Establishment of the Dutch nationwide, interdisciplinary infrastructure and biobank for fundamental and translational ovarian cancer research: Archipelago of Ovarian Cancer Research (AOCR)

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Establishment of the Dutch Nationwide, Interdisciplinary Infrastructure and Biobank for Fundamental and Translational Ovarian Cancer Research: Archipelago of Ovarian Cancer Research

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Abstract
Objectives: Ovarian cancer has the worst overall survival rate of all gynecologic malignancies. For the majority of patients, the 5-year overall survival rate of less than 50% has hardly improved over the last decades. To improve the outcome of patients with all subtypes of ovarian cancer, large-scale fundamental and translational research is needed. To accommodate these types of ovarian cancer research, we have established a Dutch nationwide, interdisciplinary infrastructure and biobank: the Archipelago of Ovarian Cancer Research (AOCR). The AOCR will facilitate fundamental and translational ovarian cancer research and enhance interdisciplinary, national, and international collaboration. ***Design:*** The AOCR biobank is a prospective ovarian cancer biobank in which biomaterials are collected, processed, and stored in a uniform matter for future (genetic) scientific research. All 19 Dutch hospitals in which ovarian cancer surgery is performed participate and collaborate in the AOCR biobank. ***Participants/Materials, Setting, Methods:*** Patients of 16 years and older with suspected or diagnosed ovarian, fallopian tube, or primary peritoneal cancer are recruited for participation. Patients who agree to participate give written informed consent for collection, storage, and issue of their biomaterials for future studies. After inclusion, different blood samples are taken at various predefined time points both before and during treatment. In case of a diagnostic paracentesis or biopsy, the residual biomaterials of these procedures are stored in the biobank. During surgery, primary tumor tissue and, if applicable, tissue from metastatic sites are collected and stored. From each patient, a representative histological hematoxylin and eosin stained slide is digitalized for research purposes, including reassessment by a panel of gynecologic pathologists. Clinical and pathological data are obtained on a per-study basis from Dutch registries. Research proposals for the issue of biomaterials and data are evaluated by both the Archipelago Scientific Committee and the Steering Committee. Researchers using the biomaterials from the AOCR biobank are encouraged to enrich the biobank with data and materials resulting from their analyses and experiments. ***Limitations:*** The implementation and first 4 years of collection are financed by an infrastructural grant from the Dutch Cancer Society. Therefore, the main limitation is that the costs for sustaining the biobank after the funding period will have to be covered. This coverage will come from incorporation of budget for biobanking in future grant applications and from fees from external researchers and commercial parties using the biomaterials stored in the AOCR biobank. Moreover, we will apply for grants aimed at sustaining and improving research infrastructures and biobanks. ***Conclusions:*** With the establishment of the Dutch nationwide, interdisciplinary Archipelago of Ovarian Cancer Research infrastructure and biobank, fundamental and translational research on ovarian cancer can be greatly improved. The ultimate aim of this infrastructure is that it will lead to improved diagnostics, treatment, and survival of patients with ovarian cancer.

Introduction

Ovarian, fallopian tube, and primary peritoneal cancer (hereinafter referred to as "ovarian cancer") is the leading cause of death among women with gynecologic malignancies. The 5-year overall survival rate is less than 50% and has hardly improved over the last decades for the majority of patients [1–4]. In order to improve prognosis, large-scale research is needed. In the Netherlands, collaboration in clinical ovarian cancer research is established within the Dutch Gynecological Oncology Group. However, no equivalent for fundamental and translational research existed, hampering large-scale conduction of these types of research.

