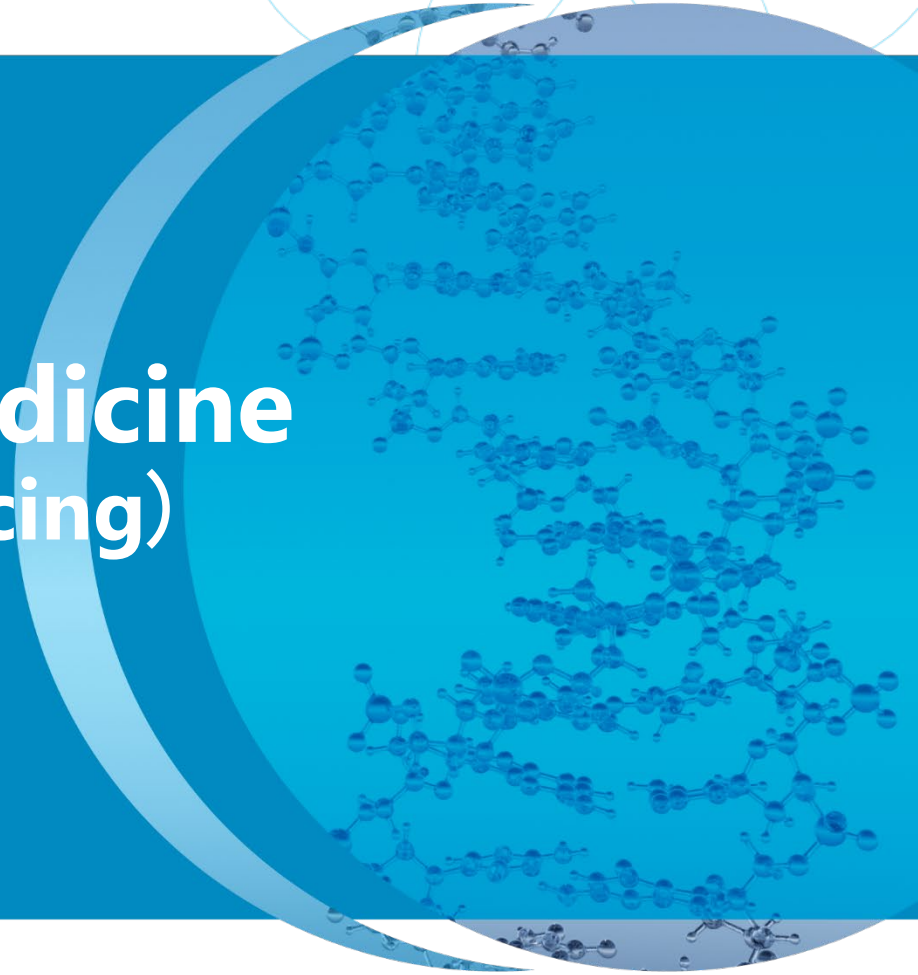
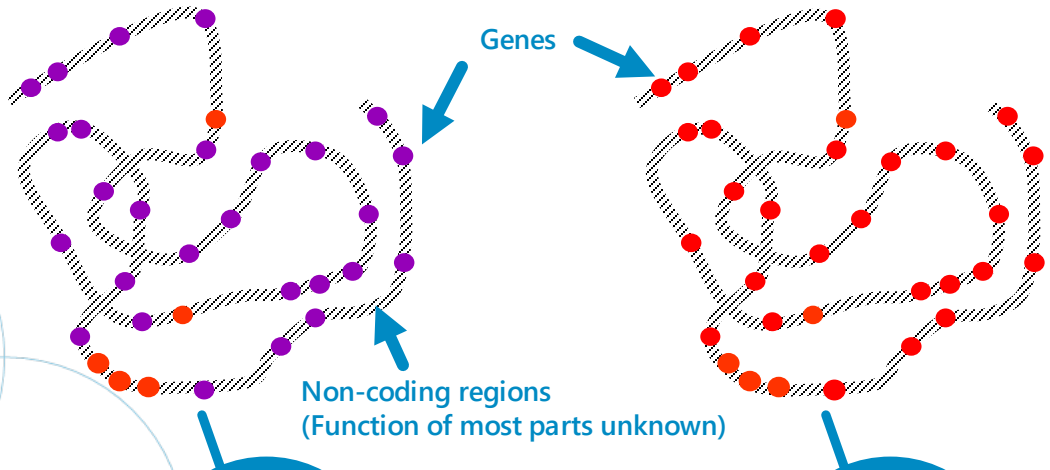
Cancer Genomic Medicine
(Whole Genome Sequencing)



Whole Genome Sequencing (WGS)

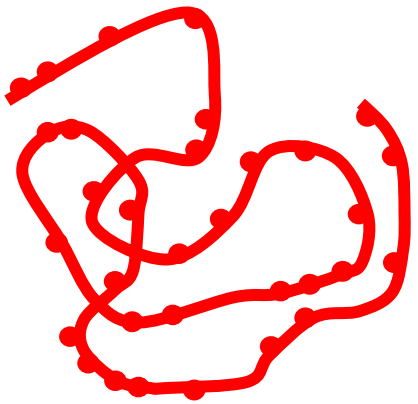
WGS surveys regions whose function and association with diseases is little known. It is anticipated to drive our understanding of the causes of cancer, and with its findings, the development of new diagnostics and therapies.

Gene Panel Tests	*Whole Exome Sequencing*	*Whole Genome Sequencing*
(Tests multiple genes associated with cancer)	(Tests all coding DNA)	(Tests all coding/non-coding DNA)



0.02% of whole genome

1.5% of whole genome



Entire genome sequenced
Towards understanding causes of cancer, development of new diagnostics and therapies

Whole Genome Sequencing (WGS) Action Plan (20 Dec 2019)

Objective

- Whole genome sequencing drastically improves precision of individual treatments and advances precision medicine. Its deployment aims to advance medicine, developing treatments for cancers and intractable diseases.

Steps

- **Cancer WGS** will start with a preliminary study to identify genomic variants characteristic of Japanese, as the guidelines and full WGS scheme is developed. **Biobank specimens of maximum 64,000 subjects (130,000 genomes) stored, plus additions,** will be examined up to three years.

