RESEARCH PROTOCOL

(Development and Utilization of a Comprehensive Genetic-Clinical Database)

Principal Investigator	Professor Jeeyun Lee, Division of Hematology-Oncology
Version No.	1.7.11
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1. PROTOCOL SYNOPSIS

Study Title	Development and Utilization of a Comprehensive Genetic-Clinical Database
Study Classification	Non-interventional clinical research
Study Design	Prospective human biospecimen study
Study Sponsorship	Investigator-initiated
Supporting (Collaborating) Organizations	Samsung Electronics, Samsung C&T, Samsung Biologics, Samsung Bioepis
Study Institution	Samsung Medical Center
Principal Investigator	Samsung Medical Center Division of Hematology-Oncology, Jeeyun Lee
Co-Investigator	Samsung Medical Center Division of Hematology-Oncology, Young Seok Park
	Samsung Medical Center Division of Hematology-Oncology, Joon Oh Park
	Samsung Medical Center Division of Hematology-Oncology, Se Hoon Park
	Samsung Medical Center Division of Hematology-Oncology, Seung Tae Kim
	Samsung Medical Center Division of Hematology-Oncology, Jung Yong Hong
	Samsung Medical Center Division of Hematology-Oncology, Sung Hee Lim
	Samsung Medical Center Division of Hematology-Oncology, Min Seok Kwon
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Samsung Medical Center Division of Gastroenterology, Yang Won Min
Samsung Medical Center Division of Gastroenterology, Tae Se Kim
Samsung Medical Center Division of Gastroenterology, Ji Eun Kim
Samsung Medical Center Division of Hepatobiliary and Pancreatic Surgery, In Woong Han
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Samsung Medical Center Department of Colorectal Surgery, Jeong Kyung Shin
Samsung Medical Center Department of Colorectal Surgery, Yoon Ah Park
Samsung Medical Center Division of Gastrointestinal Surgery, Jun Ho Lee
Samsung Medical Center Division of Gastrointestinal Surgery, Min Kyu Choi
Samsung Medical Center Division of Gastrointestinal Surgery, Ji Young Ahn
Samsung Medical Center Division of Gastrointestinal Surgery, Sang Hoon Ahn
Samsung Medical Center Division of Gastrointestinal Surgery, Seong Eun Oh
Samsung Medical Center Division of Breast Surgery, Jae Min Yoo
Samsung Medical Center Division of Transplantation Surgery, Jae Berm Park
Samsung Medical Center Division of Transplantation Surgery, Gyu Seong Choi
Samsung Medical Center Division of Transplantation Surgery, Gyo Won Lee
Samsung Medical Center Division of Transplantation Surgery, Nam Gi Oh
Samsung Medical Center Division of Thoracic Surgery, Jong Ho Cho

	Samsung Medical Center Division of Thoracic Surgery, Young Jung Jeon
	Samsung Medical Center Department of Urology, Hyun Hwan Sung
	Samsung Medical Center Department of Obstetrics and Gynecology, You Young Lee
	Samsung Medical Center Department of Orthopedic Surgery, Sung Wook Seo
	Samsung Medical Center Department of Orthopedic Surgery, Young Geun Lee
	Samsung Medical Center Department of Radiology, Min Woo Lee
	Samsung Medical Center Department of Radiology, Woo Kyoung Jeong
	Samsung Medical Center Department of Radiology, Kyung Doo Song
	Samsung Medical Center Department of Radiology, Jae Seung Shin
	Samsung Medical Center Department of Radiology, Jung Hyun Lee
	Samsung Medical Center Department of Radiology, Ji Hye Min
	Samsung Medical Center Department of Radiology, Dong Ik Cha
	Samsung Medical Center Department of Radiology, Gyo Won Koo
	Samsung Medical Center Department of Radiation Oncology, Hee Chul Park
	Samsung Medical Center Department of Radiation Oncology, Jung Il Yu
	Samsung Medical Center Department of Radiation Oncology, Na Ri Kim
	Samsung Medical Center Department of Pathology, Kyung Mi Kim
	Samsung Medical Center Department of Laboratory Medicine, Young Gon Kim
	Samsung Medical Center Technology Strategy Office, Yong Jae Shin
Study Personnel	Samsung Medical Center Cancer Center Clinical Support Team, Mi Jung Ahn
	Samsung Medical Center, Cancer Center Clinical Support Team, Sun Lee
	Samsung Medical Center Cancer Center Clinical Support Team, Ji Sook Park
	Samsung Medical Center Samsung Precision Genome Medicine Institute, Su Jin Hyung
	Samsung Medical Center Samsung Precision Genome Medicine Institute,

<table>
<tr><td></td><td>Yu Jeong Huh</td></tr>
<tr><td></td><td>Samsung Medical Center Samsung Precision Genome Medicine Institute, Min Ae Ahn</td></tr>
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<tr><td></td><td>Samsung Medical Center Samsung Precision Genome Medicine Institute, Eun Jin Choi</td></tr>
<tr><td>Study Objectives</td><td>To discover and validate novel diagnostic and therapeutic biomarkers using longitudinal genomic analyses of patients at different treatment time points.
① Identify disease-related biomarkers for development of therapeutics or diagnostic technologies.
② Examine differences in treatment response associated with genomic variation to select optimal therapies.
③ Identify biomarkers for cancer diagnosis.
④ Develop data resources to support pharmaceutical and diagnostic-device research and development.</td></tr>
<tr><td>Study Period</td><td>From IRB approval through December 31, 2030 (6 years).</td></tr>
<tr><td>Target Enrollment</td><td>
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<tr><th>Task</th><th>Target populations</th><th>Target enrollment / analyses</th></tr>
<tr><td>Task 1: Genomic variant database (400–500 DNA variants)</td><td>13 categories: lung, colorectal, liver, breast, gastric, head/neck, pancreatic/biliary, gynecologic, brain, prostate, bladder, kidney, sarcoma; metastatic solid tumors</td><td>75,000 participants (60,000 target allowing for 80% success); approximately 10,000 annually.</td></tr>
<tr><td>Task 2: Tumor tissue and organoid biobank</td><td>Primary/recurrent cancers in the study disease groups; establish organoids from patient tissue</td><td>31,910 participants (25,528 target allowing for 80% success). Disease-specific targets include 2,804 for</td></tr>
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			major cancer groups, 1,605 each for bladder and kidney cancer, and 660 for sarcoma.
	Task 3: Tumor tissue sequencing database	The same disease groups as Task 2; DNA coding and noncoding regions, single-cell mRNA, total RNA, and proteomics (e.g., mass spectrometry)	31,910 participants (25,528 target allowing for 80% success).
	Task 4: Blood-based cancer sequencing database	Gastric, esophageal, pancreatic/biliary cancers, healthy individuals, and gastric/pancreatic high-risk groups	12,500 participants (10,000 target allowing for 80% success): gastric 1,500; esophageal 1,000; pancreatic/biliary 2,500; healthy 2,500; gastric high-risk 1,250; pancreatic high-risk 1,250.
Inclusion Criteria	• Patients scheduled for tissue collection for surgery, diagnosis, or treatment because of confirmed or suspected cancer. • Consenting individuals undergoing health screening at Samsung Medical Center. • Patients who have consented to this study. • Patients aged 19 years or older. • Biospecimens (tissue and blood) supplied by the Samsung Medical Center Biobank may also be used (gastric, colorectal, liver, pancreatic, biliary tract, lung, breast, esophageal, hematologic, and kidney cancers). • Specimens from participants in an existing study [IRB File No. 2020-02-015] may be used without additional consent when secondary use was authorized within the retention period.		
Exclusion Criteria	• Participants judged by the investigator to be unsuitable for the study. • Participants who request withdrawal after signing informed consent.		