Ovarian cancer can arise from epithelial, stromal, or germ cells [5, 6]. Over 90% of malignant ovarian tumors are of epithelial origin, of which high-grade serous adenocarcinoma is the most common subtype (70%), followed by endometrioid (10%), clear cell (10%), mucinous (3%), and low-grade serous (<3%) adenocarcinoma [7]. Advances in molecular technologies have revealed different mutational signatures for each of these subtypes [8]. In addition, further molecular subclassification of high-grade serous ovarian cancer has been established [9, 10]. This illustrates an important issue in ovarian cancer research: the focus is on high-grade serous adenocarcinoma and less on the other subtypes, due to their lower incidence and thus lower availability of biomaterials. This makes reliable and impactful fundamental and translational research on nonhigh-grade serous epithelial and nonepithelial ovarian cancer challenging.

It has become increasingly evident that there are differences in tumorigenesis, genetic profile, clinical presentation, sensitivity to therapy, and overall survival between the different subtypes of ovarian cancer [5, 11, 12]. Nevertheless, the subtype of the tumor currently plays only a

minor role in determining the treatment. The standard treatment consists of surgery and, in case of advanced stage disease, platinum-based chemotherapy [8, 12]. Only recently, targeted therapies like poly-adenosine diphosphate-ribose polymerase inhibitors have become available, showing promising activity, especially in specific patient groups, such as BRCA-1/2 mutation carriers [13, 14]. In order to develop more targeted therapies, extensive fundamental and translational research is essential.

Another promising contribution to improving the diagnosis and treatment of ovarian cancer is the use of liquid biopsies. A liquid biopsy is a minimally invasive tool to analyze tumor-derived materials in fluids, such as blood, which can be stored in a biobank [15]. In research settings, liquid biopsies have been useful in detecting ovarian cancer, predicting and monitoring therapy response, detecting early recurrence, and estimating prognosis [16–18]. However, to date, liquid biopsies for ovarian cancer are not used in clinical practice since there are not yet unequivocal methods for analyzing tumor-derived materials, the majority of studies recruited only small numbers of patients, and results still have to be validated [16–18]. Availability of biomaterials from large cohorts could expedite translation of research results into clinical practice.

In order to overcome the abovementioned issues, we established a nationwide, interdisciplinary infrastructure, including a national biobank, for fundamental and translational research on ovarian cancer in the Netherlands: the Archipelago of Ovarian Cancer Research (AOCR). All 19 hospitals in which surgery on patients with ovarian cancer is performed contribute to this biobank. The AOCR infrastructure and biobank will lead to enhanced collaboration in fundamental and translational research between disciplines and between Dutch hospitals as well as improved and intensified international collaborations. Overall, this infrastructure has the potential to greatly improve fundamental and translational ovarian cancer research in the Netherlands with the ultimate aim to improve the diagnostics, treatment, and survival of patients with ovarian cancer.

Materials and Methods

Study Design

The AOCR biobank is a Dutch national prospective biobank in which blood, ascites, and tumor tissue of patients with ovarian cancer are collected. This biobank is a collaboration of all 19 Dutch hospitals in which ovarian cancer surgery is performed by a gynecologic oncologist. These hospitals include both tertiary (academic) and large general hospitals.

The Dutch Cancer Society provided funding for setting up the infrastructure, the establishment of the biobank, and the collection of biomaterials for a period of 4 years [19]. The aim is to build a sustainable infrastructure. Operational costs beyond the funding period will be covered by fees incorporated in grant applications and by fees from external parties requesting tissue or collection of biomaterials and data. The details of the AOCR biobank as described in the Netherlands Trial Register are included in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000528330) [20].

Study Population

Women ≥16 years with (suspected) ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who are diagnosed and/or treated at a participating AOCR hospital are eligible for inclusion in the biobank.