- The cancer preliminary analysis will first pick samples of assured quality, with patients' consent and clinical information. Of them, samples of **intractable cancers with low 5-year survival rates, rare cancers (including childhood), and hereditary cancers (including childhood), from 16,000 subjects (33,000 genomes) plus additions,** will be sequenced, utilizing available human resources and facilities.*

- Intractable diseases WGS will also conduct a preliminary study whilst guidelines and a full-scale analysis scheme are formed. **Specimens of maximum 28,000 subjects (36,000 genomes) stored, plus additions, will be analyzed onsite,** for up to three years.

- The intractable diseases preliminary study will first select samples of assured quality, with patients' consent and clinical information. They will be classified **into monogenic diseases, multifactorial diseases, and those difficult to diagnose. 5,500 subjects (6,500 genomes) plus additions,** identified most likely to benefit from WGS will be examined further, utilizing available human resources and facilities.*

- In view of the results from the preliminary studies, and developments in international research, promising areas for new diagnoses and treatments development will be identified. Targets will be set for specimen collection and analyses, to be reviewed as required.

- *Prioritization follows the expert committee recommendation, as WGS capacity is still limited, in development.

Establishing a framework, training specialists, issues for future discussions

- In preparation for full-scale WGS, a framework will be developed, as deliberations on personnel training, ethical, legal, and social implications, partnerships with industry and information sharing, intellectual property policies, cost sharing, and synergies with priority research will continue.

Excerpts from submissions to Expert Committee for the Promotion of WGS (31 May 2021)

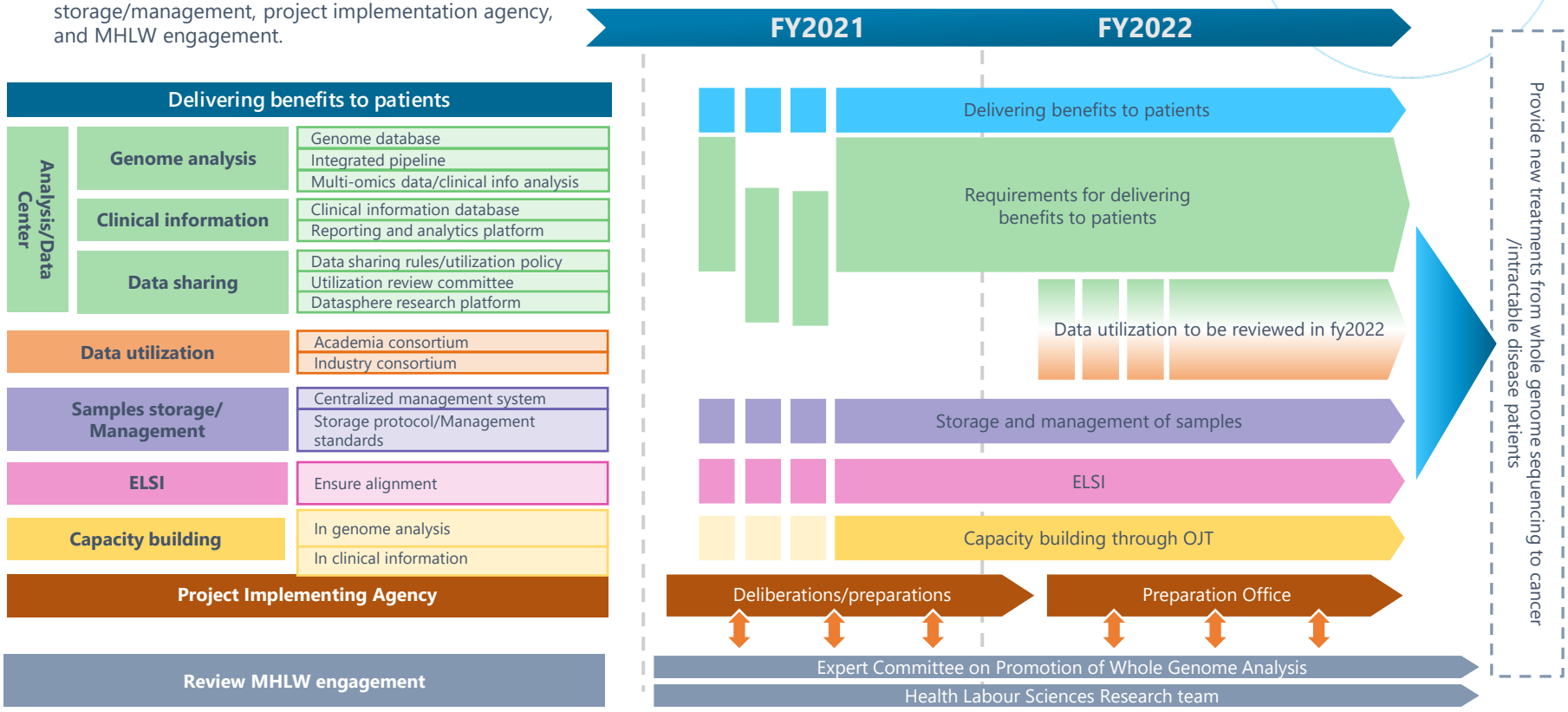
WGS Initiative Objectives

- Expedite the delivery of whole genome sequencing benefits to patients
- Implement novel individualized treatments, and incorporate into routine medicine
- Utilize whole genome sequencing in research and in drug development

Partially revised from submissions to the Expert Committee for the Promotion of Whole Genome Sequencing (2 Mar 2022)

Action Plan for Whole Genome Sequencing Roadmap 2021

- Implementation plan fy2021-2022 on delivering benefits to patients, analysis/data center, data utilization, samples storage/management, project implementation agency, and MHLW engagement.



