Abstract. Biobanks constitute an integral part of precision medicine. They provide a repository of biospecimens that may be used to elucidate the pathophysiology, support diagnoses, and guide the treatment of diseases. The pilot biobank of rare malignant neoplasms has been established in the context of the Hellenic Network of Precision Medicine on Cancer and aims to enhance future clinical and/or research studies in Greece by collecting, processing, and storing rare malignant neoplasm samples with associated data. The biobank currently comprises 553 samples; 384 samples of hematopoietic and lymphoid tissue malignancies, 72 samples of pediatric brain tumors and 97 samples of malignant skin neoplasms. In this article, sample collections and their individual significance in clinical research are described in detail along with computational methods developed specifically for this project. A concise review of the Greek biobanking landscape is also delineated, in addition to recommended technologies, methodologies and protocols that were integrated during the creation of the biobank. This project is expected to re-enforce current clinical and research studies, introduce advances in clinical and genetic research and potentially aid in future targeted drug discovery. It is our belief that the future of medical research is entwined with accessible, effective, and ethical biobanking and that our project will facilitate research planning in the ’omic’ era by contributing high-quality samples along with their associated data.

Correspondence to: Professor Penelope Korkolopoulou, First Department of Pathology, Medical School, National and Kapodistrian University of Athens, 75 Mikras Asias Street, 11527 Athens, Greece E-mail: pkorkol@med.uoa.gr

Abbreviations: AML, acute myelogenous leukemia; AES, Advanced Encryption Standard; BioSHaRE-EU, Biobank Standardization and Harmonization for Research Excellence in the European Union; BBMRI, Biobanking and BioMolecular Resources Research Infrastructure; BRFAA, Biomedical Research Foundation of the Academy of Athens; CS-IT, Common Service IT; CRUD, Create, Read, Update, Delete; CBCLs, cutaneous B-cell lymphomas; cSCC, cutaneous squamous cell carcinoma; CTCLs, cutaneous T-cell lymphomas; ELSI, ethical, legal and societal issues; ERIC, European Research Infrastructure Consortium; FFPE, formalin-fixed paraffin-embedded; FF, fresh-frozen; GDPR, General Data Protection Regulation; GSR1, General Secretariat of Research and Innovation; HDPA, Hellenic Data Protection Authority; HNPM, Hellenic Network of Precision Medicine; HTO/EMO, Hellenic Transplant Organization; HGP, Human Genome Project; IARC, International Agency for Research on Cancer; IHC, immunohistochemistry; ICGC, International Cancer Genome Consortium; ISBER, International Society of Biological and Environmental Repositories; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; MIABIS, minimum information about Biobank data sharing; NKUA, National and Kapodistrian University of Athens; NCI, National Cancer Institute; NGS, next-generation sequencing; OECD, Organization for Economic Co-Operation and Development; PBMS, Pilot Biobank Management System; PM, precision medicine; P3G, Public Population Project in Genomics and Society; QA, quality assurance; QC, quality control; REDCs, Research Ethics and Deontology Committees; RECs, Research Ethics Committees; SLNB, sentinel lymph node biopsy; SNVs, single nucleotide variants; SOPs, standard operating procedures; SPREC, Standard PREanalytical Code; TCGA, The Cancer Genome Atlas; UDHR, The Universal Declaration of Human Rights; WPF, Windows Presentation Foundation

Key words: Biobank, cancer, ELSI, FFPE, precision medicine, rare neoplasms
Background

**Precision medicine.** The paradigm shift (1) that emphasizes preemptive over responsive medicine, while also actively involving the individual patients in their therapy, is coined with the term precision medicine (PM) (2). PM, in essence, is a medical approach that uses individual genotypes and phenotypes for tailoring the right therapeutic strategy to the right individual at the right time (3). This medical process classifies patients into subgroups based on their characteristics, which is a significant divergence from the ‘one-size-fits-all’ model, rather than forming strategies unique to each patient (4). Oncology currently stands at the forefront of the medical fields which has benefited from PM (5) due to the in silico, *in vitro* and *in vivo* improvements in disease modelling (6), and also due to the genomic characterization of thousands of cases (7).

The majority of cancerous malignancies are driven by genomic alterations that influence key oncogenic pathways leading to the genesis and progression of the disease (5,8). Early detection of those drivers brings forth the promise of genome-driven oncology care (9). Neither the idea of the characterization of malignancies based on the genomic profile of a patient, nor the notion that medicine needs to be more anthropocentric and preemptive, are novel approaches. For example, the relevance of karyotypes to the decision as to whether a patient with acute myelogenous leukemia (AML) should be administered chemotherapy (10), and the mention of the ‘4Ps’ (predictive, preventive, personalized and participatory) in medicine (11-14), are both ideas that were proposed at times when both the expertise and the technological capabilities were inadequate for addressing them any further.