Inclusion criteria are as follows:

- Suspected or diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer
- Age ≥16 years
- Written informed consent

Exclusion criteria are as follows:

- Mental disabilities
- Not able to understand the patient information

Informed Consent

Patients provide written informed consent for participation in the study (online suppl. File 1). They consent to collection and storage of their biomaterials for future (genetic) research for 50 years. They also consent to linkage with other Dutch registries for obtaining clinicopathologic data. Moreover, patients approve of being informed by their general practitioner or treating physician(s) in case of incidental findings relevant for their or their family members' health, like the discovery of a hereditary disease. Before the general practitioner or treating physician(s) is informed by the AOCR coordinator about this, the Medical Research Ethics Committee or Biobank Review Committee of the hospital where the patient was treated is consulted. If a patient does not wish to be informed, she cannot participate in the biobank, adhering to the strictest standard biobank policies of the participating hospitals. Additionally, patients consent to the issue of their biomaterials and data to other domestic or foreign noncommercial institutes with privacy measures according to Dutch standards. Patients can choose whether their biomaterials may be issued to commercial parties and/or foreign institutes with privacy measures distinct from the Dutch standards. Lastly, patients can decide whether they may be approached for follow-up research.

Even after written informed consent has been given, patients can refuse collection of biomaterials at any moment. Patients can withdraw from participation in the biobank without providing any reason (online suppl. File 2). In that case, personal data are deleted and biomaterials and data that have not yet been used for research are either destroyed or anonymized, depending on the choice of the patient. After anonymization, the biomaterials of these patients will remain available for research in case no clinical data of these patients are needed, for example, for technical validation of methods or techniques.

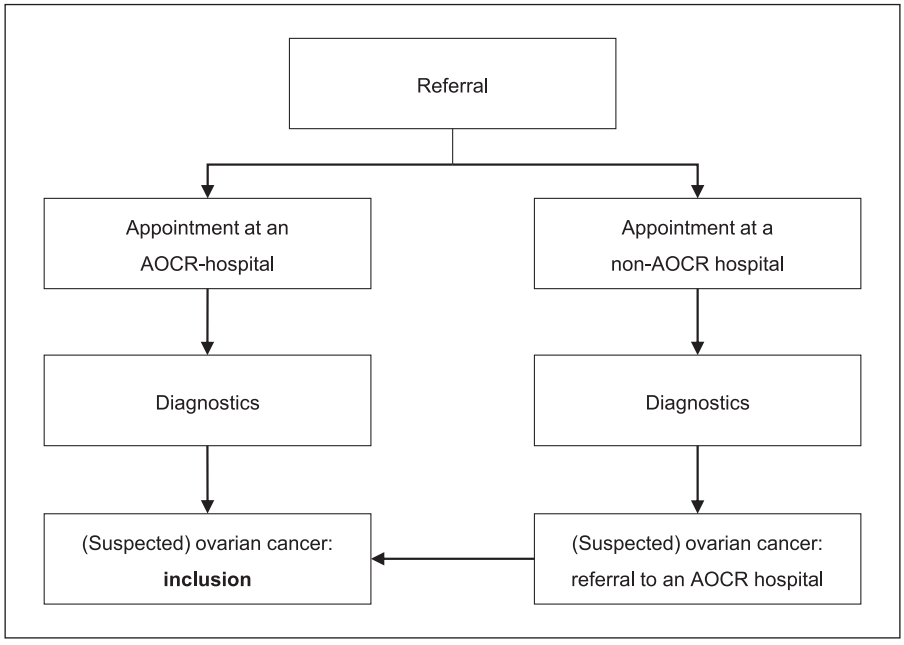

Fig. 1. Flowchart of the recruitment procedure. AOCR, Archipelago of Ovarian Cancer Research.

Recruitment Procedure

See Figure 1 for the flowchart of the recruitment procedure. A general practitioner or other medical specialist can refer a patient with suspected ovarian cancer to a gynecologist in either a participating AOCR or a nonparticipating hospital. If diagnostics in a participating AOCR hospital show ovarian cancer as the most probable diagnosis and the patient is eligible, she is informed and recruited for participation. It is also possible that the patient is referred to a gynecologist in a nonparticipating hospital. If ovarian cancer is confirmed or is the most probable diagnosis, the patient will be referred to a hospital in which ovarian cancer surgery is performed, thus a participating AOCR hospital. If the patient is eligible, she will be informed and recruited for participation during her appointment at the participating AOCR hospital.