(Excerpts from submissions to the Expert Committee for the Promotion of Whole Genome Sequencing (2 Mar 2022))

Whole Genome Sequencing (WGS) Action Plan -Track Record

The WGS Action Plan Priorities:

Cancers - Intractable cancers with low 5-year survival rates, Rare cancers (Including childhood) associated with rare genetic mutations, Hereditary cancers (Including childhood)

Intractable Diseases – Monogenic diseases, Multifactorial diseases, and Those difficult to diagnose

WGS achievements/Future plans

Oncology	*Analyses results*		***Analyses plans***
	(FY 2020)	(FY 2021)	(FY 2022)
• Intractable cancers (leukemia, esophageal cancer, liver cancer, biliary tract/pancreatic cancer, lung cancer, ovarian cancer)	500 Subjects ▪ Pancreatic cancer ▪ Leukemia ▪ Sarcoma	10,000 subjects, with stored specimens, of survivors to whom results may prove beneficial, with the following cancers: • Blood • Digestive tract • Gynecologic tract • Respiratory tract • Rare • Childhood to include 600 new patients	Intractable cancers, Hereditary cancers, Childhood , etc. 2000 new subjects
• Rare cancers (Childhood included)			
• Hereditary cancers (Childhood included)	3,250 Subjects		
Intractable diseases			
• Monogenic • Multifactorial • Those difficult to diagnose	2,500 Subjects	800 Subjects	2,500 Subjects

Action Plan for Whole Genome Sequencing

- Objectives, Strategic Deliverables

Objectives	Strategic deliverables	Implementation specifics
Deliver benefits to patients as early as possible	Approval as advanced medical care, then insurance coverage, of treatments/new diagnostics with efficacy underpinned by evidence. Delivery timeframe: short term	● Basic cohort - Establish means to deliver off-label drugs expediently to patients clinically indicated
Establish new personalized medicine, implement into routine medical care	Establish new personalized medical care through novel clinical trials, towards implementation in routine clinical practice. Delivery timeframe: several years ahead	● Strategic cohort - Establish means to expand indications of approved drugs for known and newly identified mutations - Conduct clinical studies for new personalized medical care
Utilize whole genome sequencing in research and drug discovery	Further collaborate with academia and industry, promoting research and drug discovery. Delivery timeframe: longer term	● Set up industry/academic consortiums, supported by preparation agencies of project implementation agency ● Data utilization promotion by project implementation agency ● Promotion of multi-omics data/clinical info analysis

Basic Cohort

Establish means to deliver off-label use drugs to patients clinically indicated

Strategic Cohort ***a***	Establish means to expand indications of approved drugs for known and newly identified mutations
Strategic Cohort ***b***	e.g. Immunogenomic cohort assembly, clinical trials for new personalized medical care
Strategic Cohort ***c***	e.g. Liquid, omics analysis additional cohort assembly, clinical trials for new personalized medical care
Strategic Cohort ***d***	e.g. Cohorts by organ (scirrhous gastric cancer, pancreatic cancer, TN breast cancer), AI analysis cohort

(1) Centralized management, (2) Whole genome sequencing, (3) Clinical data collection, (4) Data sharing/ Research support system establishment

Basic cohort, strategic cohort a envisaged to enroll all patients. Strategic cohorts to be established by clinicians, drawing on the experience of Group A.
Each cohort will appoint a leader, each being unique, some cases can be assembled into multiple cohorts.
Each strategic cohort to start a prospective clinical study during fy2022.

Action Plan for Whole Genome Sequencing

- Government Policies

Basic Policy on Economic and Fiscal Management and Reform 2023 (Cabinet decision, 16 Jun 2023)

To address the 'lag/loss' drug issues, the following to be enacted, to empower drug discovery, promote development of innovative pharmaceuticals, medical devices, regenerative medicine products, shifting to an R&D-oriented business model:

- Incorporate innovative value in setting/regulating drug prices, particularly upon inclusion in insurance coverage
- Develop platform for multiomics analyses and clinical information, through Action Plans for Whole Genome Sequencing (MHLW, 30 Sep 2022)
- Establish means to deliver benefits from the analysis to patients
- Support startups from academia
- Strengthen hubs in Asia for harmonizing clinical development and regulations
- Review data requirements for Japanese patients participating in global clinical trials
- Expedite review/approval of drugs for pediatric and rare diseases, with pharmaceutical policy adjustments and augmenting resources for review teams

Grand Design for New Capitalism and Action Plan (Cabinet decision, 16 Jun 2023)

Whole genome sequencing of cancer/intractable diseases built up to 100,000 genomes, for benefits to be delivered to patients, with an information platform developed. Legal entity structure to be determined within fy2023, for launching project implementation agency within fy2025. The agency, genome biobank to lead collaborations with medical/research institutes, start-ups, of medicine, pharmaceuticals, biotechnology, and mathematics, to utilize whole genome/multiomics analyses and clinical information for successful drug discovery.

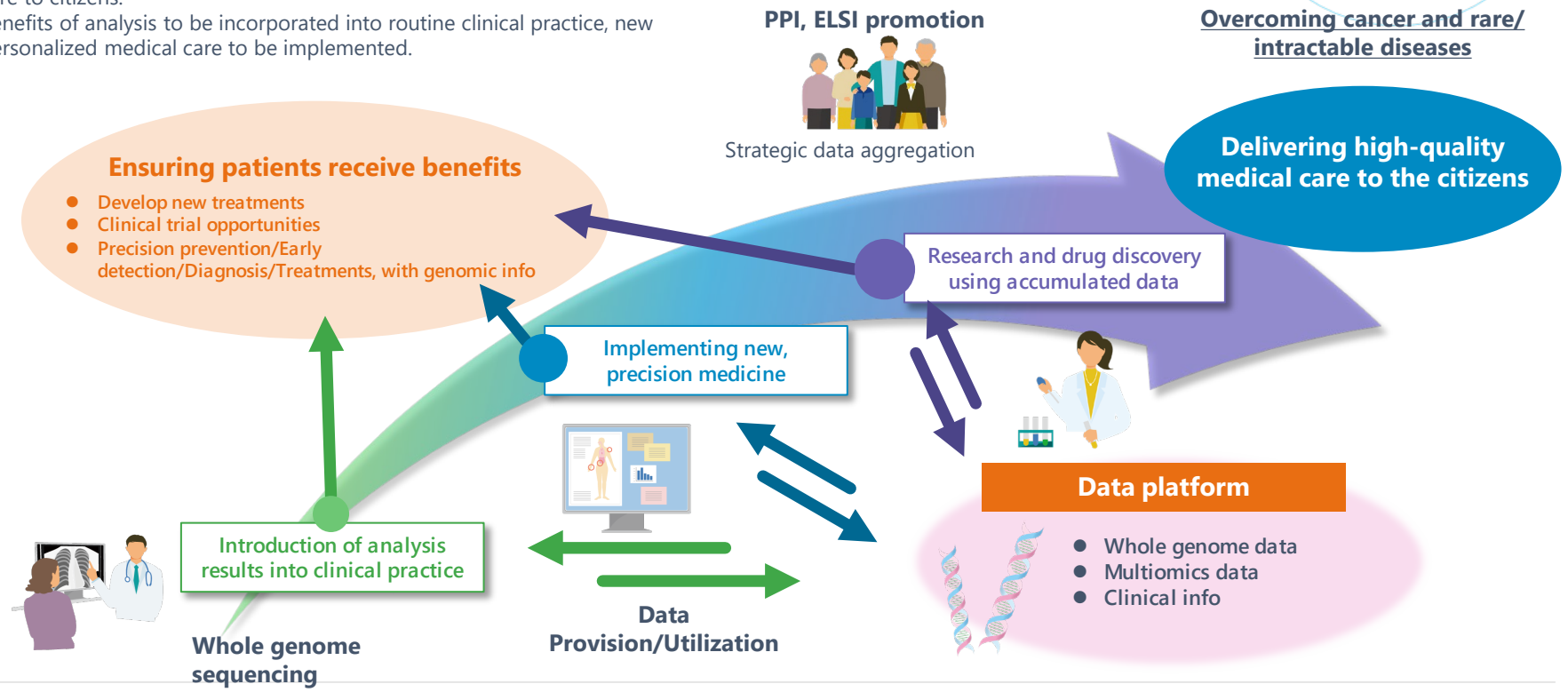
Integrated Innovation Strategy 2023 (Cabinet decision, 9 Jun 2023)