Study Methods	• Residual clinical specimens will be used from patients undergoing tissue collection for surgery or diagnosis. Biospecimens (tissue and blood) from the Samsung Medical Center Biobank will also be included. • Task 1: Establishment and analysis of a genomic sequence-variation database. Compare genomic variants and clinical information across treatment time points to develop treatment prediction algorithms. • Task 2: Establishment and analysis of a tumor tissue (organoid) biobank. Generate organoids from primary and recurrent tumors and compare drug-response results with genomic and clinical information. • Task 3: Establishment and analysis of a longitudinal patient genomic database. Compare treatment responders and nonresponders at different time points, perform tissue sequencing and protein isolation, and identify novel biomarkers through analysis of genomic variants and expression. • Task 4: Establishment and analysis of a blood-based tumor sequencing database. Compare blood-based genomic alterations, selected gene patterns, and proteins before and after treatment to develop diagnostic and cancer-progression prediction models.

2. Study Title

• English title: Development and Utilization of a Comprehensive Genetic-Clinical Database

3. Name and Address of the Study Institution

• Institution: Samsung Medical Center

• Address: 81 Irwon-ro, Gangnam-gu, Seoul, Republic of Korea

4. Names and Addresses of Collaborating Organizations

No.	Organization	Address
1	Samsung Electronics	11 Seocho-daero 74-gil, Seocho-gu, Seoul, Republic of Korea
2	Samsung C&T	26 Sangil-ro 6-gil, Gangdong-gu, Seoul, Republic of Korea
3	Samsung Biologics	300 Songdo Bio-daero, Yeonsu-gu, Incheon, Republic of Korea
4	Samsung Bioepis	76 Songdo Education-ro, Yeonsu-gu, Incheon, Republic of Korea

5. Names and Positions of the Principal Investigator, Co-Investigators, and Study Personnel

Role	Name	Department / Division	Position
Principal Investigator	Jeeyun Lee	Samsung Medical Center Division of Hematology-Oncology	Professor
Co-Investigator	Young Seok Park	Samsung Medical Center Division of Hematology-Oncology	Professor
	Joon Oh Park	Samsung Medical Center Division of Hematology-Oncology	Professor
	Se Hoon Park	Samsung Medical Center Division of Hematology-Oncology	Professor
	Seung Tae Kim	Samsung Medical Center Division of Hematology-Oncology	Professor
	Jung Yong	Samsung Medical Center Division	Associate

	Hong	of Hematology-Oncology	Professor
	Sung Hee Lim	Samsung Medical Center Division of Hematology-Oncology	Associate Professor
	Min Seok Kwon	Samsung Medical Center Division of Hematology-Oncology	Clinical Assistant Professor
	Ji Eun Shin	Samsung Medical Center Division of Hematology-Oncology	Clinical Assistant Professor
	Seo Yoon Jang	Samsung Medical Center Division of Hematology-Oncology	Clinical Assistant Professor
	Byung Hoon Min	Samsung Medical Center Division of Gastroenterology	Professor
	Hyuk Lee	Samsung Medical Center Division of Gastroenterology	Professor
	Yang Won Min	Samsung Medical Center Division of Gastroenterology	Associate Professor
	Tae Se Kim	Samsung Medical Center Division of Gastroenterology	Clinical Assistant Professor
	Ji Eun Kim	Samsung Medical Center Division of Gastroenterology	Clinical Assistant Professor
	In Woong Han	Samsung Medical Center Division of Hepatobiliary and Pancreatic Surgery	Professor
	Jung Wook Huh	Samsung Medical Center Department of Colorectal Surgery	Professor
	Jeong Kyung Shin	Samsung Medical Center Department of Colorectal Surgery	Assistant Professor
	Yoon Ah Park	Samsung Medical Center Department of Colorectal Surgery	Attending Professor
	Jun Ho Lee	Samsung Medical Center Division of Gastrointestinal Surgery	Professor
	Min Kyu Choi	Samsung Medical Center Division of Gastrointestinal Surgery	Professor
	Ji Young Ahn	Samsung Medical Center Division of Gastrointestinal Surgery	Professor
	Sang Hoon	Samsung Medical Center Division	Professor

	Ahn	of Gastrointestinal Surgery	
	Seong Eun Oh	Samsung Medical Center Division of Gastrointestinal Surgery	Clinical Assistant Professor
	Jae Min Yoo	Samsung Medical Center Division of Breast Surgery	Associate Professor
	Jae Berm Park	Samsung Medical Center Division of Transplantation Surgery	Professor
	Gyu Seong Choi	Samsung Medical Center Division of Transplantation Surgery	Professor
	Gyo Won Lee	Samsung Medical Center Division of Transplantation Surgery	Associate Professor
	Nam Gi Oh	Samsung Medical Center Division of Transplantation Surgery	Clinical Assistant Professor
	Jong Ho Cho	Samsung Medical Center Division of Thoracic Surgery	Professor
	Young Jung Jeon	Samsung Medical Center Division of Thoracic Surgery	Assistant Professor
	Hyun Hwan Sung	Samsung Medical Center Department of Urology	Professor
	You Young Lee	Samsung Medical Center Department of Obstetrics and Gynecology	Professor
	Sung Wook Seo	Samsung Medical Center Department of Orthopedic Surgery	Professor
	Young Geun Lee	Samsung Medical Center Department of Orthopedic Surgery	Clinical Assistant Professor
	Min Woo Lee	Samsung Medical Center Department of Radiology	Professor
	Woo Kyoung Jeong	Samsung Medical Center Department of Radiology	Professor
	Kyung Doo Song	Samsung Medical Center Department of Radiology	Associate Professor
	Ji Hye Min	Samsung Medical Center Department of Radiology	Associate Professor
	Jae Seung	Samsung Medical Center	Assistant