Patients who agree to participate give written informed consent according to Good Clinical Practice guidelines. They are registered in Ldot, a Web-based tool for storing privacy sensitive data from study patients. Ldot is part of the Maastricht University Medical Center+ and is ISO27001 certified [21]. For each registered patient, Ldot generates patient-specific study numbers that are used for the storage of biomaterials and linkage to other data sources.

Study Procedures

If a patient is referred directly to a participating AOCR hospital, she is preferably recruited for participation before biomaterials from paracentesis and/or biopsy are collected for diagnostic purposes. This enables storage of residual biomaterials before treatment is started, thus without any therapy effect (Fig. 2).

In case a paracentesis and/or biopsy does not lead to a definitive diagnosis of ovarian cancer, exploratory surgery including fresh frozen section analysis is performed (Fig. 2). All hospitals in which this surgery is performed are participating AOCR hospitals, so residual materials can be stored in the biobank.

Diagnostic procedures can lead to the following pathological outcomes: benign or borderline tumor, ovarian cancer (including fallopian tube and primary peritoneal cancer), or other primary cancer. If the patient is diagnosed with a benign tumor or other primary cancer, the study procedure stops. Since the patient already gave informed consent, the stored biomaterials can be used as controls in future studies.

The first blood sample is taken before treatment starts (Fig. 2). If exploratory surgery is needed to confirm the diagnosis, blood is drawn prior to this procedure.

During surgery for a borderline tumor or ovarian cancer, tissue from the primary tumor and, if applicable, metastatic sites is collected and stored in the biobank. In case of neoadjuvant chemotherapy, an additional blood sample is taken between the first cycle of chemotherapy and interval debulking surgery. In case of primary debulking, blood is drawn before adjuvant chemotherapy, as well as between the first and fourth cycle of chemotherapy. Since the timing of patient appointments can differ between AOCR hospitals, the exact timing of the blood draws depends on local logistics.

In case of a recurrence, the treating physician(s) and pathologist determine which biomaterials should preferably be collected for storage in the biobank. These biomaterials may include ascites and tumor tissue. There is no guideline for storage during recurrence since there can be a considerable variability in the availability of biomaterials between these patients.

Participation in this biobank is not an extra burden for patients. First, ascites and tumor tissue stored in the biobank are residual materials that are obtained during regular diagnostic and treatment procedures. Second, blood samples for the biobank are taken during venipunctures needed for the regular treatment. Lastly, the amount of blood collected specifically for the biobank is only 50 mL.