To implement 'Action Plan for Whole Genome Analysis 2022' (Sep 2022) and deliver high-quality medical care, a high-quality information platform with whole genome data from patients with cancer/intractable diseases will be developed, industry and academia encouraged to utilize data to develop new treatments. For expedient introduction of analysis results into medical care, and pioneering new personalized medical care, discussions towards establishing such an agency will be held.

Action Plan for Whole Genome Sequencing 2022 (30 Sep 2022)

Future vision of medicine, with whole genome sequencing

Overcome cancer and rare/intractable diseases by strategically aggregating data and utilizing in research and drug development, deliver high quality medical care to citizens.
Benefits of analysis to be incorporated into routine clinical practice, new personalized medical care to be implemented.



Partially revised from submissions to Expert Committee for the Promotion of Whole Genome Sequencing (15 Nov 2022)

Action Plan for Whole Genome Sequencing 2022 (Sep 2022) - Features

Context/Objective

- At initial phase, benefits from analyses were incorporated into routine clinical medicine and new personalized medical care
- Full-scale analyses is to overcome cancer and rare/intractable diseases, by delivering high quality medical care to citizens. Towards this aim, data is to be strategically aggregated to be utilized in research and drug development.

	FY2019 - 2021	FY2022	FY2023	FY2024	FY2025-
Phases	Initial analysis (Existing samples)	*Full-scale analysis (new patient specimens)*			
Action plan	1st edition	Action plan 2022			
	○ Policy set, full-scale analysis means established	○ Strategically aggregate data ○ Incorporate benefits into medical care at early stages ○ Implement new personalized medical care → Deliver high-quality medical care to citizens			
Achievements/plans	**19,200 cases** Cancer*: 13,700 (with 600 new patients) rare/intractable diseases†: 5,500	○ Analyse 100,000 genomes, multiomics (comprehensive information on biomolecules) analysis			
Deliver benefits to patients	○ Established means of delivery	○ Deliver high-quality medical care throughout the nation, through the utilization of whole genome sequencing outcomes			
Information platform	○ Verified technical issues ○ Established integrated pipeline	○ Establish an integrated information platform connecting clinical data with whole genome analyses, while also implementing supplementary provisions for its utilization, with a focus on advancing drug discovery for cancer and rare/intractable diseases.			
Project implementation agency	○ Discussed structure of agency for full-scale analysis	○ Set up the Project Implementation Preparation Office within the Japan Health Research Promotion Bureau (JH) in fy2022, finalize its organizational structure. ○ Finalize organizational structure under MHLW leadership by approximately fy2023, in preparation for launching in fy2025.			
ELSI/PPI	○ Discussed ELSI/PPI issues for full-scale analysis	○ Set up an ELSI Division within the agency staffed with specialists, to ensure all aspects of the initiative are cleared for ELSI elements ○ Set up a Patient and Public Involvement Division within the agency, to reflect patients/public opinion in the initiatives implemented at research/medical institutions.			

* Intractable cancer, rare cancers (including childhood), hereditary cancers (including childhood) † monogenic/multifactorial/difficult-to-diagnose diseases