	Shin	Department of Radiology	Professor
	Jung Hyun Lee	Samsung Medical Center Department of Radiology	Assistant Professor
	Dong Ik Cha	Samsung Medical Center Department of Radiology	Assistant Professor
	Gyo Won Koo	Samsung Medical Center Department of Radiology	Clinical Assistant Professor
	Hee Chul Park	Samsung Medical Center Department of Radiation Oncology	Professor
	Jung Il Yu	Samsung Medical Center Department of Radiation Oncology	Associate Professor
	Na Ri Kim	Samsung Medical Center Department of Radiation Oncology	Assistant Professor
	Kyung Mi Kim	Samsung Medical Center Department of Pathology	Professor
	Young Gon Kim	Samsung Medical Center Department of Laboratory Medicine	Assistant Professor
	Yong Jae Shin	Samsung Medical Center Technology Strategy Office	Head of Office
Study Personnel	Mi Jung Ahn	Samsung Medical Center Clinical Support Team	Precision Cancer Medicine Center Coordinator
	Sun Lee	Samsung Medical Center Clinical Support Team	Precision Cancer Medicine Center Coordinator
	Ji Sook Park	Samsung Medical Center Clinical Support Team	Precision Cancer Medicine Center Coordinator
	Su Jin Hyung	Samsung Medical Center Samsung Precision Genome Medicine Institute	Principal Researcher
	Yu Jeong Huh	Samsung Medical Center Samsung Precision Genome Medicine Institute	Principal Researcher

	Min Ae Ahn	Samsung Medical Center Samsung Precision Genome Medicine Institute	Principal Researcher
	Jinha Hwang	Samsung Medical Center Samsung Precision Genome Medicine Institute	Principal Researcher
	Seongkeun Yoo	Samsung Medical Center Samsung Precision Genome Medicine Institute	Principal Researcher
	Geum Seon Lee	Samsung Medical Center Samsung Precision Genome Medicine Institute	Principal Researcher
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	Ja Yeon Kim	Samsung Medical Center Samsung Precision Genome Medicine Institute	Principal Researcher
	Da Som Kim	Samsung Medical Center Samsung Precision Genome Medicine Institute	Senior Researcher
	Yeon Ok Seo	Samsung Medical Center Samsung Precision Genome Medicine Institute	Principal Researcher
	Eun Jin Choi	Samsung Medical Center Samsung Precision Genome Medicine Institute	Senior Researcher

6. Study Objectives and Background

1) Study objective: To identify and validate novel diagnostic and therapeutic biomarkers through longitudinal genomic analyses of patients at different treatment time points.

① Identify disease-associated biomarkers → develop related therapeutics or diagnostic technologies.

② Identify differences in treatment response associated with genomic variation → select optimal treatments.

③ Discover biomarkers applicable to cancer diagnosis.

④ Establish a database to support research and development by pharmaceutical and diagnostic-device companies.

2) Background

□ What is genomic research?

• Genomic research characterizes features such as genetic alterations and identifies biomarkers that can be used for precision diagnosis and treatment. Genes are extracted from patient specimens and sequenced; the resulting profiles are compared with those of the general population to identify disease-associated differences (genomic biomarkers).

• Types of genomic biomarkers and examples of their applications

① Pathogenic variants in genes associated with specific diseases:

Pathogenic variants in BRCA1/2

→ increased risk of breast cancer (BRCA1/2 pathogenic variants serve as biomarkers for predicting breast cancer risk).

② Nucleotide sequence variants within genes:

An EGFR T790M substitution involving amino acid 790 in patients with lung cancer

→ treatment with Tagrisso (synthetic agent) among available anticancer therapies

(the EGFR T790M alteration serves as a biomarker for selecting an appropriate anticancer therapy).

③ Abnormally low or high amounts of gene-encoded proteins: the HER2 gene in patients with breast cancer encodes HER2 protein → excessive HER2 protein expression may warrant Herceptin antibody therapy (HER2 protein expression level serves as a

biomarker for selecting anticancer treatment).

□ Patient-derived organoid models

• Patient-derived organoids (PDOs) preserve characteristic cellular features and genomic alterations or expression profiles of the original cancer and can recapitulate selected functions of the primary tissue. These three-dimensional cultures can organize spatially in a manner resembling native organs and have become an important next-generation in vitro model system for research.

• In recent years, organoid models have been established from a variety of human organs. Organoid-based platforms are being applied to disease modeling, regenerative medicine, drug toxicity and efficacy assessment, compound screening, and personalized medicine, with expanding research and commercial applications.

• Organoid models are actively used in oncology research, including drug-screening studies across multiple organoid systems.

□ Need for new translational research platforms in drug development

• Accurate preclinical prediction is critical to successful clinical trials; however, animal-based preclinical efficacy and toxicity studies have limited predictive accuracy in clinical settings. For anticancer drugs, only approximately 8% of candidates have reportedly reached successful clinical use, prompting growing interest in organoids as a platform for improving development success rates.

• Organoids are a powerful three-dimensional in vitro model for evaluating drug effects. More accurate assessments require multimodal data that integrate organoid findings with medical records and genomic information.

• To evaluate therapies such as immune checkpoint inhibitors, co-culture of organoids with immune cells is essential. Although co-culture is technically feasible, standardized and optimized methods applicable across diverse patient-derived organoids are urgently needed. This requires the establishment of organoids from many patients, along with the collection and storage of blood for immune cell isolation. This study aims to establish cancer organoids from at least 175 patients for each of ten cancer types[1]) and at least 100 patients for each of two additional cancer types[2]), and to develop an optimized drug-response assessment model through co-culture with

autologous immune cells.

• Establishing optimized co-culture technology for patient-derived organoids and immune cells and integrating it with medical data would support the development of an advanced drug-efficacy assessment platform for patient-specific drug screening. Such a platform may contribute to future standards of care and improve patients' survival and quality of life while reducing associated societal costs.

☐ A comprehensive genomic database is a core resource for biomarker discovery.

1) Ten cancer types: lung, colorectal, liver, breast, gastric, head and neck, pancreatic/biliary tract, gynecologic, brain, and prostate cancers. 2) Two cancer types: bladder and kidney cancers.

→ Approaches include a large-scale database (Type 1) and a patient-centered longitudinal database (Type 2).

※ Relative to leading institutions, SMC has comparatively limited data volume (Type 1); differentiation is needed through high-quality, patient-centered longitudinal datasets (Type 2).

7. Target Diseases

• Tissue database: lung, colorectal, liver, breast, gastric, head and neck, pancreatic/biliary tract (including gallbladder and bile duct), gynecologic (including ovarian, endometrial, and cervical), brain, and prostate cancers, bladder and kidney cancers, esophageal cancer, sarcoma, and metastatic solid tumors.