The framework changed with the completion of the Human Genome Project (HGP) (15) followed by the emergence and establishment of next-generation sequencing (NGS) as the de facto sequencing method. While triggering fundamental changes in the field of biology and practically encouraging biological research to adopt more data-driven approaches (16), the unique features of NGS also cover the needs of the routine clinical practice (17), by improving the clinical outcomes for many patients with cancer. Using NGS (also known as massively parallel or deep sequencing), an entire human genome can be sequenced within a single day, whereas with the previous Sanger sequencing technology, the first assembly of the human genome required over a decade (18). With the availability of the genome sequence and the technological advancements in sequencing technologies, which became progressively more accurate and affordable, large-scale initiatives such as The Cancer Genome Atlas (TCGA), and the International Cancer Genome Consortium (ICGC) (19), have paved the road for the development of the ‘cancer genomics’ field (5). In cancer genomics the fundamental premise is that cancer is caused by somatically acquired mutations and therefore it is a disease of the genome (18).

**Biobanking.** The ‘fuel’ that drives progress in cancer genomics consists of the samples that individual patients provide to the research teams worldwide. These samples are stored in biorepositories that accept, process, store and distribute them along with their associated data and meta-data (20). These biorepositories are referred to as ‘biobanks’, a term that was used for the first time by Loft and Poulsen in 1996 (21), and are ranked among the most important research infrastructures in cancer research (22). The Organization for Economic Co-Operation and Development (OECD) defines a biobank, ‘as a collection of biological material and the associated data and information stored in an organized system, for a population or a large subset of a population’ (23,24). While the biobanking taxonomy incorporates a wide area of biobank types (e.g., commercial, DNA/RNA, project-driven, virtual and more) (20), a generic distinction can be made between disease-centric and population-based biobanks (25). An important issue of biobanks is their heterogeneity and therefore, a proper biobank and sample classification is of utmost importance (26).

The field of biobanking is constantly evolving. Individual and small university-based repositories and sample collections have gradually become institutional, commercial, and government supported repositories, while the complexity of the data associated with the samples has also increased exponentially, from basic information such as the date of the sample's collection, to the extensive information accompanying the various ‘-omic’ (genomic, transcriptomic, proteomic) technologies (20). The number of samples and the available data that accompany them should adequately cover the broad spectrum of sub-entities emerging in malignant neoplasm diseases in reference to PM; these are constantly growing and differentiating, thus offering more and more areas of study for the application of both the available targeted therapies and those that are being developed at a rapid pace. Additionally, the operating regulations of modern biobanks must guarantee both the management of high-quality samples, as well as the compliance with ethical, legal, and societal requirements, while allowing transparency and effective procedures regarding access to samples and data (3).

**Pan-European initiatives.** While decentralized individual collections can be well organized and accessible, there is a need for harmonization between the collections. Accessibility and funding issues, ethical frameworks and protocols regarding the sample collections and their storage, must be approached in a way that ensures interoperability and ‘common ground’ between biobanks. The difference between ‘harmonization’ and ‘standardization’ of biobanks is that the former is a more flexible approach that facilitates the effective interchange of valid information and samples, while the latter is an approach that demands that the same protocols and standard operating procedures (SOPs) are used by all biobanks (27,28).

To address these issues, the European Commission developed a Biobanking and BioMolecular Resources Infrastructure (BBMRI) (http://www.bbmri-eric.eu/), providing a legal and ethical framework for biobanking across the European Union. BBMRI includes comprehensive collections of biological samples from different sub-populations of Europe, linked with continuously updated data on the health status, lifestyle, and environmental exposure of the sample donors (29). Another project that has worked in tandem with BBMRI inside the EU is the Biobank Standardization and Harmonization for Research Excellence in the European Union project (BioSHaRE-EU) (http://www.bioshare.eu/). Biobank development has been stated as one of the key challenges of the last two decades in EU. Europe is not the only continent that progresses the
biobanking field. In the international landscape, the effort for
instigating the inter-communication in biobanking is driven
by the National Cancer Institute (NCI) (https://biospecimens.
cancer.gov/), the International Cancer Genome Consortium
(ICGC) (https://daco.icgc.org/), the Public Population
Project in Genomics and Society (P²G, renamed to P³G2)
(http://p3g2.org/), and the International Society of Biological
and Environmental Repositories (ISBER) (https://www.isber.
org/). As also indicated by the current SARS-CoV-2 pandemic,
the collaboration between ISBER and BBMRI is expanding so
as to cover a broader spectrum (30).

