

“Gene Editing Technology: Application in Agriculture and Regulations on
Food Derived from Gene Editing Technology”
20 October 2021,
Bangkok, Thailand (Online Seminar)

Japanese handling policy of genome- edited organisms and their science communication

TABEI Yutaka (Ph.D.)

New Technology Promotion Section, Strategic Planning Headquarters,
National Agriculture and Food Research Organization (NARO)

1. R&D of genome editing (**GE**) for agriculture and fishery fields in Japan
2. Regulatory framework for genome editing in Japan
 - Current framework for genetically modified organisms (**GMO**)
 - The regulatory framework for biodiversity influence by genome edited organisms
 - The regulatory framework for food safety of genome edited foods and food additives
 - How do we confirm null segregant?
3. Labeling policy of genome-edited foods
4. Promoting the Public Understanding of Genome editing

Commercialization of tomato and red sea bream, and examples under development by genome editing in Japan

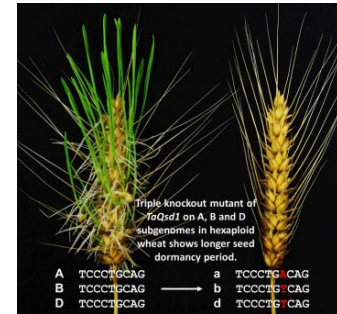
High GABA
tomato



Low solanine
potato



Alteration of seed
dormancy in wheat



Left: Wild type
Right: GE wheat

High yield rice



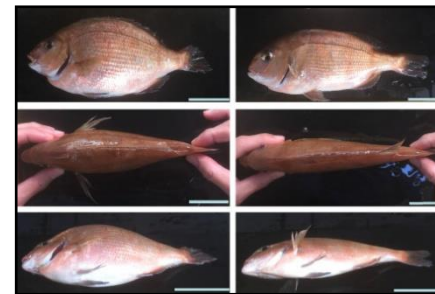
Skin color
modified grape



Gentle Tuna



Thick red sea
bream



Left: GE red sea bream
Right: Wild type

Appetite controlled
puffer fish

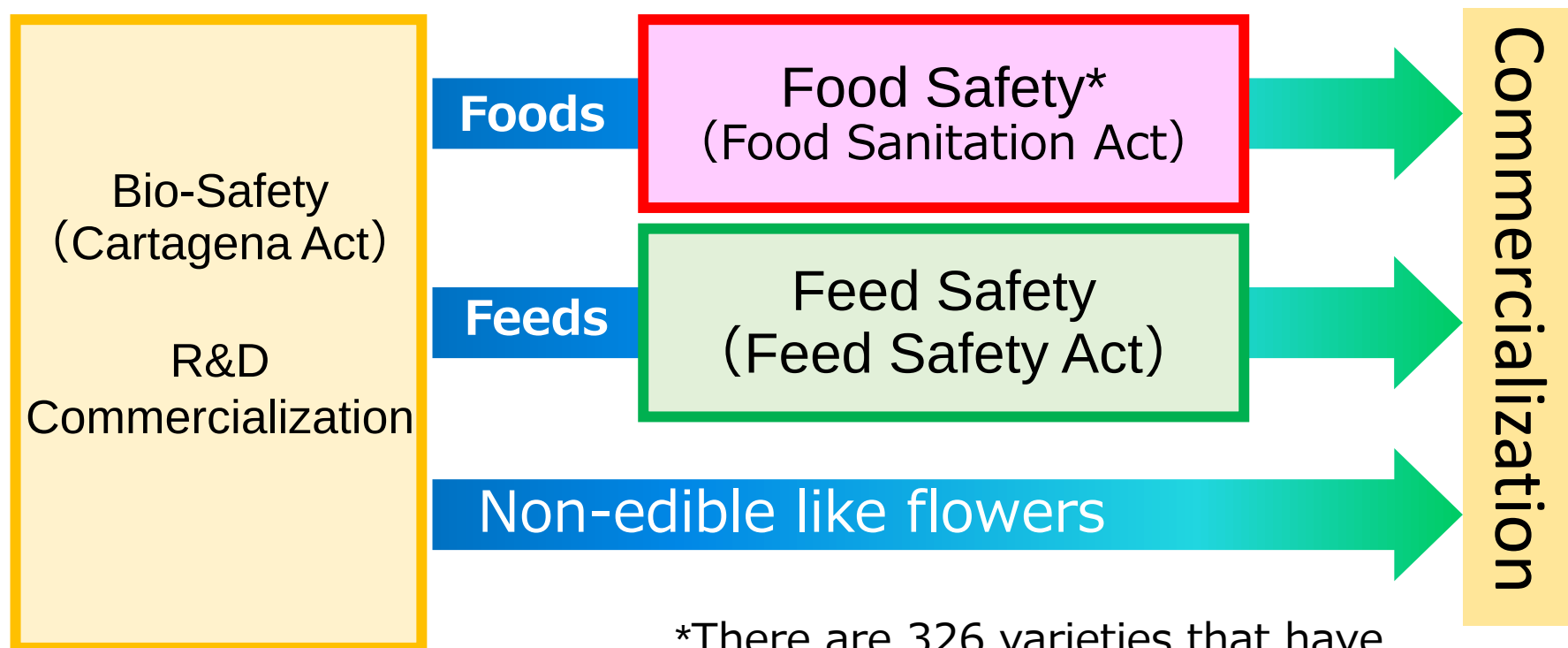


Top: GE puffer fish
Bottom: wild type

Safety Category	Legislation
Bio-Safety	Cartagena Act*
Food Safety	Food Sanitation Act
Feed Safety	Feed Safety Act

- Handling of genome-edited (GE) organisms was discussed whether GMO regulations are applicable to GE products.
- The handling policies of genome-edited organisms have been established from the perspective of biodiversity impact, food and feed safety.