• Blood database: gastric and esophageal cancers, pancreatic/biliary tract cancers, healthy individuals, and populations at high risk for gastric or pancreatic cancer.

8. Inclusion and Exclusion Criteria, Target Enrollment, and Rationale

1) Inclusion Criteria

• Patients with diagnosed or suspected cancer who are scheduled for tissue collection for surgery, diagnosis, or treatment.

• Individuals undergoing health screening at Samsung Medical Center who consent to this study.

• Patients who have consented to this study.

• Patients aged 19 years or older.

- In addition, human biospecimens (tissue and blood) obtained from the Samsung Medical Center Biobank will be used (gastric, colorectal, liver, pancreatic, biliary tract, lung, breast, esophageal, hematologic, and kidney cancers; approximately 7,500 individuals).
- Specimens from participants enrolled in a previous study [IRB File No. 2020-02-015] who consented to secondary use within the specified retention period will be used without additional consent (see the table below).

IRB File No.	Principal Investigator	Specimen Enrollment Period
2020-02-015	Sung Wook Seo	2020.02~

2) Exclusion Criteria

- Individuals judged by the investigator to be unsuitable for the study for any other reason.
- Participants who request withdrawal after providing informed consent.
- Participants enrolled in the previous study specified in the inclusion criteria whose original consent retention period has expired or who declined secondary use of their specimens will be excluded.

3) Target Enrollment and Rationale

- Target enrollment: 118,750 participants
- Rationale

① Task 1 (Establishment of a genomic sequence-variation database):

- 75,000 participants (target of 60,000 across 13 disease categories, assuming an 80% success rate).
- The 13 disease categories include lung, colorectal, liver, breast, gastric, head and neck, pancreatic/biliary tract (e.g., gallbladder and bile duct), gynecologic (e.g., ovarian, endometrial, and cervical), brain, prostate,

bladder, kidney, and sarcoma, as well as metastatic solid tumors.

② Tasks 2 (Establishment of a tumor tissue biobank) and 3 (Establishment of a tumor tissue sequencing database):

31,910 participants (target of 25,528 across 13 disease categories, assuming an 80% success rate).

- The disease categories include lung, colorectal, liver, breast, gastric, head and neck, pancreatic/biliary tract, gynecologic, brain, prostate, bladder, kidney, and sarcoma, as well as metastatic solid tumors.

③ Task 4: Blood-based tumor sequencing database

- 12,500 participants (target of 10,000 across three cancer categories and healthy individuals, assuming an 80% success rate).
- Targets: 1,500 gastric cancer; 1,000 esophageal cancer; 2,500 pancreatic/biliary tract cancer; 2,500 healthy individuals; 1,250 at high risk of gastric cancer; and 1,250 at high risk of pancreatic cancer.

9. Anticipated Study Period

From IRB approval through December 31, 2030 (6 years).

10. Study Procedures and Methods

1) Informed Consent Procedures

- Investigators may enroll individuals meeting the inclusion and exclusion criteria. They must explain the study in language the participant can understand and obtain voluntary written informed consent.
- Investigators must ensure that complete and appropriate written and verbal information about the study's nature, objectives, and potential risks has been provided.
- Participants must also be informed that they are free to discontinue study participation at any time.
- Participants will be given an opportunity to ask questions and adequate time to consider participation.

- Signed informed consent must be obtained before any study-specific procedure is performed. A copy will be provided to the participant upon request.

2) Biospecimen Collection Methods

- Residual tissue and blood will be collected from eligible participants as described below.
- Tissue analyses will use residual specimens from surgery undertaken for treatment or procedures performed for clinical diagnosis, including fresh tissue; archived FFPE blocks from the Department of Pathology may be used when necessary.
- Additional blood will be collected at the time of clinically indicated blood tests; no blood draws will be performed solely for research.
    - Isolation of circulating nucleic acids (including ctDNA), proteins, and PBMCs from blood: EDTA 20 mL + EDTA 6 mL.
    - Fresh tissue or FFPE specimens archived in the Department of Pathology.
    - Endoscopic biopsies: 8–10 pieces, each approximately 2–3 mm in diameter.
    - Surgical tissue: 2–3 pieces, each approximately 1–2 cm in diameter.
- A total of two blood collections are planned, performed together with clinically indicated diagnostic testing. Only participants who consent to genetic testing may enroll. At the investigator's discretion, an additional 26 mL blood sample may be collected at tumor assessment using the same procedure.
- For blood analysis, consenting individuals undergoing health screening at Samsung Medical Center will provide one additional 20 mL blood sample during their screening visit.
- Human biospecimens (tissue and blood) supplied by the Samsung Medical Center Biobank will also be used (approximately 7,500 individuals).
- Residual biospecimens collected by the research team of Professor Sung Wook Seo, Department of Orthopedic Surgery, Samsung Medical Center [IRB File No. 2020-02-015], will be used.
- The overall study design and biospecimen collection pathways for each participant group are shown in Figures 1 and 2. The ongoing subcohorts covered by this protocol are listed in Appendix 1, Detailed Cohort List.

Figure 1. Study Overview

Prospective collection of residual tissue and blood, linked to clinical information, to establish an integrated genomic–clinical database.