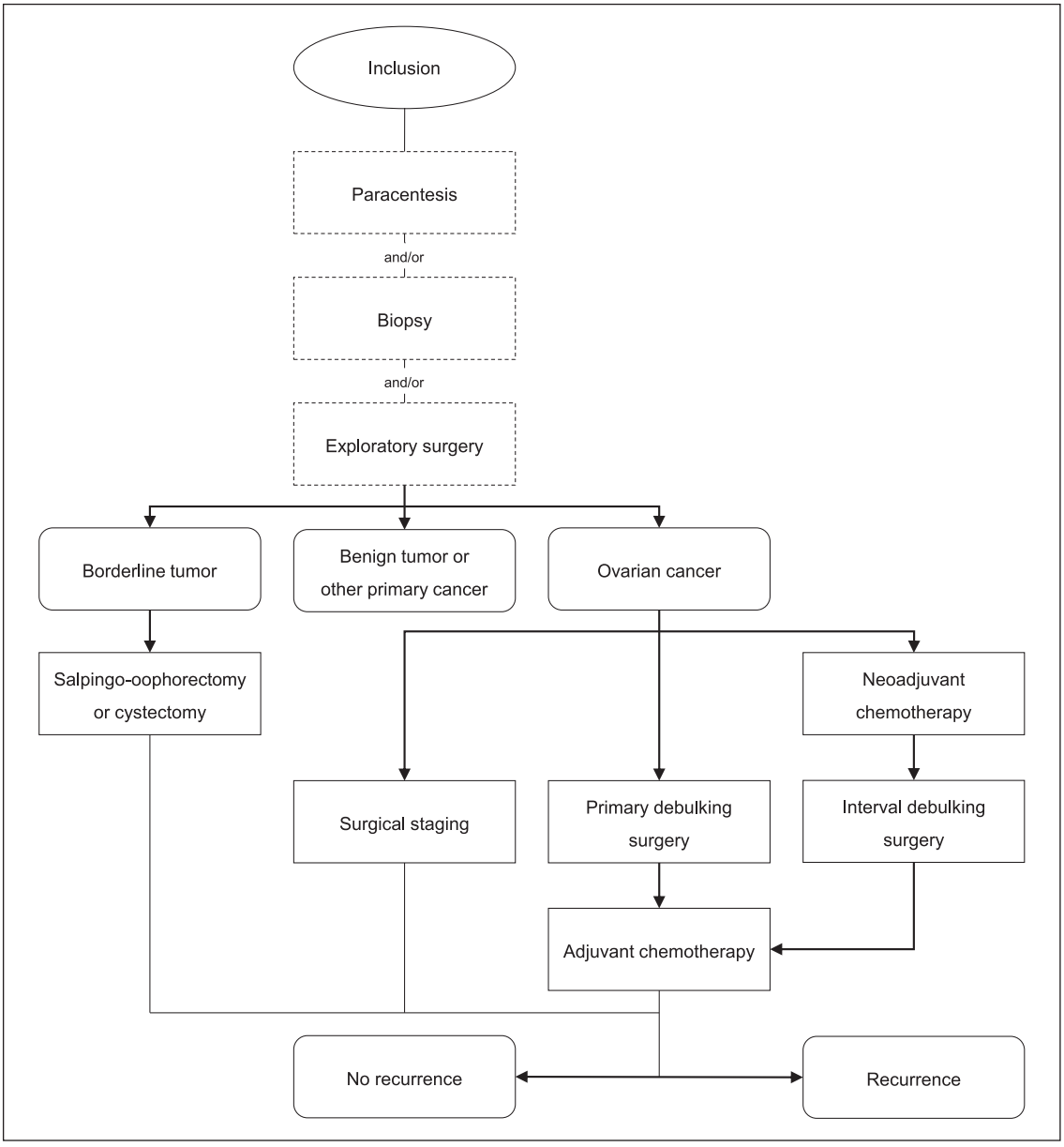

Fig. 2. Flowchart of the study procedures. Rectangles, diagnostic or treatment procedures (dotted lines: if applicable); rounded rectangles, diagnoses.

Biomaterials

Three types of biomaterials are collected and stored in the biobank: blood, ascites, and tumor tissue. For a complete overview, see Table 1. See online supplementary Files 3 and 4 for the standard operating procedures (SOPs) of tissue and blood, respectively. The SOPs were drafted in such a manner that all hospitals could meet the requirements set in these SOPs. If hospitals do not have the capacity to process blood for cell-free plasma according to the SOP, blood is collected in a Streck tube and sent to the Amsterdam University Medical Center (UMC) for processing. Storage of all other biomaterials takes place in the hospital where the biomaterials are obtained. When no long-term storage is available, the biomaterials are stored for a short time and periodically transferred to either the affiliated academic hospital or the Amsterdam UMC.

The residual biomaterials of a paracentesis or biopsy are stored in the biobank if they are performed following inclusion. In case of a paracentesis, a cellblock from at least 10 mL of ascites is prepared using the agar cellblock method or Cellient™ automated cell block system, depending on the local procedures, and stored at room temperature. If a biopsy is performed, tissue remaining after a pathology diagnosis has been made is stored in the biobank, at ≤−80°C, and as formalin-fixed paraffin-embedded tissue.