* The law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms



*There are 326 varieties that have been confirmed food safety (as of October 17, 2021)

In this Act, “genetically modified organism and others” refers to **an organism having a nucleic acid obtained by use of the following technology or a copy thereof.**

- (i) Technology to process nucleic acid outside cells, which is specified by the ordinance of the competent ministry
- (ii) Technology to fuse cells of organisms belonging to different taxonomical families, as specified by the relevant ministry ordinance



GMO is defined as “*the organism **containing extracellularly processed nucleic acid or its replicate***”

Food Sanitation Act, Article 2(excerpt).

GM Food is defined as

*“the food including the organism which was obtained by recombinant DNA technique; the technique to generate recombinant DNA by cleavage/ligation, **insert the DNA into living cell and multiply**”.*

Cabinet Decision : June 15, 2018,

Clarify each handling policy for GE organisms and GE Foods under respective competent laws by the end of Mar 2019 and promote actions toward international harmonization.

Above decision accelerated the policy development.

New Biotech policy 2019 (draft)

Proposal from the Cabinet Office : June 11, 2019

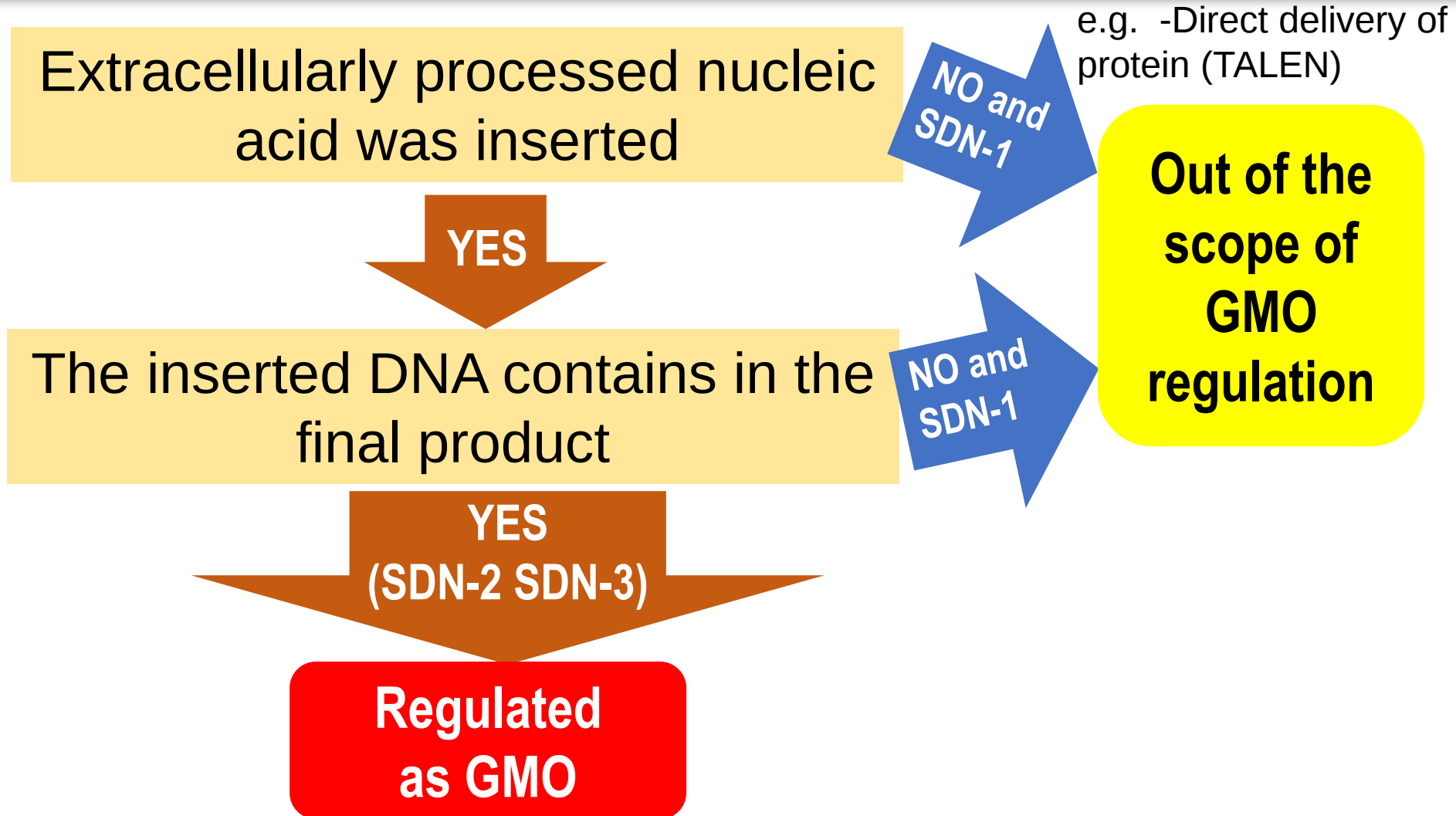
Operation of the handling system for non-regulated GE organism/food should be discussed and finalized by March, 2021 in order to encourage appropriate use of GE technology.