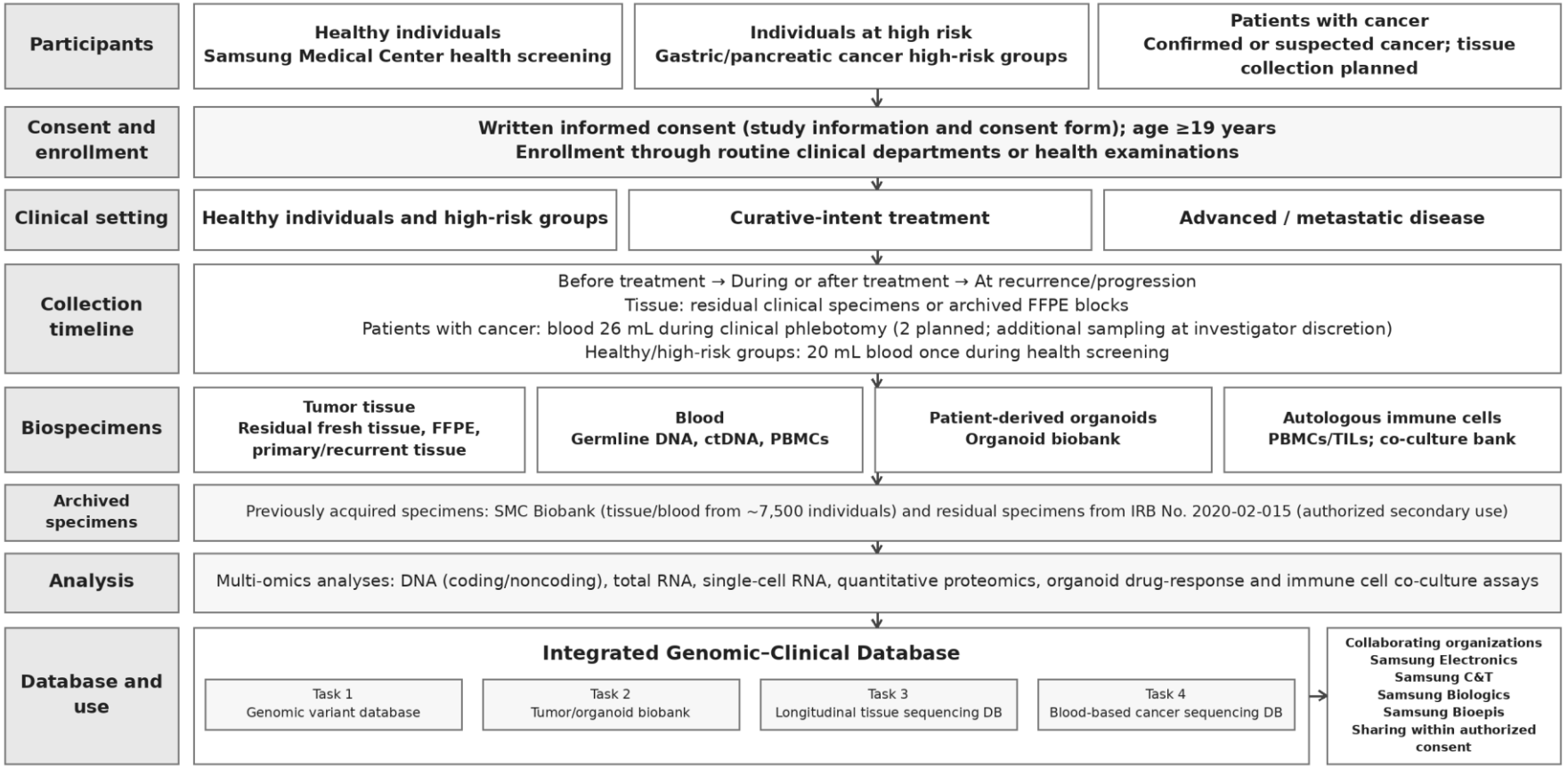
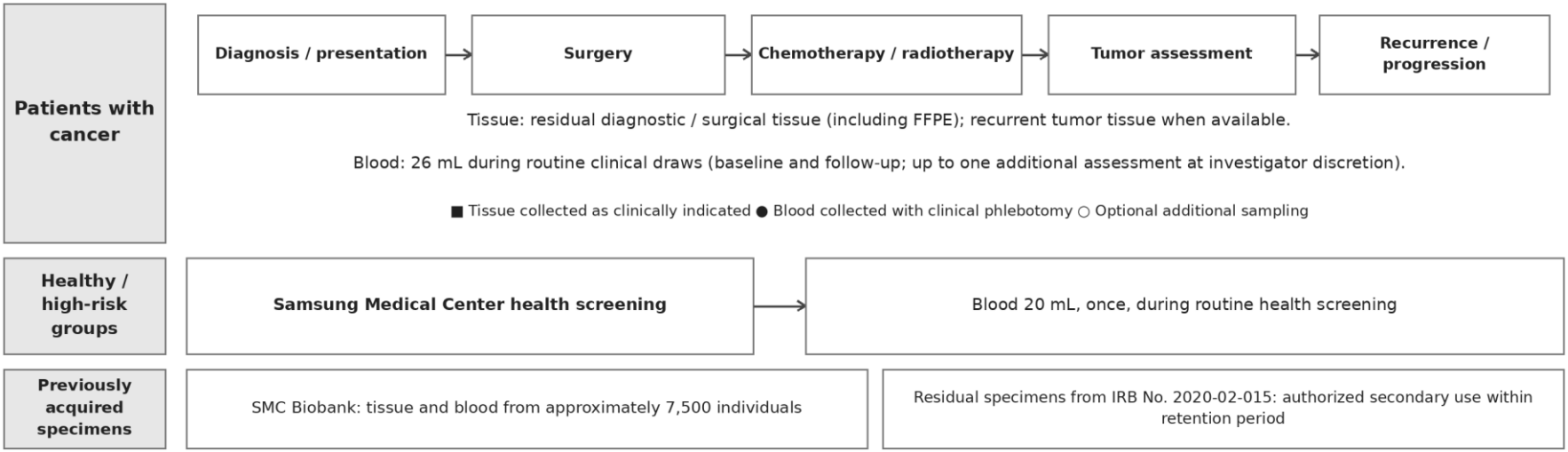


Figure 2. Biospecimen Collection by Clinical Course

Specimens are collected alongside clinically indicated procedures and blood draws; no additional procedures are scheduled solely for research.



Biospecimen Collection by Participant Group

Participant group	Enrollment pathway	Biospecimens	Timing / frequency	Related task
Cancer patients	Diagnostic, surgical, or treatment-related tissue collection	Residual tissue (fresh/FFPE); blood 26 mL	Tissue: at clinical collection; blood: 2 planned + 1 optional	Tasks 1–3 (Task 4: selected cancer types)
Healthy individuals	SMC health screening	Blood 20 mL	One collection	Task 4
High-risk participants	SMC health screening (gastric/pancreatic cancer risk)	Blood 20 mL	One collection	Task 4
SMC Biobank	Biobank distribution under approved procedures	Tissue and blood	No new collection; archived	By specimen type
Prior IRB study	Residual specimens from IRB 2020-02-015	Archived residual specimens	No new collection; archived	By specimen type

3) Preprocessing for Pathology and Genomic Analyses

- All samples will be obtained and transported as follows:
  - Blood will be collected into EDTA or heparin tubes in the outpatient phlebotomy unit.
  - Tumor tissue obtained from the diagnostic laboratory or operating room will be placed in dedicated specimen trays.
  - Specimens will be labeled accurately (ID, initials, sequencing number) and transported to the laboratory.
  - All specimens will be transferred promptly to the preprocessing site after collection.
  - Tissue specimens will be stored as research-use FFPE blocks or snap-frozen specimens.

4) Genomic Analysis

- Samples sent to the sequencing vendor will undergo additional quality and quantity assessment to determine whether analyzable data can be obtained.
- Because optimal sample criteria have not yet been established, all collected specimens will initially be assessed and submitted for sequencing. When specimens are provided to external institutions, identifying information will be coded to protect privacy. After analysis, tissue and blood will be retained for the period designated by the participant.