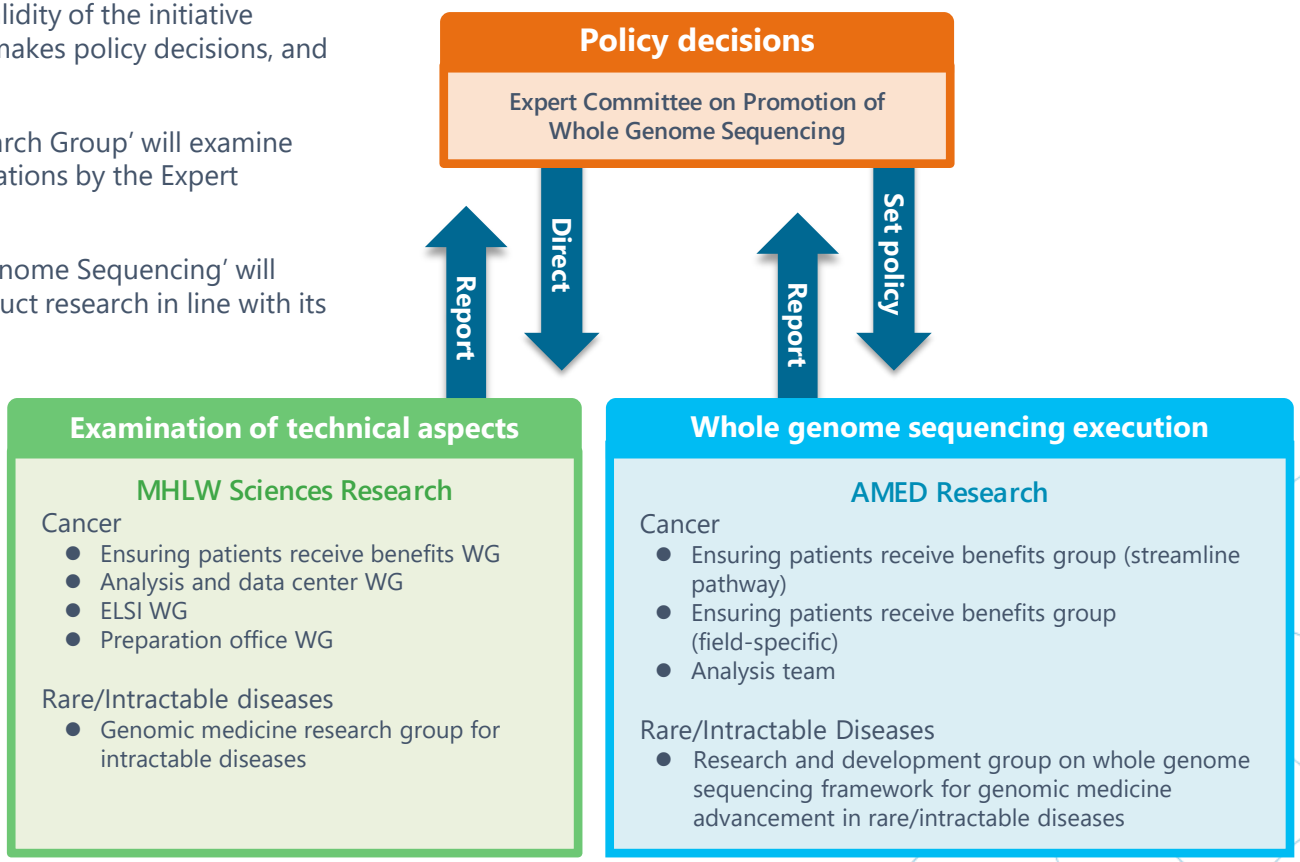
Partially revised from submissions to the Expert Committee for the Promotion of Whole Genome Sequencing (15 Nov 2022)

Whole Genome Sequencing - Execution (FY 2022)

'Expert Committee on Promotion of Whole Genome Sequencing' evaluates, and verifies validity of the initiative execution, as set on the action plan, makes policy decisions, and sets out necessary instructions.

'MHLW Health Labour Sciences Research Group' will examine technical matters, prepare for deliberations by the Expert Committee.

'AMED research groups for Whole Genome Sequencing' will report to the Expert Committee, conduct research in line with its policies and set timelines.



Excerpts of submissions to Expert Committee for the Promotion of Whole Genome Sequencing (10 Jul 2022)

Research Group On whole genome sequencing of cancer and its clinical application, data analysis/storage center, patient confidentiality, and ELSI（MHLW Science Research Nakagama Group）

Representative
Hitoshi Nakagama
(National Cancer Center)

(1) Delivering benefits to patients WG

- Takashi Kohno (NCC)
  - Katsutoshi Oda (The University of Tokyo)
  - Collaborators

(2) Analysis and Data WG

- Seiya Imoto (The University of Tokyo)
  - Yuichi Shiraishi (NCC)
  - Collaborators

(3) ELSI WG

- Megumu Yokono (Waseda University)
  - Shimon Tashiro (Tohoku University)
  - Collaborators

(4) Preparation Office WG

- Kazunori Aoki (NCC)
  - Katsushi Tokunaga (NCGM)
  - Collaborators

WGs (1), (2), and (3) to deliberate with experts representing various fields, relevant academic societies, patient groups, data utilization organizations, and report to the Expert Committee on Promotion of Whole Genome Sequencing.

WG (4) to discuss towards the establishment of a preparation office for the launch of the Project Implementation Organization.

Excerpts from submissions to Expert Committee for the Promotion of Whole Genome Sequencing (10 Jul 2022)

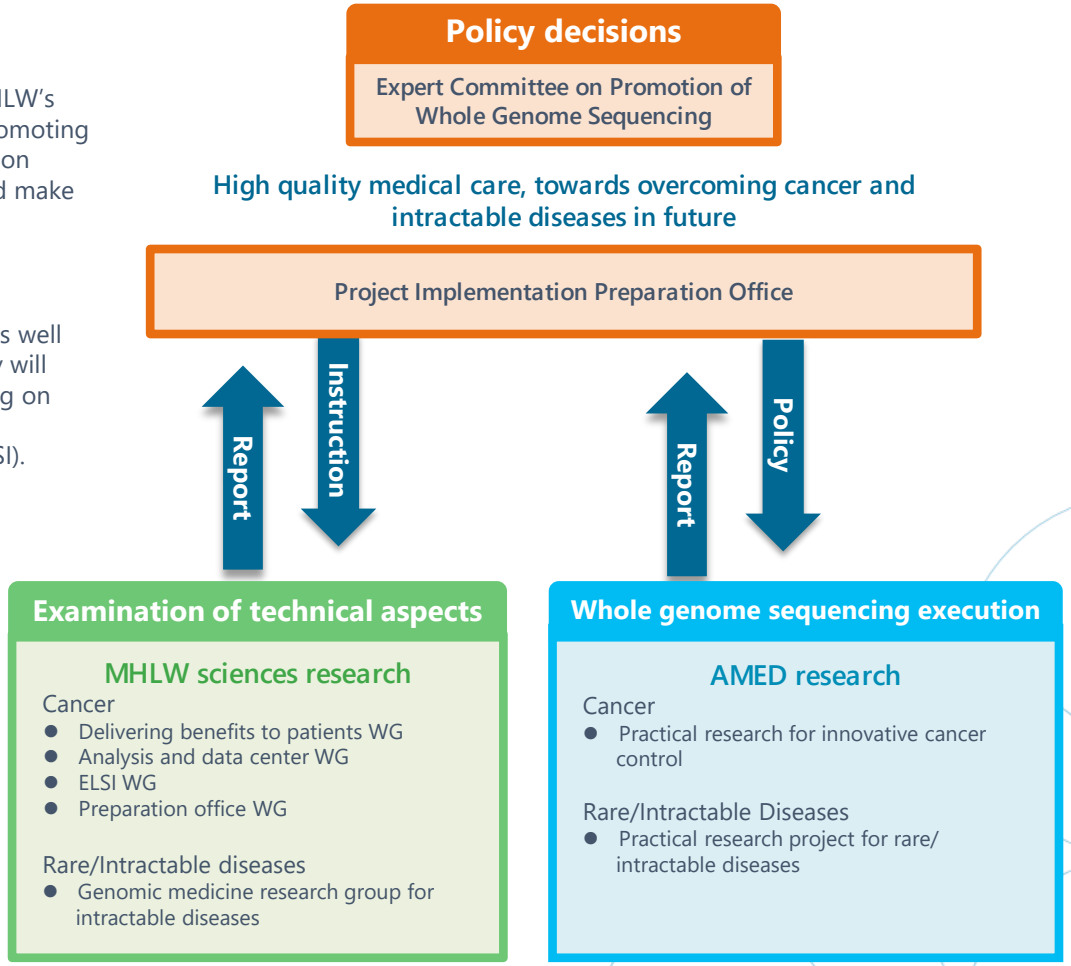
Whole Genome Sequencing - Execution (FY 2023)