- 2019/2 Basic Handling Policy of Genome-edited Organisms under the Cartagena Act by the Ministry of the Environment
- 2019/3 Basic the Handling Policy of Genome Edited Foods by the Ministry of Health, Labour and Welfare (MHLW)
- 2019/5 Handling Policy of Genome-edited Organisms in the Research Field by the Ministry of Education, Culture, Sports, Science and Technology
- 2019/6 Handling Policy of Genome-edited Organisms in the field of mining and industry by the Ministry of Economy, Trade and Industry
- 2019/9 Handling Policy of Genome Edited Foods by MHLW.
- 2019/10 Handling Policy of Genome-edited Organisms in the Field of Agriculture, Forestry and Fisheries Ministry of Agriculture, Forestry and Fisheries (MAFF)
- 2020/2 Handling Policy of Genome Edited Feed and Feed Additives by MAFF

Handling of GE under Cartagena Act

Note: Cartagena Act is a regulation for bio-diversity of GMO

Handling of GE organisms under Cartagena Act



Cases GE is regulated as GMO

- ◆ Foreign gene (e.g. CRISPR/Cas-9) remains into a host genome or If we haven't confirmed that there are no foreign genes remaining.
 - However, null segregant of SDN-1 will be authorized as out of regulation after notification to competent authorities is accepted.
Note: Developers should handle genome-edited organisms under regulated until the notifications are accepted.
- ◆ Genome-edited organism contains extracellularly processed nucleic acid or its replicate (SDN-2, 3.)
 - Because SDN-2 and SND-3 contain integrated-extracellularly-processed nucleic acid into the genome.
 - However self-cloning* and natural occurrences ** are excluded from regulation of genetically modified organisms

*Self-cloning: Only the nucleic acid derived from an organism belonging to the same taxonomic species as the host are used.

**Natural occurrence: Only the nucleic acid derived from an organism belonging to sexually compatible under the nature conditions are used.

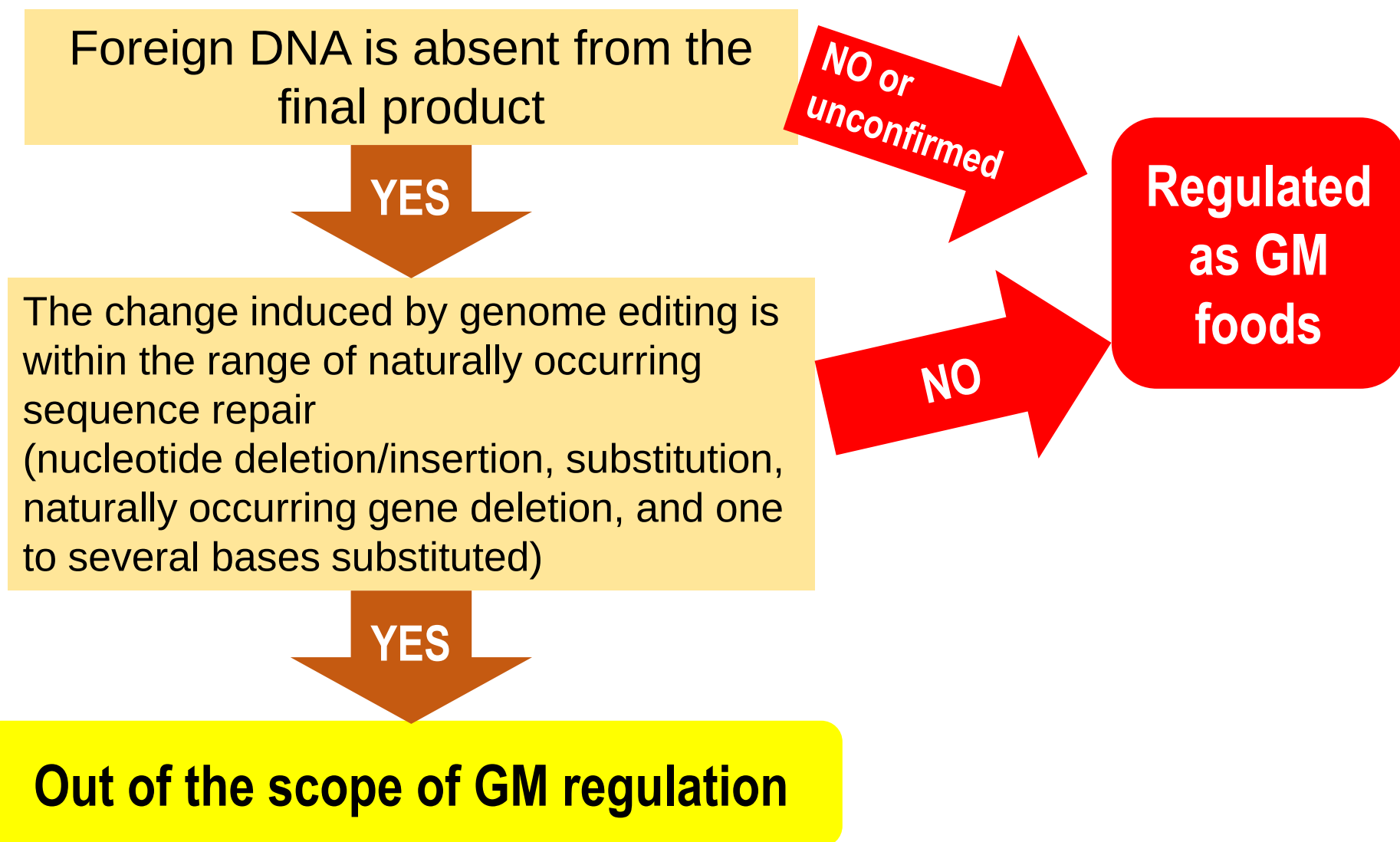
Considering the purpose of the Convention on Biological Diversity and Cartagena Protocol on Biosafety,