The Hellenic Network of Precision Medicine on Cancer. In
order to address the needs of oncology patients, the Hellenic
Network of Precision Medicine on Cancer (HNPM) was
founded in Greece on 17/05/2018 at the initiative of the Research
and Innovation Department of the Ministry of Education,
Research and Religion in close collaboration with the Ministry
of Health. The project is supervised by the General Secretariat
of Research and Innovation (GSRI) and funded by the Hellenic
Republic-Siemens Settlement Agreement framework. This
multi-stakeholder initiative has grown rapidly since its incep-
tion and aims to establish a nation-wide infrastructure which
provides high-quality healthcare to Greek citizens, enrich
diagnosis knowledge and prediction outcome and improve the
targeted therapeutic treatments of cancer patients (3).

A partner institution collaborating for the formation of the
HNPM is the 1st Department of Pathology, which belongs to the
Medical School of the National and Kapodistrian University of
Athens (NKUA). In addition to academic activities, it conducts
histologic examinations for ‘Laiko’ Hospital and a substan-
tial number of other hospitals all over Greece. More than
200,000 paraffin blocks are stored in the files of the depart-
ment, making it the largest tissue collection in Greece. The vast
majority of specimens represent malignant neoplasms, among
which, solid tumors, hematologic malignancies, myoskeletal
and nervous system tumors, figure prominently. This is because
the 1st Department of Pathology is a reference center for these
tumors. New diagnostic techniques include, but are not limited
to, the analysis of biomarkers in the context of molecular
targeted therapeutic approach of malignant neoplasms. During
the last decade, the 1st Department of Pathology has been
actively involved in a European brain tissue bank network
named BrainNet Europe II (Network of European Brain and
Tissue Banks for Clinical and Basic Neuroscience), a
project funded by the European Commission's 6th Framework
Program for Research, aiming to define ‘gold-standards’ in
tissue sampling practice and neuropathological diagnostics.
In the context of the HNPM, the 1st Department of Pathology has
implemented the biobanks sub-project, in close cooperation
with the Biomedical Research Foundation of the Academy of
Athens (BRFAA), which is the central hub of the Greek
biobanks, all of which together form the BBMRI-GR network,
an official member of the pan-European Biobanking and
BioMolecular resources Research Infrastructure, European
Research Infrastructure Consortium (BBMRI-ERIC).

Purpose. This publication focuses on a) delineating the regula-
tory framework regarding biobanking development in Greece,
b) analyzing the methodologies that were followed in order
to create a pilot biobank of rare malignant neoplasms, in the
context of the HNPM, and c) presenting the clinical impor-
tance of the biobank. In respect to the multidimensionality of
the pilot biobank project, the basic goals that were set are the
following: i) the organization of sample collections consisting
of specimens from patient cohorts with specific types of
malignant neoplasms and with available clinical information;
ii) implementation of a Pilot Biobank Management System
(PBMS) compatible with the Minimum Information About
Biobank data Sharing (MIABIS) model; iii) harmonization of best practices regarding biobank functions; iv) ethical
and legal framework clarifications aligned with the General
Data Protection Regulation (GDPR); and v) connection of the
biobank of rare malignant neoplasms of the 1st Department
of Pathology with the BBMRI-GR network.

Methodologies and tools

Research and methods. Throughout the course of the HNPM's
biobank project, including this publication, a wide selection
of manuals and schemas were reviewed, and a number of best
practices were adopted (Table I) (27,31-47). The following
sections analyze the methodologies and the tools that were
utilized in creating the infrastructure of the pilot biobank of
rare malignant neoplasms.

Biological material. The Biobank currently comprises of
553 samples, specifically 384 samples of hematopoietic and
lymphoid tissue malignancies, 72 samples of pediatric brain
tumors and 97 samples of malignant skin neoplasms. These
samples have been collected from the collaborating groups
of scientists at the 1st Department of Pathology and the
Laboratory of Biological Chemistry, Medical School of the
NKUA, and also from the ‘Andreas Syggros’ Hospital of
Cutaneous and Venerable Diseases, under the supervision of
the 1st department of Pathology (Fig. 1). All formalin-fixed
paraffin-embedded (FFPE) samples were evaluated by hema-
toxylin and eosin (H&E) and microscopy regarding the quality
of tissue, histological aspects, and any potential damage during
processing. The samples that deviated from optimal quality
have been excluded from the biobank. A number of these
samples have also been evaluated by PCR and immunohisto-
chemistry (IHC) to assess the genetic and molecular profile of
the tissues. Cryopreserved samples were evaluated by qPCR,
RT-PCR, and western blot analysis for assessment of RNA and
protein quality. The majority of the samples have also been
included in research protocols and published studies in inter-
national peer-reviewed journals, indicating both their quality
as biological materials as well as their reliability (48-62).