- 'Expert Committee on Promotion of Whole Genome Sequencing, established under the Science and Technology Division of the MHLW's Health Sciences Council, is vested with the highest authority in promoting whole genome sequencing. The Expert Committee will deliberate on advancing the current Action Plan, monitor initiative progress, and make requisite decisions.

- 'MHLW Health Labour Sciences Research Group' comprises experts well versed in the practical aspects of whole genome sequencing. They will draft a basic plan for discussions at the Expert Committee, focusing on technical aspects related to ensuring patients receive benefits, analysis/data center, and ethical, legal, and social implications (ELSI).

- The AMED research groups on Whole Genome Sequencing will report on the analysis status to the Expert Committee. They will conduct research in alignment with the Expert Committee's policy, collaborating with the Project Implementation Preparation Office. Progress management will be overseen by AMED to ensure appropriate advancement.

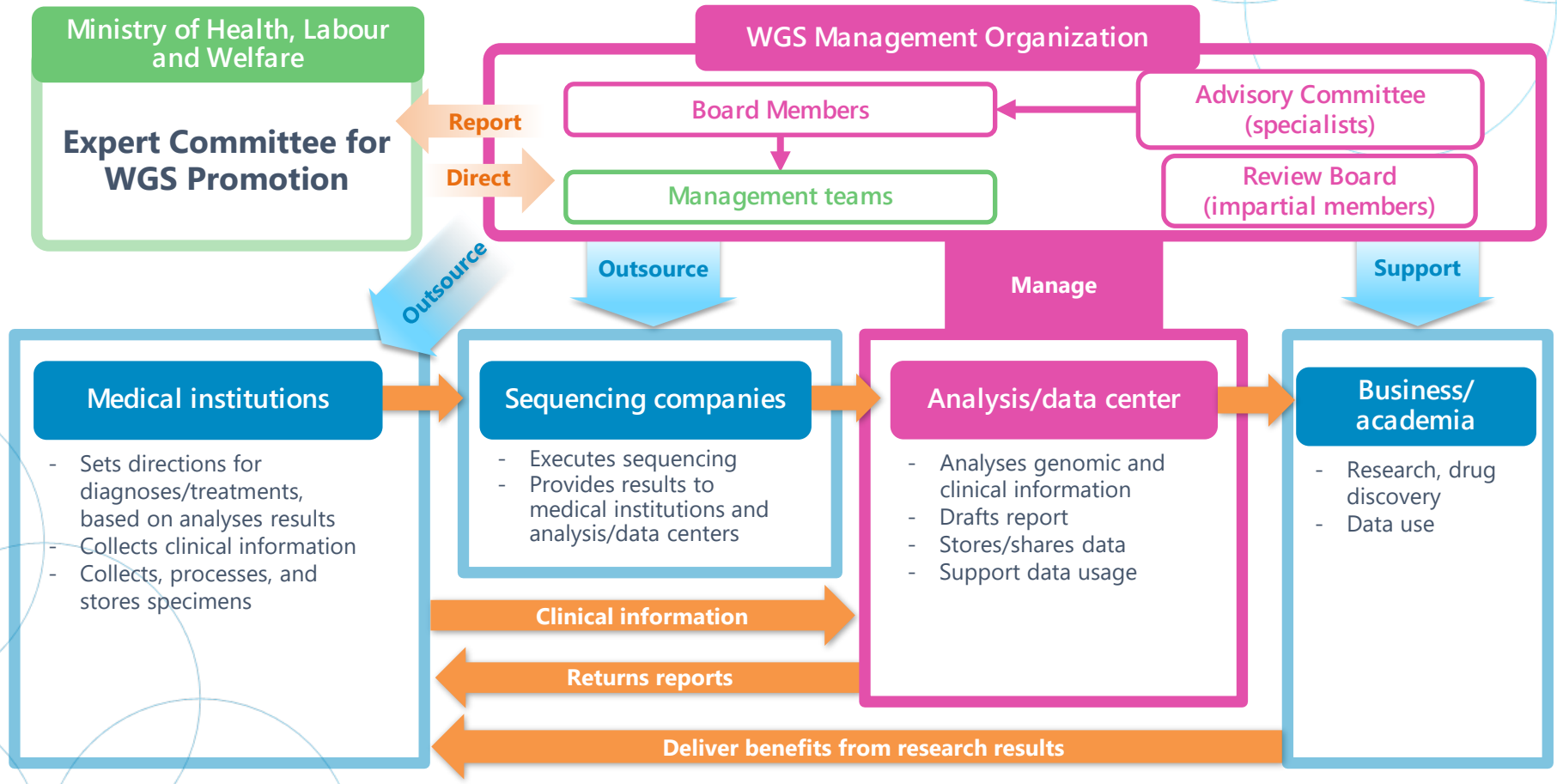
- The Project Implementation Preparation Office will lay out the specifics for establishing the project implementation agency. Furthermore, consortia will be established to encourage industry-academic collaboration, facilitating the utilization of data for research and development in drug discovery and diagnostic technologies. This initiative aims to expedite the delivery of results to patients.