Table 1. Overview of the biomaterials collected and stored in the biobank

Procedure	Biomaterial	Moments of collection			Storage temperature
		before treatment	during treatment	follow-up	
Paracentesis	Ascites	Once	–	Optional	Room temperature
Biopsy	Tumour tissue	Once	–	Optional	≤−80°C and room temperature
Venepuncture	Serum	Once	–	–	≤−80°C
Venepuncture	Plasma	Once	–	–	≤−80°C
Venepuncture	Whole blood	Once	–	–	≤−80°C
	Genomic DNA				≤−20°C or 4°C
Venepuncture	Cell-free plasma	Once	Once or twice	–	≤−80°C
Surgery	Primary tumor tissue	–	Once	–	≤−80°C and room temperature
Surgery	Metastatic tumor tissue	–	Optional	–	≤−80°C and room temperature
Surgery	Tumor tissue of recurrence	–	–	Optional	≤−80°C and room temperature

Prior to the start of treatment for a borderline tumor or ovarian cancer, the first blood collection takes place. The blood is stored at ≤−80°C as serum, plasma, whole blood, and cell-free plasma. Whole blood can be used for future isolation of genomic DNA from normal white blood cells. Where possible, genomic DNA is isolated directly and stored at ≤−20°C or 4°C. Cell-free plasma can be used for future isolation of circulating tumor DNA. The type of tube for the collection of cell-free plasma depends on the local procedures and can be an EDTA, a PAXgene, or a Streck tube. Blood collection for storage as cell-free plasma also takes place during chemotherapy in case of advanced stage ovarian cancer (Fig. 2).

When surgery for a borderline tumor or ovarian cancer is performed, primary tumor tissue is collected. Both snap-frozen and formalin-fixed paraffin-embedded tissue are collected and stored at ≤−80°C and room temperature, respectively. In case of insufficient material, the storage of snap-frozen tissue is prioritized. The same applies to the storage of metastases. Collection and storage of metastases is optional but promoted, especially in the case of rare metastases such as subcutaneous/abdominal wall, umbilical, extra-abdominal lymph node, parenchymal (liver, spleen, lung), and bone metastases.

Digital Pathology

From each patient, at least one representative hematoxylin and eosin stained histological section of tumor tissue collected at surgery is scanned and uploaded to Slide Score, an online platform to digitally assess and score histological sections [22]. Information on immunohistochemistry is made available either by scanning and uploading the concerned sections or by providing information on the outcome of the staining. A panel of gynecologic pathologists reassesses and scores all scanned histological sections. The outcomes of the reassessment are intended for research purposes only and not for clinical use. These outcomes can be issued in conjunction with the biomaterials. This ensures that researchers do not have to reassess all histological sections on a per-study basis. Furthermore, these digital slides themselves can be used for research, for example, for artificial intelligence algorithms. Slide Score is hosted on a secured virtual server of the Amsterdam UMC.

Clinical and Pathological Data

In the Netherlands, clinical data on diagnosis, treatment, outcome, and survival of all patients with ovarian cancer are recorded by the Netherlands Cancer Registry (NCR), part of the Netherlands Comprehensive Cancer Organisation [23]. Pathological data are collected by the Dutch Pathology Registry (PALGA) [24]. Both institutes have the goal to reduce the impact of cancer by supporting scientific research [23, 24]. The AOCR biobank uses the clinical and pathological data as collected and recorded by the NCR and PALGA. Therefore, there is no collection of data specifically for the AOCR biobank. This ensures that clinicians do not have to invest extra time and effort to collect and deliver data for the AOCR biobank. Moreover, it is not necessary to construct and maintain a database specifically for the biobank, which contributes to the aim of sustainability.