As far as hematologic malignancies are concerned, the
tumor sample collection and its associated data consisted of
a multistep procedure that required the collaboration of clini-
cians from the Hematology Department of General Hospital
‘Laiko’, NKUA. First, patients with hematologic malignan-
cies were retrieved throughout a clinical database according
to their initial histologic diagnosis. The treating physician
of each patient was responsible to decide who was eligible for
the biobank formation depending on the availability of data
regarding each case. A process of matching the selected
patients to their respective biological material, consisting
mainly of FFPE tumor samples (lymph node, bone marrow and spleen biopsies) was the next step. A specially authorized team collected, assessed, archived, and stored the samples of each collection. The team consisted of experienced pathologists who confirmed the diagnosis based on the histological examination of each sample in respect to the clinical information collected from the treating physician and biochemists who evaluated the quality of the samples, and other life scientists who performed the collection/archiving processes. Finally, a list of FFPE tumor samples and the associated clinical data for each individual hematologic disease was obtained. Patient anonymity as well as confidentiality of the clinical information was ensured at every step of this procedure.

Regarding the pediatric brain tumors, two different tissue collections were assembled from the 1st Pediatric Neurosurgery Department of ‘Mitera’ Hospital and the...
Department of Neurosurgery of ‘Aghia Sofia’ Children’s Hospital along with their histopathological diagnosis. All cases included were of clinical interest due to their rarity and their heterogeneous clinical/pathological characteristics. The executive clinician for the malignant brain tumors, collected all FFPE samples, archived, and stored the samples of each collection separately.

Concerning malignant skin tumors and their metastatic sites, two different collections were created based on the clinical information from the Plastic Surgery Department of ‘Andreas Syggros’ Hospital and the histological diagnosis from the Department of Pathology of ‘Andreas Syggros’ Hospital. The two collections concern metastatic (late-stage) cutaneous squamous cell carcinomas (CSCCs) along with metastatically involved lymph nodes and primary melanomas with adjacent surrounding tissue and either regional or distant metastases (lymph nodes, lung, brain). All cases included were of clinical interest due to their rarity or distinguishing clinical/pathological characteristics. The executive clinician for the malignant skin tumors, collected all FFPE samples, archived, and stored the samples of each collection separately. All collections were formed guarantying patient anonymity, each of whom was enrolled with a code number based on the number of their FFPE tumor sample.

The pilot biobank of rare malignant neoplasms mainly consists of FFPE samples (535 samples). FFPE blocks are stored in a controlled low-humidity environment at room temperature (20-25°C), as per the current best practice for FFPE tissue block and slide storage (40,63). The biobank also contains 18 cryopreserved astrocytoma samples, stored at -80°C.

Qualification of samples. Downstream analysis largely depends on the existence of homogenous biobanks. Preanalytical factors may have an impact on the quality of the collected biospecimens by introducing uncontrollable variables (64). At any failure sample testing process, the results of subsequent analysis may be of little to no value. Inappropriate sample collection can obstruct the identification of novel biomarkers, while also having a negative economic impact; e.g. up to 10 million euros of funding are lost each year in clinical trials due to preanalytical and analytical problems (63). Therefore, qualification processes, such as quality assurance (QA) and quality control (QC) processes, are mandatory in order to assess the quality of biospecimens before their storage into a biobank. The terms are utilized as they were defined in the study of Dr Fay Betsou in ‘Quality Assurance and Quality Control in Biobanking’. In the aforementioned work, detailed definitions of common terms used in biobanking are also provided (65). There are two main approaches for qualification: a) the careful collection of samples with pre-analytical annotation by implementing the Standard PReanalytical Code (SPREC) (46), and b) the classification of biospecimens, contained in retrospective collections, in different categories corresponding to *in vivo* parameters (quality stratification) or *b*) the examination and validation of a single biospecimen or a collection on the basis of objective analytical parameters (sample qualification) (25,66). The quality process used in the biobank of rare malignant neoplasms, considering that the biobank mainly consists of FFPE tissues, was quality stratification (Table II) (66) of archival samples stored in the collection of the 1st Department of Pathology. All pediatric brain tumor samples have been evaluated by H&E staining and microscopy. Astrocytoma samples have also been evaluated by qPCR, RT-PCR, and western immunoblotting.