Excerpts of submissions to Expert Committee for the Promotion of Whole Genome Sequencing (10 Jul 2022)

Ministry of Health, Labour and Welfare Review

- Whole Genome Sequencing（WGS）Future Perspective: Proposal -



Excerpt from documents submitted to Expert Committee for the Promotion of WGS (31 May 2021)

Whole Genome Sequencing Implementation Summary

Outline

Name: Whole Genome Sequencing Implementation Agency

Summary: Support prompt return of results/outcomes to patients, promote personalized medical care, establish framework to promote utilization of strategically aggregated data to promote research and drug discovery and deliver high-quality medical care to the public.

Context

In recent years, significant advancements are made in global whole genome research. Upholding principles of patient-centeredness and to deliver tangible benefits to patients, it is imperative to establish a data platform that integrates clinical information with whole genome sequencing. Moreover, a framework for promoting drug discovery and introducing new personalized medical care should be developed. It is crucial to incorporate the perspectives of patients, their families and the public in these initiatives. Ultimately, patients should swiftly reap the benefits of their contributions.

Objectives

Provide the public with high quality medical care and overcome cancer/intractable diseases in future.

Fundamental Strategy

○ Domains

- Cancer — Intractable/rare/childhood/AYA generation/hereditary cancers
- Rare/intractable diseases — Monogenic/multifactorial/difficult to diagnose diseases, cases with anticipated outcomes

○ Strategy

1. Utilization in research and drug discovery
- Strategic data aggregation
- Engagement with and proactive support for industry and academia

2. Towards early integration into routine medical care
- Support establishment of mechanisms for integration within medical institutions
- Support expedited delivery of drugs, through clinical research

3. To realize new personalized medical care

Cancer

Research and development of prevention methods, early detection, early recurrence diagnosis, and new treatment methods enhanced with multi-omics data

Rare/Intractable diseases

Early diagnosis: Offer whole genome sequencing to patients with conditions where diagnostic possibilities can be refined. Establish an international collaborative framework for rare diseases with few patients.

Elucidating underlying mechanisms: Unravel through high-quality clinical information and whole genome sequencing data, advance development of treatment and diagnostic methods

Functions

(1) Support for rapid return of results and outcomes of whole genome sequencing to patients
Support for medical institutions to improve their systems
Patient support using ICT/AI technology

(2) Promote personalized medicine
Support clinical trials

(3) Establish and operate a premier information platform
- Strategic data aggregation, robust security
- Automated clinical data collection via API
- Facilitate collaboration between academia and industry
- Develop a system for facilitating prompt, fair, and secure data exchange, and support its utilization

(4) Engage patients and the public, communication outreach raising public awareness