- **Request developers to submit a notice** including the information such as development processes and no impact on biodiversity in order to accumulate knowledge regarding GE organisms.
- Disclose a part of the notified information, with attention to confidential information, on Japan Biosafety Clearing House website.
- **Notification is not mandatory.**
 - ✓ However, regulatory agencies strongly urge developers to submit the notification.

- (a) The organism must be confirmed to be free of residual nucleic acids or copies of nucleic acids that have been processed outside the cell as defined in the Cartagena Act (including the basis for this)
- (b) The taxonomic species of the modified organism
- (c) The method of genome editing used for the alteration
- (d) The gene(s) that have been modified and the function of the gene(s)
- (e) Changes in the traits conferred by the modification
- (f) Whether or not there is any change in the trait other than (e) (and if so, the nature of the change)
- (g) The intended use of the organism
- (h) Consideration of the potential for biodiversity impact if the organism is used.

Handling of GE under Food Sanitation Act

Handling of GE foods and food additives under Food Sanitation Act

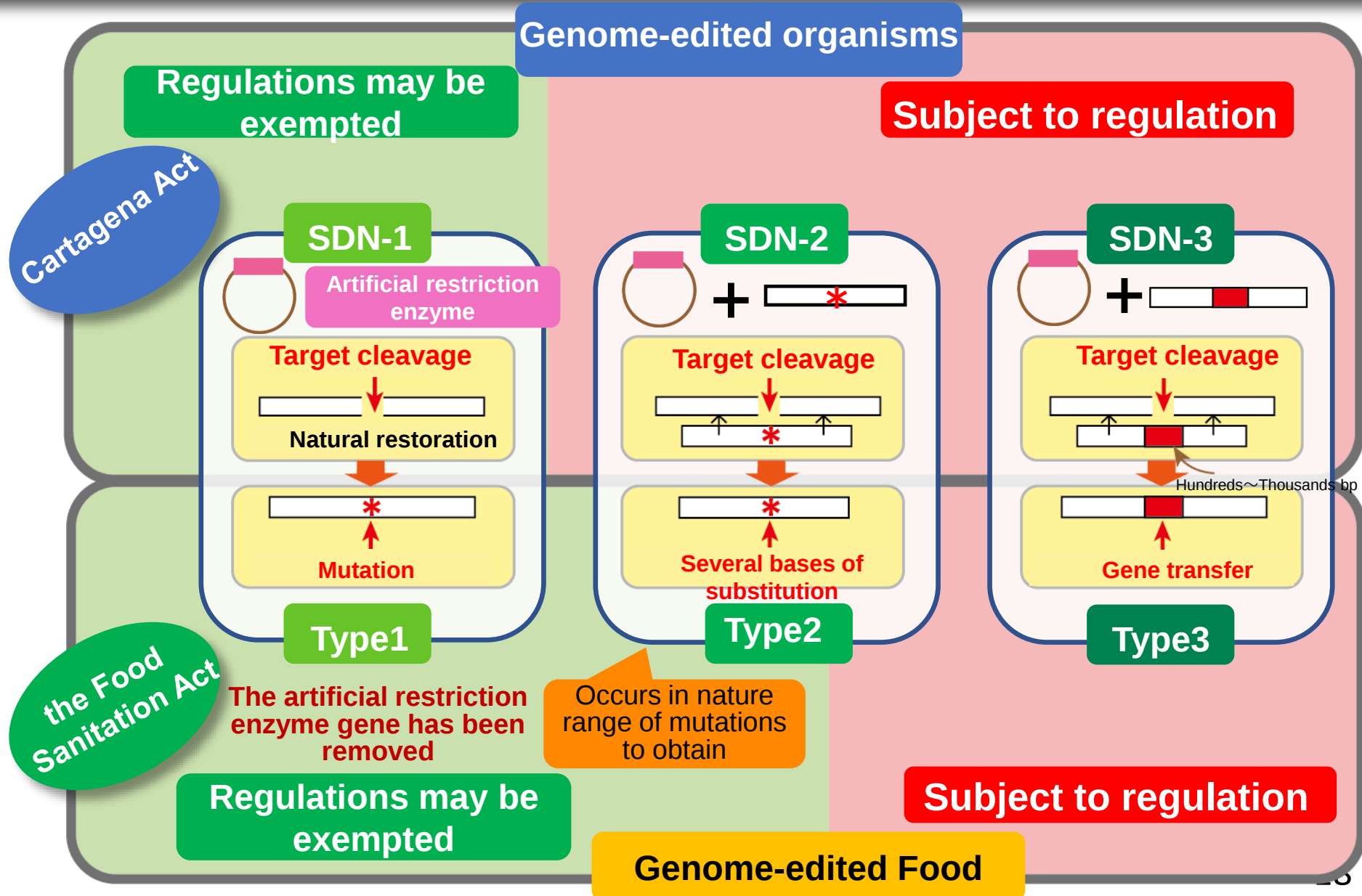


- ① Name and description of the food item/variety that was developed (method and purpose of use)
- ② Method of genome editing technology used and details of the modification
- ③ Information on the confirmation that there are **no remaining foreign genes or their parts**.
- ④ Information on the confirmation that the confirmed DNA changes do not result in the production of new allergens that adversely affect human health or an increase in known toxic substances contained.