5) Establishment of Procedures for Isolation and Maintenance of Autologous Immune Cells

- Immune cells will be isolated from peripheral blood mononuclear cells (PBMCs) or tumor-infiltrating lymphocytes (TILs) obtained from patients with cancer and stored in liquid nitrogen at − 180°C.
- The most effective isolation method will be selected from established approaches, including cell sorting, density-gradient media, and pre-rapid expansion protocols.

- Successful isolation of the target immune cell populations will be verified using flow cytometry or other appropriate assays.

6) Establishment of a Co-Culture Platform for Autologous Immune Cells and Cancer Organoids

- Culture media conditions suitable for both immune cells and cancer organoids will be established to support co-culture of cells maintained under different conditions.
- An organoid co-culture platform suitable for assessing drug efficacy will be developed, and organoid drug responses will be compared with patients' clinical responses.

7) Data Collection and Variables

- Personal identifiers associated with all study specimens will be coded, separately stored, and managed securely.
- Clinical information accompanying collected specimens will be obtained from medical records, limited to items specified in the case report form. The clinical data collection period ends on December 31, 2030.
- Clinical information for biospecimens (tissue and blood) obtained from the Samsung Medical Center Biobank will be collected and managed through a designated research information intermediary, limited to the case report form variables (intermediary: Mi Jin Lee).
- Data analysis methods:
  - ① Compare genomic variations with clinical information across treatment time points to develop treatment-response prediction algorithms.
  - ② Establish organoids from participants' tumor tissue (primary and recurrent cancers) and compare drug efficacy findings with genomic and clinical information.
  - ③ Identify treatment responders and nonresponders across time points, perform sequencing and protein isolation using tissue samples, and analyze genomic alterations or expression to discover new biomarkers.

④ Compare blood-based genomic alterations, specific gene patterns, and proteins before and after treatment to develop diagnostic and cancer-progression prediction models.

8) Clinical Information Used in This Study

- De-identified clinical information to be used includes sex, age, diagnosis, diagnosis date, tissue acquisition procedure and site, tumor histology and genotype (biomarker test results for the 13 cancer categories), dates of initial diagnosis, recurrence and metastasis, cancer stage, serum biomarkers (e.g., CEA, CA19-9, AFP, PSA), anticancer treatment records (number of administrations, treatment duration, recurrence), responses to anticancer therapies (best response, progression-free survival), disease progression and survival status (including survival at 1, 2, and 3 years after treatment initiation), tumor markers, alcohol use, smoking history, family history, and other health-related information.

9) Roles of Participating Organizations

Organization	Responsibilities
Samsung Medical Center	Samsung Medical Center will oversee the activities listed below. • Obtain and maintain IRB approval. • Select participants and analyze clinical information. • Perform genomic (DNA/RNA) sequencing and protein analyses using patients' tissue and blood. ① Task 1: Establishment of a genomic sequence-variation database • Manage clinical information and select patients with genomic variant testing among 12 cancer types. • Compare genomic variants and clinical data across treatment time points. • Compare genomic variants and clinical data from primary and recurrent tumors. • Establish and maintain an integrated genomic variant and clinical database. ② Task 2: Establishment of a physical tumor tissue biobank • Manage clinical data and select participants with primary or recurrent cancers across 12 cancer types. • Establish cancer organoid banks from approximately 100–175 participants per cancer type (at least 5 vials per participant), and store and manage the materials. • Establish a PBMC cell bank from blood collected from the same participants (at least 2.0×10^7 cells; at least 2 vials per participant). • Link participants' medical and sequencing information to their organoid data. ③ Task 3: Establishment of a tumor tissue sequencing database • Manage clinical information across treatment time points and select participants. • Perform longitudinal genomic testing for 12 cancer types and link results with

	clinical information. • Develop treatment prediction algorithms by comparing longitudinal genomic and clinical data. • Identify novel biomarkers by comparing longitudinal genomic and clinical data. • Discover biomarkers for recurrent cancer by comparing genomic, proteomic, and clinical data from primary and recurrent tumors. ④ Task 4: Blood-based tumor sequencing database • Collect blood before and after treatment from 125–250 participants in each of the gastric cancer, esophageal cancer, pancreatic/biliary tract cancer, healthy-individual, high-risk gastric cancer, and high-risk pancreatic cancer groups (more than 2 vials per participant). • Establish PBMC cell banks from the same individuals (more than 2.0×10^7 cells and more than 1 vial per participant). • Link participants' medical information with tissue and blood sequencing data.
Samsung Electronics	Provide funding and personnel necessary to support the research activities below. ① Task 1: Establishment of a genomic sequence-variation database • Develop treatment prediction algorithms by comparing genomic variants (DNA data), gene expression patterns (RNA data), and clinical information across treatment time points. • Develop recurrence prediction algorithms by comparing variants, gene expression patterns, and clinical information from primary and recurrent cancers. • Compare and analyze genomic data from patients with 12 cancer types using at least two sequencing platforms.
Samsung Biologics	Provide funding and personnel necessary to support the research activities below. ② Task 2: Establishment of a physical tumor tissue biobank • Establish organoid-based drug-response assessment methods for 12 cancer types. • Validate the drug-response evaluation platform by testing drug sensitivity and comparing results with medical data. • Analyze genomic sequencing information from each participant's tumor tissue and compare gene-specific drug-response data with clinical findings. • Develop immune cell co-culture systems. • Compare the efficacy of new anticancer agents and existing treatments using cancer organoids.
Samsung Bioepis	Provide funding and personnel necessary to support the research activities below. ③ Task 3: Establishment of a tumor tissue sequencing database • Validate existing anticancer therapies and novel therapeutic targets using longitudinal genomic and proteomic databases from patients with 12 cancer types. • Develop novel therapeutics targeting newly identified molecular features and assess their efficacy based on comparative analyses of genomic and clinical data across treatment time points. • Develop and assess candidate therapies targeting recurrent cancer using comparisons of genomic, proteomic, and clinical information from primary and recurrent tumors. • Select optimal clinical candidates, including new drugs and biosimilars, and identify appropriate clinical trial populations through longitudinal comparisons of genomic and clinical data.

Samsung C&T	Provide funding and personnel necessary to support the research activities below. ④ Task 4: Blood-based tumor sequencing database • Develop diagnostic algorithms by analyzing blood-based genomic and protein profiles from participants with gastric cancer, esophageal cancer, pancreatic/biliary tract cancer, healthy individuals, and groups at high risk of gastric or pancreatic cancer. • Develop diagnostic algorithms using participants' medical data, tissue sequencing results, blood sequencing results, and other relevant information. • Obtain and analyze genomic and protein information from each participant's tissue and blood.

