research, but only two areas where it has strengths in applied research. The problem is that Japan's strengths in basic research are not linked to applications.

Based on the above, the following six directions of R&D that are important for Japan have been

identified (Figure S2).

Themes	Examples
1. Preparing for future pandemics	■ Enabling comprehensive data and sample collection including facilitating appropriate legal infrastructure. ■ Strengthening basic research on infectious diseases, including virology, immunology.
2. Delivering personalised healthcare and preventive care	■ Exploring novel disease factors and relevant interventions based over real world data, with taking advantages of data-driven approaches. ■ Identifying personally optimized medications and cures based on real world data.
3. Novel modalities in drug discoveries	■ New Therapeutic targets. ■ Development of the foundations of sustainable healthcare system.
4. Sustainable agriculture and bio-production	■ Sustainable biomass production and bio-production design with cutting-edge biotechnology. ■ Deciphering the chemical networks underlying organismal interaction. ■ Development and assessment of sustainability criteria.
5. Widening linkages of various research topics and disciplines	■ Interactions of organ systems (liquid factors, neural, and symbiosis net works), etc. ■ Cross-scale analysis, novel analytical modalities; spatial omics analysis, mesoscope, etc
6. Unleashing the potential of big data in biology	■ Innovative data acquisition, storing, and analysis over wide range of life science related data.
7. Improvement of research environment	■ Facilitating the development of life science related innovation eco-system. ■ Increasing the number of core facility. ■ Provide better career development/training program.

Fig. S2 Identified high priority topics

Common to all these directions is the increasing importance of research utilising data-driven approaches. Whereas in conventional research, a wide variety of data has been used to formulate equations deductively, in recent years the big data has increasingly been used in the form of making data-driven models in the way where the models are automatically generated from the data (data-driven). Data-driven model generation, as typified by deep learning, is an important technology in all situations involving life sciences and clinical research, as it is powerful for modelling phenomena that are difficult to describe explicitly using governing equations. As information science skills are essential for data-driven approaches, it is important to establish a system that can bring together researchers from different fields, including mathematical and informatics researchers.

In addition, it has been said that the construction of an innovation ecosystem, including the fostering of start-ups and venture companies, and the importance of human resource development are important in promoting these research and development systems, and it is important to continue to make strategic efforts based on Japan's systems and structures. The importance of strategic initiatives based on Japan's systems and structures will continue to be important.