- ⑤ Information on changes in major components (limited to nutritional components) related to the target metabolic system, in the case of products that have been modified to affect the metabolic system in order to increase or decrease a specific component.
- ⑥ Date of launch (*notified to the Ministry of Health, Labour and Welfare after launch)

Need to confirm that safety of genome edited foods is equivalent to that of conventional foods. Thus

- Request developers to submit a notice including the information such as development processes, in order to accumulate knowledge regarding genome-edited food.
- Disclose a part of the notified information, with attention to confidential information.
- Notification is not mandatory.
 - ✓ However, MHLW also strongly urges developers to submit the notification.

Comparison of handling policies under Cartagena Act and the Food Sanitation Law



Why does the regulatory agencies urge the notification even though it is not mandatory ?

- Mandatory notification system cannot be set under the situation that non-regulated GE organisms are considered to be indistinguishable from organisms derived from conventional mutations.
- On the other hand, regulatory agencies need to keep track of development and commercialization of GE organisms because some people are worried about GE organisms and foods.
- If genome edited organisms containing foreign genes are marketed as null segregants, developers and regulatory agencies will lose their reliability from the public.
- Consultation with agencies prior to the notification shall be very important.

Null Segregant is a prerequisite for exempting genome-edited organisms from regulation.

Southern blot analysis

PCR: Polymerase Chain Reaction

NGS: Next Generation Sequencing

NGS-Kmers method

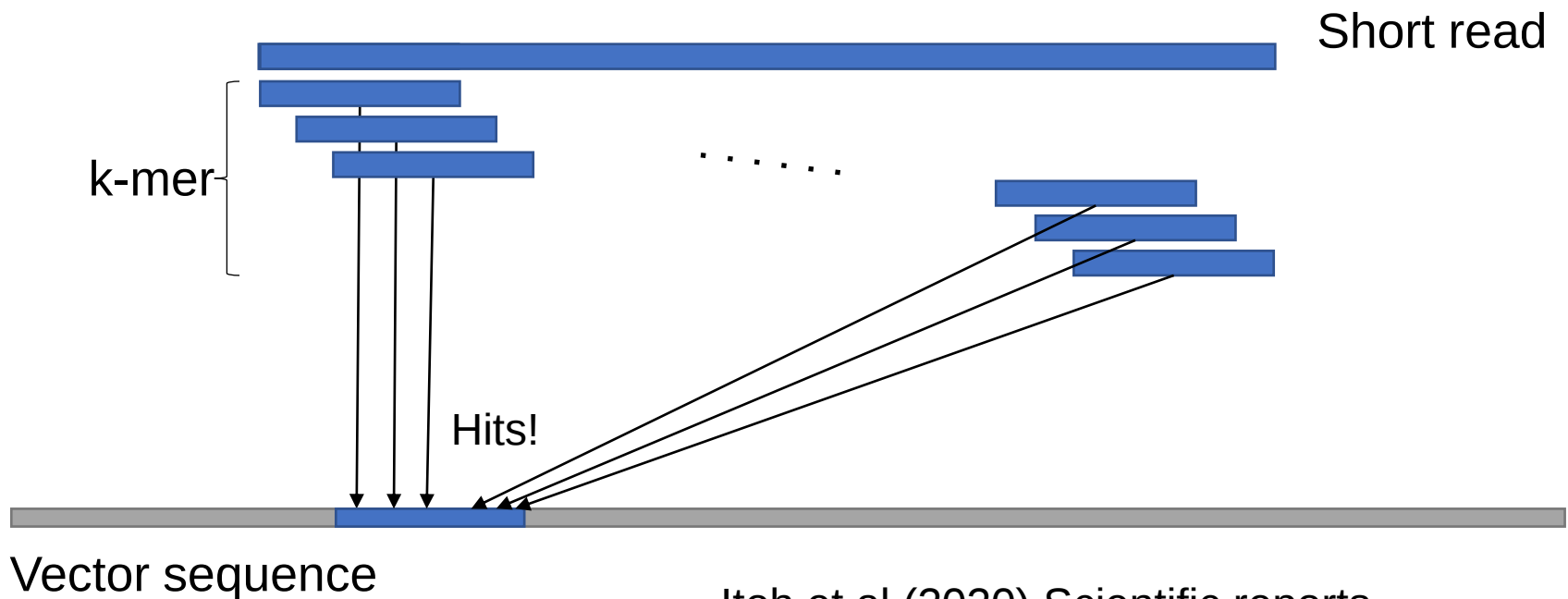
Ito et al. (2020)

Foreign DNA detection by high-throughput sequencing to regulate genome-edited agricultural products.