**Formalin-fixed paraffin-embedded tissues.** FFPE is a form of biopsy specimen preservation which prevents tissue degradation and has become the standard preservation procedure for diagnostic pathology. The biobank of rare malignant neoplasms largely consists of FFPE blocks. Although there are other alternatives such as fresh-frozen (FF) tissue, FFPE blocks remain the most common and cost-effective preservation method. FFPE samples can sometimes match with FF samples in the quality of the data produced by NGS experiments (67-71). NGS can be used to study FFPE specimens in both prospective and retrospective archive-based studies in which FF specimens are not available (71). Both DNA and RNA can be successfully extracted from FFPE blocks, but it is a more delicate procedure than extraction from FF tissues. The long-term storage at room temperatures, may

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**Table II. QC measurands for quality stratification of FFPE tissue specimens (66).**

| Biospecimen type | Quality stratification parameter | Quality stratification parameter category | Measurand | Quality stratification threshold | Measurement method and reference |
|------------------|---------------------------------|------------------------------------------|-----------|-------------------------------|----------------------------------|
| Tumor FFPE       | % tumor                         | Tumor-rich                               | Tumor     | >70%                          | H&E staining, digital pathology  |
|                  | Fixation time NBF               | >72 h                                    | None to date | TBD                           | RT-qPCR                          |
|                  | Fixation conditions             | NBF (no acidic formalin)                 | Size range | ~250 bp                       | RT-PCR                           |
|                  | Cold ischemia                   | >12 h                                    | None to date | TBD                           | RT-qPCR                          |
|                  | Tumor frozen tissue             | Cold ischemia                            | None to date | TBD                           | H&E staining, RT-PCR              |

FFPE, formalin-fixed paraffin-embedded; NBF, neutral buffered formalin; H&E, hematoxylin and eosin; TBD, to be defined.
generate genomic mutations resulting in the identification of false single nucleotide variations (SNVs); this is correctable by choosing high sequencing depths (80X at least) when analyzing FFPE materials (72). Another study suggests that the routine processing of FFPE samples may have a detectable, albeit negligible effect on NGS data, therefore not impacting the reliability of clinical NGS testing (67). The last potential threat to the quality and amplifiability of the extracted DNA is the method of deparaffinization. Higher melting temperature can result in the denaturation of the double-stranded DNA, while lower melting temperature can result in improper melting of paraffin and therefore reducing the DNA yield. It is suggested that using a temperature of 75˚C for 5 min, results in no loss of DNA content (72).

Other sample types. Frozen samples of 18 pediatric astrocytomas are stored at −80˚C. Fresh freezing is currently the preservation method that is most compatible with subsequent proteomic analyses. Fixation by formaldehyde crosslinking is incompatible with some proteomic analyses, necessitating a change in the routines of histopathological sample handling, such that the tissue must be received unfixed.

Associated data and clinical information. All pediatric brain as well as hematologic tumor samples are accompanied by histopathological records, demographic data, and informed consent of patients/parents of the patients or their legal guardians. All samples have additional clinicopathological data (molecular data, IDH1, R132H, H3K27M, BRAF mutations, treatment information, response to therapy and patient follow up). To ensure the anonymity of patients and the confidentiality of their information, each patient is assigned a number and only authorized members have access to this data.

Creating the pilot biobank management system

Minimum information about biobank data sharing model. A crucial tool for effective networking and resource sharing that was adopted in this present work is the MIABIS model (Fig. 2). MIABIS 1.0 was launched in 2012 and aimed to facilitate data discovery through harmonization of data elements describing a biobank at the aggregate level (44). It recommended the minimum data items and the format of the items required to enable the exchange of biological samples and data (64). MIABIS 2.0 was released in 2016 and provided the ontology that represents the administrative entities regarding a biobank, while also defining the core components needed to describe biobanks (biobanks, sample collections and studies) (41,43). An extension of MIABIS was released in 2020 and included an updated terminology to describe samples, sample donors and events (42). MIABIS is currently being updated to version 3.0 and will include updates identified by BBMRI-ERIC Common Service IT (CS-IT) working group (73,74). Every MIABIS
Table III. Legally binding or non-binding instruments regarding biobank regulation within Europe.