Issue

When researchers want to use biomaterials of the AOCR biobank, they can request an inventory of the number of available biomaterials based on clinical and pathological characteristics. The inventory is made possible by linkage of the AOCR with NCR and PALGA. If a sufficient number of biomaterials for the intended study is available, the researcher can apply for issue of these biomaterials by submitting a research proposal via Podium, a portal to request biomaterials and data from biobanks [25]. Podium is managed by Health-RI: the Dutch national initiative to facilitate and stimulate an integrated health data infrastructure [26]. The submitted research proposal should contain a study objective or research question(s), the required type of biomaterials, the clinical and pathological data that are needed, and a statistical analysis plan. All research proposals are reviewed by the AOCR Scientific Committee, which gives a positive judgment, when the study objective falls within the scope of the biobank and the privacy of the patients can be assured. The AOCR Scientific Committee is composed of members from different hospitals and from different disciplines who contributed to the implementation of the AOCR biobank. The AOCR Steering Committee, composed of members from different hospitals and different disciplines who were involved in the grant application, design, and implementation of the AOCR biobank, takes the judgment of the Scientific Committee into consideration and makes the final judgment. If clinical or

pathological data are required, the study proposal needs to be approved by the NCR or PALGA, respectively. The aim is to complete the issue of both data and biomaterials within 2 months after submission of the study protocol.

Enrichment

Genomic data generated as part of a single study can have substantially more impact on ovarian cancer research when shared with other researchers. Furthermore, it can reduce costs by preventing the conduction of identical analyses on the same biomaterials. Therefore, one of the principles of the AOCR biobank is enrichment. Researchers who use biomaterials from the AOCR biobank are encouraged to enrich the biobank with data (such as genomics and proteomics) and materials from which the data were derived (such as DNA, RNA, and tissue microarrays) resulting from analyses and experiments conducted as part of their study. The data of these analyses are saved in cBioPortal: a Web-based resource to work with multidimensional cancer genomics data sets [27]. cBioPortal is managed by Health-RI [26]. cBioPortal is hosted at Vancis, which has ISO9001, ISO27001, and NEN7510 certificates [28]. The saved data and derived materials can be issued instead of or in addition to biomaterials. The assessment of issue of such data and derived materials is similar to the issue of biomaterials.

Patient and Public Involvement

Olive Foundation, the Dutch foundation for women with gynecologic cancer and their families, was involved in writing the project proposal to request funding for the establishment of the nationwide, interdisciplinary infrastructure and biobank [29]. To bring in the patient perspective, a representative of Olive Foundation is a member of the Scientific Review Committee.

Conclusion

Recently, the Dutch nationwide, interdisciplinary Archipelago of Ovarian Cancer Research infrastructure, including a national biobank, was established. Within this infrastructure, biomaterials and data of patients with (suspected) ovarian cancer who gave informed consent are prospectively collected to be used for future research.

The unique feature of the Archipelago biobank compared to most other biobanks is that clinicopathologic data collected in a standardized manner by national registries, such as the NCR and PALGA, are used [30, 31]. Therefore, clinicians do not have to provide data for the Archipelago biobank. This contributes to the sustainability of the biobank and minimalizes the time and effort clinicians have to invest in the biobank. Furthermore, within the Archipelago biobank a representative histological hematoxylin and eosin stained slide from each patient is stored digitally and reassessed by a panel of gynecologic pathologists. Lastly, we strongly aim for enrichment of derived materials and research data into the biobank, saving usage of biomaterials and costs for analyses.