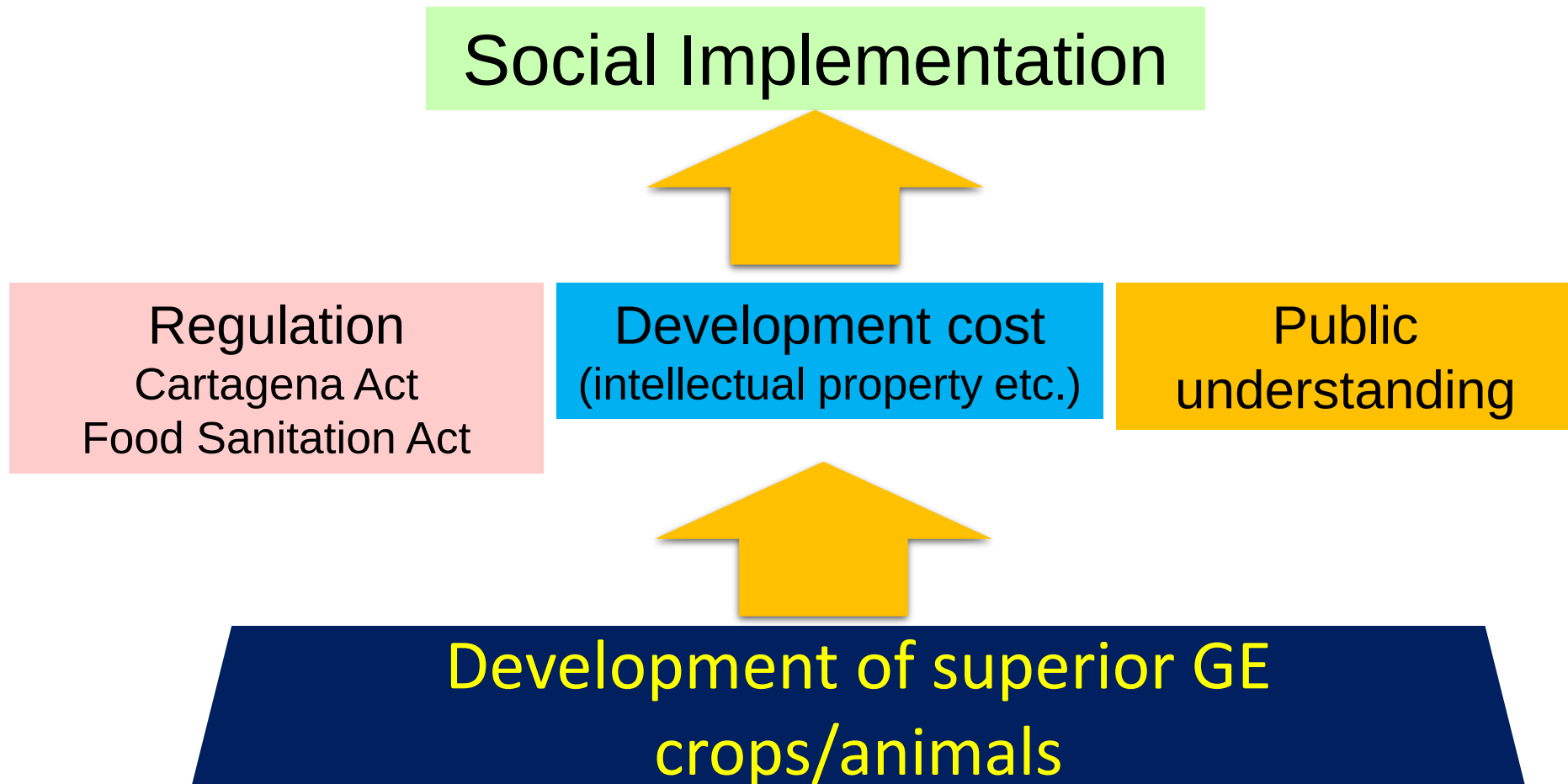
Sci Rep Mar 18, 2020 ;10(1):4914. doi: 10.1038/s41598-020-61949-5.