| Regulation no. | Brief description                                                                 | (Refs.) |
|----------------|------------------------------------------------------------------------------------|---------|
| 2001/20/EC     | Clinical Trial Directive                                                           | (77)    |
| EU 536/2014    | Clinical Trials Regulation                                                         | (77)    |
| ETS No. 5      | Convention for the Protection of Human Rights and Fundamental Freedoms             | (78)    |
| ETS No. 108    | Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data | (79) |
| ETS No. 164    | Convention on Human Rights and Biomedicine                                         | (80)    |
| 95/48/EC       | Data Protection Directive (Repealed by GDPR)                                       | (81)    |
| CM/Rec/2016/6  | Recommendation on Research on Biological Materials of Human Origin                 | (82)    |
| A/RES/217(III) | The Universal Declaration of Human Rights                                          | (83)    |
| 2004/23/EC     | Tissues and Cells Directive                                                        | (84)    |
| WMA/1964       | World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects | (85) |
| WMA/2002       | World Medical Association Declaration of Taipei: Ethical Considerations Regarding Health Databases and Biobanks | (86) |

component along with the structured data and lists [as defined in the MIABIS main repository (73)] were implemented in the PBMS.

Pilot biobank management system. The digital representation of the biobank is implemented as a relational database, using MySQL language. Tables and relations are structured in accordance with MIABIS. In order to easily access and modify the biobank's samples and their associated data, a desktop interface was developed as to enable non-IT personnel to perform basic CRUD (create, read, update, delete) operations to the database. The interface was developed via the open-source graphical subsystem: Windows Presentation Foundation (WPF), using C# as the coding language. To ensure anonymity, sensitive information is encrypted as described in the Privacy and Data Protection subsection. On top of the pseudonymization, log-in authentication was implemented on the interface and the database levels as an additional measure.

Framework and processes

The European regulatory framework. Ethical, legal and societal issues (ELSI) and certain bioethical aspects are a constantly evolving debate topic among committees, scholars, and policy makers. The ELSI approach is considered to facilitate the advancement of genomic technology rather than hinder it (75). Biobanking regulations within the EU are highly heterogeneous. Biobanks, in general, are governed under the general regulatory framework for biomedical research. Biobanking development is inhibited by the lack of EU legal-binding documents specifically applicable to biobanks, barring legislation at the national level (27). Several attempts have been made for the unification of European regulations regarding research. For example, the 04/04/1997 Oviedo Convention on Human Rights and Biomedicine (76), is the basis for safeguarding the rights of human subjects regarding scientific progress within the EU countries which have signed and ratified the convention (27). At the national level, research ethics committees (RECs) determine whether research should proceed within the national legal frameworks instead. Various other regulations that are applicable to biomedical research at the European level have been introduced (Table III) (77-86).

Regardless, due to the existence of national-level regulations, further ameliorations need implementation at a cross-border level in the EU. The complexity that researchers across the EU face, might place them at risk of operating unlawfully by sharing data and samples across borders where different laws are in force (27).

The Greek landscape. Lack of specific biobanking legislation along with the absence of discrete terminology concerning biobanking (in the context of the Greek law), heavily obstructs further scientific research. Biobanking governance in Greece consists of a complex web of generally applied constitutional provisions, laws, regulations, codes of practice, guidelines and so forth (Table IV) (34,47,87), each of which can potentially apply to biobanks (47). The only piece of legislation wherein collections of tissues are referred to in a systematic way, is the Presidential Decree (26/2008), that sets quality and safety standards for the donation, procurement, testing, processing, preservation, storage, disposal of dangerous substances, and distribution of human tissues and cells. While not directly applicable to biobanks, it applies to biobanks which store stem cells, in which case the Hellenic Transplant Organization (HTO/EOM) is responsible for authorization (34). Since biobanks contain personal data along with biological samples, the participants' privacy is regulated by Law 2472/1997 (Protections of Individuals with regard to the Processing of Personal Data) and more recently, GDPR. Furthermore, researchers and physicians acting within a biobank are bound by the Code of Medical Ethics/Deontology (Law 3418/2005), which secures protection to the donors' privacy. Several agencies are also in charge of monitoring privacy, and subsequently, biobanking in Greece.

The establishment of Research Ethics and Deontology Committees (REDCs) in all universities and research institutions, provides additional overseeing by examining whether research projects respect humans' inherent value as well as
participants' autonomy, private life, and personal data (34). The Hellenic Data Protection Authority (HDPA) is responsible for assessing data protection violations and HDPA's prior permission is a precondition for the collection and processing of sensitive data (47).