A main advantage of this national biobank is that from the great majority of patients with (suspected) ovarian cancer, fallopian tube, and primary peritoneal cancer in the Netherlands informed consent will be obtained to store biomaterials and use them for future (genetic) research. This significantly eases conduction of fundamental and translational research with ovarian cancer biomaterials since obtaining informed consent for a retrospective study after completion of treatment may be very challenging, for example, due to patients' follow-up in another hospital, changed home address, or not returning the informed consent form despite no objection to the study. Another advantage is that much higher numbers of biomaterials will be available for research, allowing proper studies on rare subtypes of ovarian cancer. Moreover, all hospitals where ovarian cancer surgery is performed collect the same biomaterials and process and store them in a uniform manner according to the SOPs. To take into account the local procedures and possibilities of the participating hospitals, some flexibility was incorporated into the SOPs. This mostly relates to the method of embedding ascites (agar cellblock method or Cellient™ automated cell block system), method of freezing tissue (isopentane cooled by dry ice of liquid nitrogen), and collection tube for cell-free plasma (EDTA, PAXgene, or Streck). However, previous studies on these differences showed no or only a limited effect on subsequent analyses and outcomes [32–34]. Therefore, this national biobank ensures that there is much less variety in the range of biomaterials or processing and storage methods, than when performing a retrospective study using biomaterials from various local biobanks applying their own unique methods.

An issue is that the costs for collection and storage of biomaterials after the funding period will have to be covered. After fully implementing the biobank in all participating hospitals, costs will be substantially lower than during development and establishment, but costs for biobanking will nevertheless continue to be made. Financing for the biobank will come from incorporation of fees for biobanking and making use of stored biomaterials in grant applications, as well as from external researchers and commercial parties making use of the biomaterials. We expect an increase in the number of research grants applied for and accepted as a result of the uniform and large collection of biomaterials in this biobank in combination with intensified collaboration between disciplines and hospitals. Moreover, we will apply for future infra-

structure grants to sustain, expand, and improve the biobank and infrastructure. This could include expansion of the clinicopathologic data collection, linkage to other Dutch data registries, and enlargement of the number of collaborating (international) hospitals.

In conclusion, the Archipelago of Ovarian Cancer Research infrastructure can greatly improve fundamental and translational ovarian cancer research in the Netherlands. We believe this can ultimately improve the care and survival of patients with all subtypes of ovarian cancer.

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Statement of Ethics

The executive board of the Medical Research Ethics Committee of the Amsterdam UMC, location Amsterdam Medical Center (University of Amsterdam) assessed this biobank as not subject to the Dutch Directive on Medical Research Involving Human Subjects (reference: W20_083). Subsequently, the Biobank Review Committee has approved the establishment of the AOCR biobank (reference: 2019_272). Since this biobank falls outside the scope of the Dutch Directive on Medical Research Involving Human Subjects, the Medical Research Ethics Committee or Biobank Review Committee of each participating hospital assessed the local establishment of the biobank. Patients sign informed consent before participating in the AOCR biobank.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Hein Zelisse: conceptualization, methodology, writing – original draft, writing – review and editing, visualization, and project administration. Mignon van Gent, Constantijne Mom, and Marc van de Vijver: conceptualization, methodology, writing – review and editing, supervision, and funding acquisition. Sander de Ridder: conceptualization, methodology, software, writing – review and editing, and visualization. Maaike van der Aa, Anne van Altena, Joost Bart, Jeroen Belien, Ingrid Boere, Steven Bosch, Annegien Broeks, Johan Bulten, Margriet Collée, Floris Groenendijk, Hugo Horlings, Maurice Jansen, Trudy Jonges, Loes Kooreman, Cornelis de Kroon, Sandrina Lambrechts, Christianne Lok, Jurgen Piek, Anna Reyners, Eva-Maria Roes, Michiel Simons, Bea Wisman, Refika Yigit, and Ronald Zweemer: conceptualization, methodology, writing – review and editing, and funding acquisition. Frederike Dijk: conceptualization, methodology, writing – review and editing, supervision, project administration, and funding acquisition.

Data Availability Statement

No data were generated or analyzed during the establishment of the biobank. All relevant data from future studies using samples from the biobank will be made available upon study completion. Further inquiries can be directed to the corresponding author.

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