Detection of External DNA Sequences by Small Fragment Pattern Matching

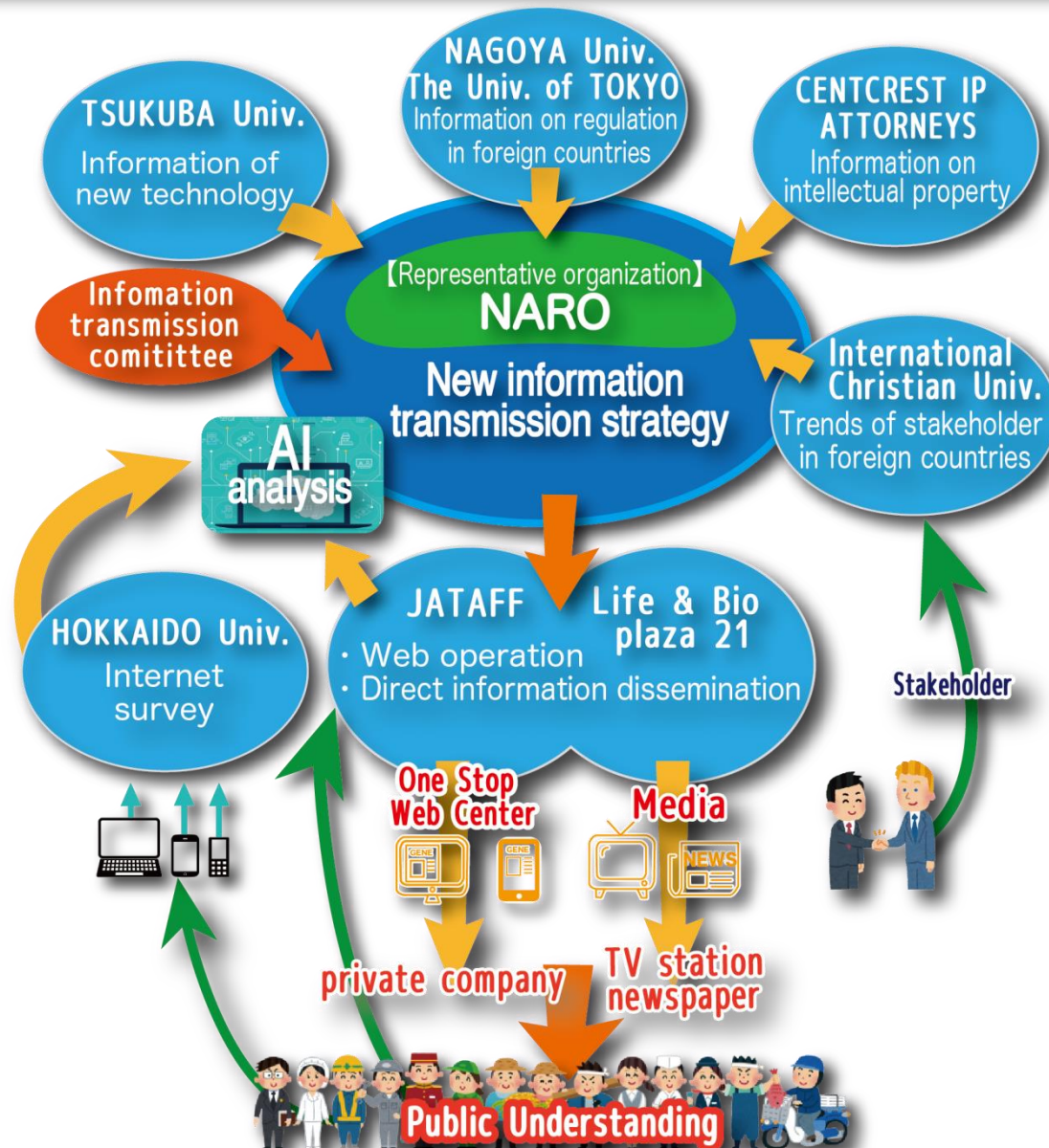
- ◆ Obtain short reads of NGS from a sample applied by genome editing.
- ◆ Extract k-mers, the sequence of k nucleotides in length, from the reads.
- ◆ If vector sequence remains in the progeny of genome editing, there should be some k-mers that match the vector sequence.



Itoh et al.(2020) Scientific reports
<https://doi.org/10.1038/s41598-020-61949-5>