※ If necessary, external collaborators (Samsung Electronics, Samsung C&T, Samsung Biologics, and Samsung Bioepis) may second personnel to Samsung Medical Center to support the research. Tissue and blood genomic data analyses, organoid culture, and drug treatment will be performed at Samsung Medical Center. Sequencing may be outsourced to an external sequencing vendor (see Sections 10.4 and 15); specimen and data sharing with collaborating organizations will follow Section 18, Additional Use.

11. Potential Adverse Effects

- This study uses tumor tissue and body fluids that would otherwise be discarded following clinical surgery, diagnosis, or treatment. Blood specimens are collected in small additional amounts during clinically indicated phlebotomy; therefore, no study-related adverse effects are anticipated.

12. Discontinuation and Withdrawal Criteria

- Participants whom the investigator considers unsuitable for this study.
- Participants who withdraw consent.

13. Protection of Participants' Rights and Informed Consent

- This study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, the Korean Good Clinical Practice (KGCP) guidelines, and applicable regulatory requirements.
- The final protocol and informed consent form must receive written IRB approval or a favorable opinion before any participant is enrolled.
- The principal investigator is responsible for notifying the IRB and obtaining

approval for protocol amendments in accordance with local regulations.

- This study also uses residual specimens remaining after use in previously conducted studies. Separate additional consent may not be required if the participants previously consented to secondary use of their biospecimens. Specimens from parent studies will be used only within the scope of the original consent and the specified retention period.

14. Protection of Participants' Personal Information

- Personal identifiers will be coded and maintained separately from epidemiologic and clinical information. A designated individual will manage coding and related data-protection procedures (coding officer: Ja Yeon Kim).

15. Retention and Disposal of Human Biospecimens

- Collected specimens will be stored and managed using appropriate procedures for each specimen type.
- Specimens will be retained and managed for the period specified in each participant's informed consent form.
- After initial analysis or experimentation at Samsung Medical Center, specimens may be transferred to other institutions for additional analyses. Only the amount needed for analysis will be sent to external sequencing vendors. Remaining specimens, established organoids, and immune cells retained at Samsung Medical Center will be stored for the period authorized in the participant's consent and then disposed of.

16. Compensation

- No additional experimental clinical treatment or testing will be conducted beyond the genomic analyses described above. Residual specimens from surgery, endoscopy, bronchoscopy, and invasive image-guided biopsies performed for routine diagnosis or treatment may be used for genomic testing.
- No biopsies will be performed solely for this research. Because the study uses materials obtained as by-products of routine diagnostic or therapeutic procedures,

compensation and management of any injuries will follow the principles applicable to the underlying clinical procedures. No study-specific compensation or treatment is provided.

17. Document Retention

- Study materials and records will be stored in locked cabinets to maintain confidentiality.
- Study-related documents will be retained for 20 years after study completion.

18. Additional Use

Specimens, clinical information, and other resources in the comprehensive genetic-clinical database established through this study may be shared with collaborating organizations (Samsung Electronics, Samsung C&T, Samsung Biologics, and Samsung Bioepis), including provision of specimens and data downloads. Collaborating organizations may use the database for their own discovery and validation of novel diagnostic or therapeutic biomarkers, development of therapeutics or diagnostic technologies, selection of optimal therapies, and other related purposes, including joint research with third parties.

Appendix 1. Detailed Cohort List (Supplementary Table 1)

Category	Cohort Name	Eligible Patients
A. Neoadjuvant and Perioperative Chemotherapy (ZENIA-PRIME)		
All patients	ZENIA-PRIME-[Tumor Type]	All patients initiating neoadjuvant or perioperative chemotherapy
Gastric cancer	ZENIA-PRIME-GC	FLOT or D-FLOT
	ZENIA-PRIME-NeoVIKTORY	Neoadjuvant or perioperative chemotherapy (IIT_NeoVIKTORY)
Colorectal cancer	ZENIA-PRIME-CRC	Total neoadjuvant therapy (TNT) or neoadjuvant concurrent chemoradiotherapy
Urothelial carcinoma	ZENIA-PRIME-UC	Neoadjuvant GP, perioperative durvalumab + GP, or EVP
	ZENIA-PRIME-UTUC	Upper tract urothelial carcinoma: neoadjuvant GP
Other tumor types	ZENIA-PRIME-Others	Neoadjuvant chemotherapy for other tumor types
B. Postoperative Adjuvant Chemotherapy (ZENIA-TRACE)		
All patients	ZENIA-TRACE-[Tumor Type]	All patients initiating postoperative adjuvant chemotherapy
By tumor type	ZENIA-TRACE-GC	Gastric cancer
	ZENIA-TRACE-CRC	Colorectal cancer
	ZENIA-TRACE-UC	Urothelial carcinoma
	ZENIA-TRACE-PDAC	Pancreatic cancer
	ZENIA-TRACE-Melanoma	Melanoma
	ZENIA-TRACE-BTC	Biliary tract cancer
	ZENIA-TRACE-Bavencio	Urothelial carcinoma (IIT_Avelumab maintenance therapy)
	ZENIA-TRACE-Others	Other tumor types
C. Palliative Systemic Anticancer Therapy (ZENIA-[Tumor Type]-Line)		
Gastric cancer	ZENIA-GC-01A	First-line: trastuzumab + FP or XP, or pembrolizumab + trastuzumab + XELOX, FP, or XP
	ZENIA-GC-01B	First-line: XELOX or FOLFOX + immune checkpoint inhibitor (nivolumab, pembrolizumab, or tislelizumab)
	ZENIA-GC-01C	First-line: zolbetuximab + XELOX or FOLFOX
	ZENIA-GC-01D	First-line: XELOX or FOLFOX alone
	ZENIA-GC-02A	Second-line: paclitaxel + ramucirumab or paclitaxel alone
	ZENIA-GC-02B	Second-line: FOLFIRI or irinotecan alone
	ZENIA-GC-03A	Third-line: FOLFIRI or irinotecan alone
	ZENIA-GC-VIKTORY1_Cera	(IIT_VIKTORY 1_Ceralasertib)
	ZENIA-GC-VIKTORY2_Savo	(IIT_VIKTORY 2_Savolitinib)
	ZENIA-GC-VIKTORY2_Afa	(IIT_VIKTORY 2_Afatinib)
	ZENIA-GC-C / -Others	Patients participating in clinical trials (C) / other gastric cancer treatments (Others)
Colorectal cancer	ZENIA-CRC-01A	First-line: bevacizumab + FOLFOX or FOLFIRI
	ZENIA-CRC-01B	First-line: cetuximab + FOLFOX or FOLFIRI