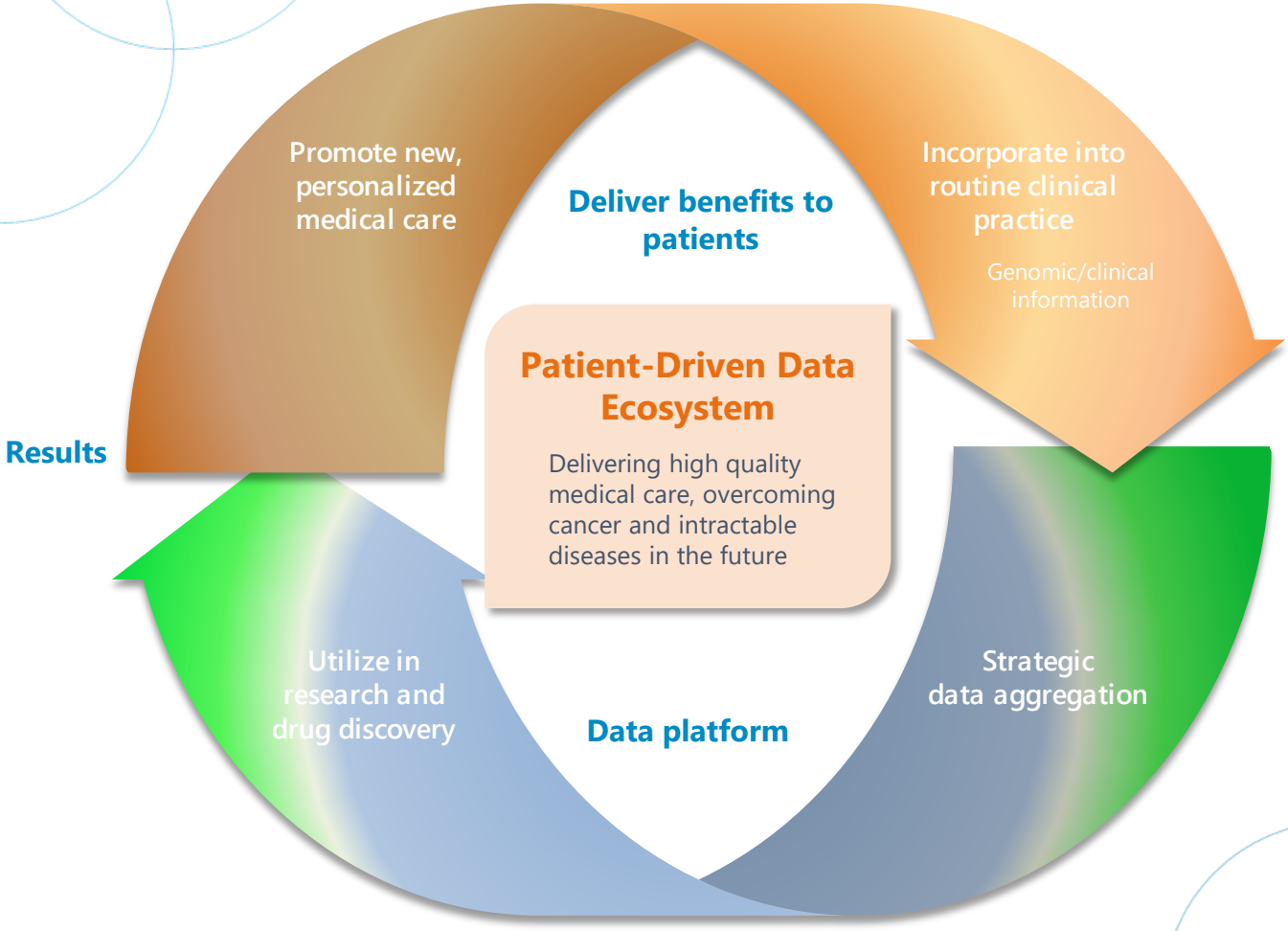
(5) ELSI Support

(6) Support capacity building

Board

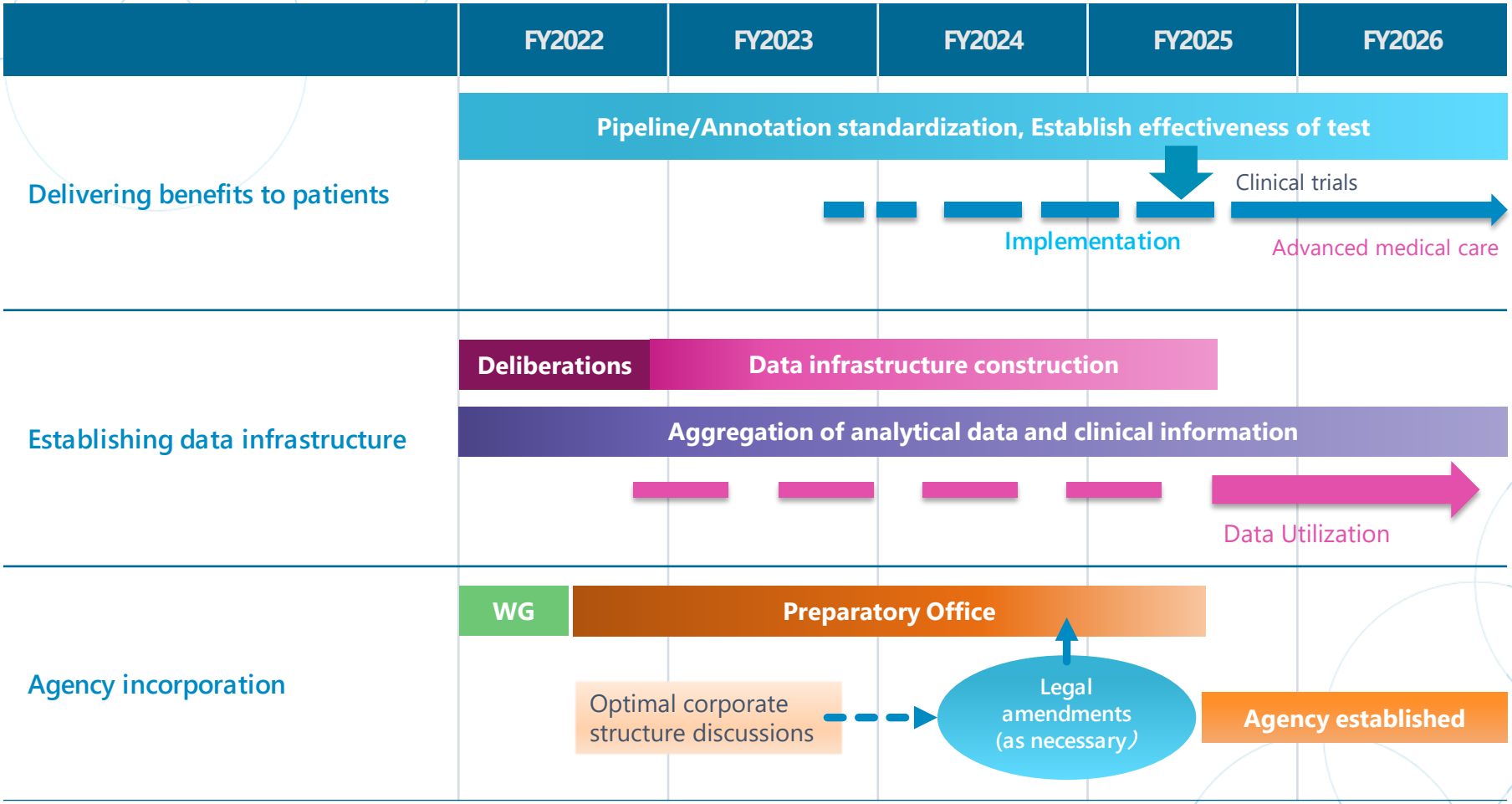
Includes the Chief Executive Officer (CEO) alongside external experts from academia and industry, representing diverse expertise across multiple domains. The CEO to demonstrate expertise and experience for implementation.

Project Implementing Agency - Vision



Excerpts from submissions to Expert Committee for the Promotion of Whole Genome Sequencing (15 Nov 2022)

Implementation Mid-Term Plan



Excerpt from Document 1-1, 12th Expert Committee for the Promotion of Whole Genome Sequencing (15 Nov 2022)

AMED Research FY 2023 (Oncology)

Team A (Delivering patient benefits, Implementation strategy):

i. Basic cohort (cross-sectional) team
Validate clinical utility of whole genome sequencing by means of analyzing genomic data and clinical information. Provide additional tests upon request from medical institutions. Towards implementation of WGS, report format and issues related to patient benefit, and its response to be deliberated, in collaboration with the MHLW Nakagama Team.

ii. Patient benefits/Strategic cohort team
Return results to patients through select medical institutions. Register all cases into the basic cohort, targeting to enroll half in clinical studies.(※） The format developed fy2022 to be used by external agencies in issuing reports. Each select institution to conduct 1-2 clinical studies (strategic cohort), collaborating with leading national clinical research networks is advantageous.

Team B (Consortium):

Working with the Preparatory Office, support consortiums establishment, conduct research utilizing aggregated WGS data, discuss the clinical significance. Study clinical implications of newly identified mutations, and present the conclusion to Teams A and C and the MHLW Nakagama Team, for the benefit of patients.

Team C (Analysis and data center):

Aggregate genomic data and clinical information, analyze and improve pipeline information handling. Establish/improve cloud storage use, set up visit analysis schemes (on-premise cloud). Establish and run a centralized system for specimen, genomic data, and clinical information. Establish, test, and modify an automatic clinical information collection system, and test data sharing utilization support system such as API. Conduct research on analysis and data center establishment liaising with MHLW Nakagama team and the Preparatory Office.

**Each team to report status to the Expert Committee for the Promotion of Whole Genome Sequencing and conduct analysis under its guidance.*
Teams A, B, and C to meet and work together to align clinical information collection and report requirements.