Promoting the Public Understanding of Genome editing



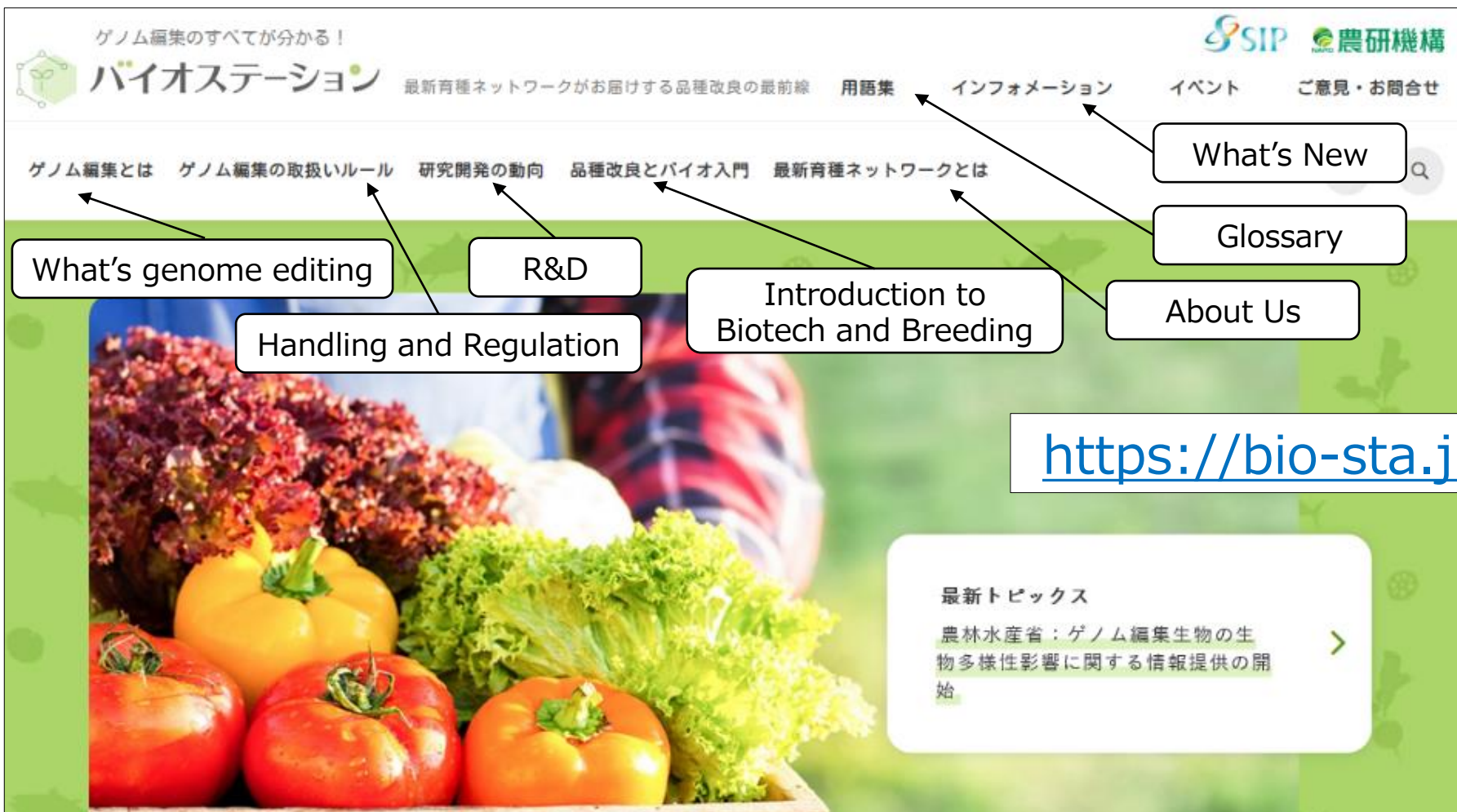
Measures

- Establishment of one-stop website for the information
- Whenever new information is posted on the website, it will be sent to those who have registered in advance.
- Research using AI for appropriate information and their distribution.

Promoting the Public Understanding of Genome editing

Communication

We have created a website named “**Bio-Station**” to provide accurate information regarding genome editing.



The screenshot shows the homepage of the Bio-Station website. The header includes the NARO logo and the text "ゲノム編集のすべてが分かる！" (Everything about genome editing is understandable!). The main navigation bar contains links for "用語集" (Glossary), "インフォメーション" (Information), "イベント" (Events), and "ご意見・お問合せ" (Opinions/Inquiries). Below this, a secondary navigation bar lists topics: "ゲノム編集とは" (What is genome editing), "ゲノム編集の取扱いルール" (Handling and Regulation), "研究開発の動向" (R&D), "品種改良とバイオ入門" (Introduction to Biotech and Breeding), and "最新育種ネットワークとは" (What is the latest breeding network?). The main content area features a large image of fresh vegetables (tomatoes, bell peppers, and lettuce) with several callout boxes pointing to specific sections: "What's genome editing" points to "ゲノム編集とは", "Handling and Regulation" points to "ゲノム編集の取扱いルール", "R&D" points to "研究開発の動向", "Introduction to Biotech and Breeding" points to "品種改良とバイオ入門", "What's New" points to "インフォメーション", "Glossary" points to "用語集", and "About Us" points to "ご意見・お問合せ". A "最新トピックス" (Latest Topics) section at the bottom right highlights a new information provision by the Ministry of Agriculture, Forestry and Fisheries regarding genome editing and biodiversity.

ゲノム編集のすべてが分かる！
バイオステーション 最新育種ネットワークがお届けする品種改良の最前線

用語集 インフォメーション イベント ご意見・お問合せ

ゲノム編集とは ゲノム編集の取扱いルール 研究開発の動向 品種改良とバイオ入門 最新育種ネットワークとは

What's genome editing

Handling and Regulation

R&D

Introduction to Biotech and Breeding

What's New

Glossary

About Us

<https://bio-sta.jp>

最新トピックス
農林水産省：ゲノム編集生物の生物多様性影響に関する情報提供の開始

Non-target DNA mutations (Off-target)

DNA mutations induced by artificial restriction enzymes such as CRISPR recognizing and cleaving similar sequences other than the original target DNA sequence

Such mutations can occur through natural mutations and mutagenesis as well

Crop and livestock breeding

- History of utilizing unexpected mutations for breeding
- Possible to remove products having undesired edits
- Off-target mutation is not an issue in breeding

Human medical treatment

Possibility of causing unexpected effects, which should not happen in gene therapy etc.

Careful handling is required

Genome editing technology hardly causes off-target effects
Researches have been being conducted all over the world to reduce off-target effects

- Sept. 2019, Consumer Affairs Agency (CAA) issues labeling policy on non-regulated genome-edited foods

Currently, it is not subject to the food labeling standards.

Reason for the policy

- It is scientifically impossible to distinguish whether a food with no residual exogenous genes was produced using genome editing technology or conventional breeding technology.
- In addition, there is currently an inadequate system of communication of information on food products using genome editing technology by means of documents such as records of transactions in Japan and abroad.
- However some consumers require labeling of genome-edited foods for selection.

In the future, CAA will consider reviewing the labeling policies as necessary after collecting information on distribution conditions and labeling systems in other countries as needed.

- The Japanese government has clarified handling policy for genome-edited organisms, and genome-edited by 2020.
- Although these policies are not mandatory, prior consultation and information provision to regulatory authorities is strongly encouraged.
- In the Food Sanitation Act, the handling policy of subsequent hybrids of notified genome-edited crops and original crops is under discussion.
- Offspring bred by conventional breeding from genome-edited crops that have been fully notified are not regulated.
- The Consumer Affairs Agency has indicated that it will not require mandatory labeling for genome-edited foods.
- We have established an "information hub" for effective communication to the media, educational circles and others, and are promoting public understanding.

Thank you for
your attention