Category	Cohort Name	Eligible Patients
	ZENIA-CRC-02A	Second-line: VEGF inhibitor (bevacizumab or aflibercept) + chemotherapy
	ZENIA-CRC-02B	BRAF-mutant: encorafenib + cetuximab
	ZENIA-CRC-03A	Trifluridine/tipiracil + bevacizumab
	ZENIA-CRC-03B	Fruquintinib
	ZENIA-CRC-IO	MSI-H: pembrolizumab or nivolumab + ipilimumab
	ZENIA-CRC-C / -Others	Patients participating in clinical trials (C) / other colorectal cancer treatments (Others)
Biliary tract cancer	ZENIA-BTC-01A	First-line: durvalumab + GP or pembrolizumab + GP
	ZENIA-BTC-02A	Nivolumab + ipilimumab
	ZENIA-BTC-02B	Liposomal irinotecan + 5-FU/leucovorin
	ZENIA-BTC-02C	Pemigatinib
	ZENIA-BTC-C / -Others	Patients participating in clinical trials (C) / other biliary tract cancer treatments (Others)
	ZENIA-BTC-Combined	Combined hepatocellular–cholangiocarcinoma
Hepatocellular carcinoma	ZENIA-HCC-01A	First-line: atezolizumab + bevacizumab
	ZENIA-HCC-01B	First-line: durvalumab + tremelimumab
	ZENIA-HCC-01C	First-line: nivolumab + ipilimumab
	ZENIA-HCC-C / -Others	Patients participating in clinical trials (C) / other liver cancer treatments (Others)
Pancreatic cancer	ZENIA-PDAC-01A	First-line: mFOLFIRINOX
	ZENIA-PDAC-01B	First-line: gemcitabine + nab-paclitaxel
	ZENIA-HCC-PDAC-C / -Others	Patients participating in clinical trials (C) / other pancreatic cancer treatments (Others)
Urothelial carcinoma	ZENIA-UC-01A	First-line: enfortumab vedotin + pembrolizumab (EVP)
	ZENIA-UC-01B	First-line: gemcitabine + cisplatin or gemcitabine + carboplatin
	ZENIA-UC-01C	Avelumab maintenance therapy
	ZENIA-UC-03A	Enfortumab vedotin monotherapy
	ZENIA-UC-C / -Others	Patients participating in clinical trials (C) / other urothelial carcinoma treatments (Others)
Other tumor types	ZENIA-Melanoma-IO	Melanoma treated with immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab)
	ZENIA-Melanoma-BRAF	BRAF-mutant melanoma (vemurafenib, dabrafenib + trametinib)
	ZENIA-Melanoma-C / -Others	Patients participating in clinical trials (C) / other melanoma treatments (Others)
	ZENIA-Sarcoma-ALBATROSS	IIT_ALBATROSS study
	ZENIA-Sarcoma-Paradigm	IIT_Paradigm study

Category	Cohort Name	Eligible Patients
	ZENIA-Sarcoma-C / -Others	Patients participating in clinical trials (C) / other sarcoma treatments (Others)
	ZENIA-PC- C / -Others	Patients participating in clinical trials (C) / other prostate cancer treatments (Others)
	ZENIA-RCC- C / -Others	Patients participating in clinical trials (C) / other renal cell carcinoma treatments (Others)
	ZENIA-GIST- C / -Others	Patients participating in clinical trials (C) / other gastrointestinal stromal tumor treatments (Others)
	ZENIA-RCC- C / -Others	Patients participating in clinical trials (C) / other renal cell carcinoma treatments (Others)
	ZENIA-NET/NEC-C / -Others	Patients participating in clinical trials (C) / other neuroendocrine tumor treatments (Others)
	ZENIA-[Tumor Type] -C / -Others	Patients participating in clinical trials (C) / other tumor types (skin, ovary, MUO, etc.)
Pan-cancer	ZENIA-PAN-Enhertu	Regimens containing trastuzumab deruxtecan
D. Special Cohorts		
Immune-related adverse events	ZENIA-irAE	Patients who develop immune-related adverse events (irAEs) during immune checkpoint inhibitor treatment
Organoid	ZENIA-IM6 org	Patients undergoing organoid generation from tumor samples obtained via ascites, pleural effusion, endoscopy, or other procedures
Metastatic gastric cancer	ZENIA-MGC	Patients with metastatic gastric cancer undergoing clinically indicated upper gastrointestinal endoscopy
Liver biopsy	ZENIA-Liver Bx	Patients undergoing clinically indicated liver biopsy
NGS	ZENIA-NGS	Patients undergoing clinically indicated tissue- or blood-based NGS testing at SMC
E. Gastroenterology Cohorts (IM1)		
Gastric and esophageal tumors	ZENIA-AGC-Endo	Advanced or metastatic gastric cancer
	ZENIA-EGC-Endo	Early gastric cancer
	ZENIA-EGC-ESD	Patients with early gastric cancer undergoing endoscopic submucosal dissection (ESD)
	ZENIA-DP-Endo	Dysplasia
	ZENIA-ESO-Endo	Endo esophageal cancer
	ZENIA-MALToma-Endo	Gastric MALT lymphoma
	ZENIA-Gastric NET-Endo	Gastric neuroendocrine tumor
	ZENIA-GIST-Endo	Gastrointestinal stromal tumor
Precancerous lesions	ZENIA-Precancer-Endo	Gastric dysplasia prior to a cancer diagnosis
Healthy controls	ZENIA-H-Endo	Healthy controls
F. Surgical Cohorts (ZENIA-OP)		

Category	Cohort Name	Eligible Patients
Curative-intent surgery	ZENIA-Resectable Cancer	Patients scheduled for curative-intent surgery (thoracic surgery, gastrointestinal surgery, urology, gynecology, etc.)
	ZENIA-Borderline/Benign	Borderline tumors / carcinoma in situ (CIS) / benign tumors or other benign conditions
	ZENIA-organoid cytology	Patients in the ZENIA-OP gastric cancer organoid cohort undergoing intraoperative peritoneal lavage
G. Radiation Oncology Cohorts (RT)		
Radiotherapy	ZENIA-RT-OMOP	Patients with oligometastasis or oligoprogression
	ZENIA-RT-RE PBT	Patients undergoing re-irradiation with proton beam therapy for any cancer type
	ZENIA-RT-HCC	Patients with hepatocellular carcinoma receiving radiotherapy alone (including proton beam therapy) with curative or salvage intent
	ZENIA-RT-TACE	Patients with hepatocellular carcinoma undergoing radiotherapy (including proton beam therapy) following TACE
	ZENIA-RT-PANCREAS	Patients with pancreatic cancer receiving radiotherapy to the pancreatic region
	ZENIA-RT-SFRT	Patients receiving spatially fractionated radiotherapy (SFRT)
	ZENIA-RT-IOPT	Participants in a comparison of radiotherapy and atezolizumab–bevacizumab therapy
	ZENIA-RT-PULSAR	Patients receiving pulsed radiotherapy (PULSAR)