**Privacy and data protection.** Biobanks should always protect the patient's identity in order to ensure their privacy. A distinction enshrined in the GDPR, is the one between anonymized and pseudonymized data. Anonymized data fall outside the jurisdiction of GDPR; even so, the act of anonymization itself is considered as an act of processing personal data, which should occur in compliance with the GDPR (34). However, in the context of biobanks, the patient must be able to be re-identified to provide relevant information back to researchers (24), so irreversible anonymization is not applicable to most types of biobanks. Contrarily, pseudonymization of personal data is a reversible act. Pseudonymized data, as defined in the GDPR, are data that ‘can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person’ (34). The cryptographic algorithm that was implemented for the confidentiality of patient and researcher data is the 128-bit block cipher: Advance Encryption Standard (AES-Rijndael) (88). AES was included in the ISO/IEC 18033-3 standard and is currently effective as a US federal government standard since 26/11/2001 (FIPS PUB 197) (89).

**Informed consent.** The collection of several samples is dated before the GDPR's implementation in EU; and therefore a number of samples were obtained by the laboratory's physicians via the 'broad consent' model, which is the agreement for the utilization of the patient's sample for an unspecified range of future or current research subjects to a few content and/or process restrictions. Broad consent is less specific than consent that changes scope overtime (e.g., 'dynamic consent'), but more narrow than open-ended permission without limitations ('blanket consent') (90,91). In the context of HNPM, a special questionnaire and leaflet were formulated to effectively inform competent individuals about the collection of their specimens. The purpose was to reassure the individual patients that their sample may be utilized, with complete anonymity and strictly for research purposes only, while underlying that 'no ownership of biological samples exists’ as declared by the International Agency for Research on Cancer (IARC) (33). In addition, as previously stated, the majority of samples are part of studies already published in international peer-reviewed journals, and ethical approval has been obtained for all tissue samples from the University Hospitals' Ethics Boards and/or the Bioethics Committee of the University of Athens Medical School.

**Governance model and access processes for samples and data.** As previously mentioned, this is a pilot biobank and therefore the final governance model has not yet been defined. An exploratory analysis has identified six types of commonly adopted biobank governance strategies: communication, compliance, expert advice, external review, internal procedures, and partnerships (92). Some strategies that were adopted in the formation of this biobank are the following.

**Communication.** The structure and the activities regarding this biobank have been included in HNPM's technical conferences/online workshops and have been presented to Greek cancer patient associations and the public, therefore gathering impactful feedback.

**Compliance.** This biobank followed GDPR regulations, and a number of best practices were adopted.

**Internal procedures.** All samples and data were collected following informed consent processes. Moreover, various QC measurands are used to assess the quality of the final

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**Table IV. Legally binding or non-binding acts and experts' opinions regarding biobank regulation in Greece.**

| Law no.          | Brief description                                                                 | (Refs.)         |
|------------------|------------------------------------------------------------------------------------|-----------------|
| Law 2472/1997    | On the Protection of Individuals with regard to the Processing of Personal Data, Implementing Directive 95/46/EC | (34,47)         |
| Law 3305/2005    | Application of the Methods of Medically Assisted Reproduction                     | (47)            |
| Law 3418/2005    | Code of Medical Ethics/Deontology                                                 | (34,47)         |
| DYG 3/89292/2003 | Ministerial Decision, Implementing Directive 2001/20/EC                          | (34)            |
| 52/2006          | National Bioethics Commission Recommendation on Banks of Biological Material of Human Origin (Biobanks) in Biomedicine Research | (87)            |
| Law 2723/1999    | On Transplantations of Tissues and Organs                                         | (47)            |
| 115/2001         | Opinion of the Hellenic Data Protection Authority on Processing Employees’ Personal Data | (47)            |
| Law 4624/2019    | Personal Data Protection Authority, Implementing Measures for Regulation EU 2016/679 | (34)            |
| 26/2008          | Presidential Decree, Implementing Directive 2004/23/EC                           | (34)            |
| Law 2619/1998    | Ratification of the Oviedo Convention                                             | (34)            |
| Law 4386/2016    | Regulations for Research, Regulating Administrative Aspects of Research           | (34)            |
| Law 4521/2018    | Research Ethics and Deontology Committees                                        | (34)            |
samples, and pseudonymization processes ensure the privacy of the donors.

Partnerships. This biobank is a result of three collaborating entities (1st Department of Pathology, Laboratory of Biological Chemistry and ‘Andreas Syggros’ Hospital of Cutaneous and Venereal Diseases) under the context of a Panhellenic initiative currently comprising more than 13 partner institutions.

While the pilot biobank of rare malignant neoplasms is currently housed at the 1st Department of Pathology, it is created in the context of HNPM and will subsequently be part of the BBMRI-GR network, therefore the governance model is subject to further change. Besides regulations of the three collaborating entities, HNPM consists of two governing entities, the Scientific Committee, and the Technical Committee.

As far as sample and data access is concerned, HNPM has comprehensive forms that interested parties need to fill, and they contain instructions for accessing the samples and associated data regarding the biobank of rare malignant neoplasms. Researchers can apply to study the samples as well as the information stored in the biobank of rare malignant neoplasms. This includes researchers from universities or research institutes, the government, and drug- or health-related companies. Each application will be reviewed by the Scientific Committee of HNPM, which evaluates each candidacy based on the following criteria: a) activity related to the subject of HNPM, b) available infrastructure, c) professionally trained and experienced staff, and d) process standardization.

When needed an REC will also be formed. This kind of review ensures that risks are minimized and that the rights and welfare of people who participate in research are protected. When a study is approved by the scientific committee, a part of each biospecimen and additional clinical information might be distributed to the researchers. Researchers will not be given any participants’ names and/or any other information that could potentially reveal patient's identity.

Pilot biobank of rare malignant neoplasms

Sample collections: 1st Department of Pathology, Medical School, NKUA

Acute leukemia. Acute leukemias are a group of life-threatening hematologic malignant disorders, affecting both children and adults. The diagnosis relies on cytology, cytochemistry, flow cytometry, immunophenotyping, and molecular genetics, including detecting recurrent genetic abnormalities. Each case requires an integrated, multimodality approach, which is a prerequisite for optimal diagnosis and management. As leukemias are characterized by extreme heterogeneity, both at the molecular level and in regards to the clinical outcome, they represent an excellent field of research, as molecular genetics has led to the identification of abnormal gene products and pathways and delineation of specific entities (93,94).

Cutaneous lymphoma. Primary cutaneous lymphomas are non-Hodgkin lymphomas affecting the skin as the primary site, without extracutaneous involvement at the time of diagnosis. The majority consists of cutaneous T-cell lymphomas (CTCLs), accounting for 65-75% of all cases. Mycosis fungoides is the most common CTCL (50% of all primary cutaneous lymphomas) (95), characterized by skin infiltrates of small to medium-sized lymphocytes, which is clinically characterized by the evolution of patches, plaques and tumors. Among the cutaneous B-cell lymphomas (CBCLs), primary cutaneous marginal zone lymphoma and follicle center cell lymphoma follow a more indolent behavior, whereas primary cutaneous diffuse large B-cell lymphoma, leg type, accounts of 4% of all cutaneous lymphomas and is associated with a significant risk of systemic dissemination (48,49,60,96-99).

Diffuse large B-cell lymphoma. Diffuse large B-cell lymphoma represents approximately 25-35% of all adult non-Hodgkin lymphomas. It is an entity mainly affecting the elderly, but it can uncommonly occur in children and young adults. It may present as nodal or extranodal disease, the latter representing 40% of the cases, affecting the gastrointestinal tract, bone, testis, spleen and virtually any body site. It can arise de novo or as aggressive transformation of an indolent B-cell lymphoma. Risk factors for development include underlying immunodeficiency and Epstein-Barr infection. Currently there is novel data elucidating the mutational landscape of diffuse large B-cell lymphoma and its pathogenesis. As a highly heterogeneous group of neoplasms, it is difficult to distinguish patients that will benefit from more aggressive treatment strategy. Therefore, it is an excellent candidate for further research in the context of PM (50,100).

Follicular lymphoma. Follicular lymphoma is a common, indolent B-cell lymphoma, clinically characterized by diffuse lymphadenopathy, bone marrow involvement, and splenomegaly with a median age at diagnosis of 65 years. It originates from germinal center B cells, and the neoplastic population is composed of centrocytes and centroblasts with at least partially follicular pattern. Hallmark genetic finding is the t(14;18) (q32;q21) translocation, present in 90% of low-grade cases, between the IGH and BCL2 genes (101,102). Transformation to diffuse large B-cell lymphoma is not uncommon, with an estimated risk of 2% per year (103).

Hairy cell leukemia. Hairy cell leukemia is a rare and indolent B-cell lymphoma, clinically characterized by pancytopenia, weakness, fatigue, and splenomegaly, due to massive infiltration of the bone marrow and the spleen by neoplastic cells, and absence of lymphadenopathy. The neoplastic lymphocytes acquire hairy-like projections and classically express annexinA1, CD25, TRAP, CD123, CD11c and cyclinD1 by immunohistochemistry. In over 95% of the cases the BRAFV600E mutation is detected, constitutionally activating the MAPK pathway, and therefore these patients are susceptible to BRAF inhibition. Interferon α, purine analogues and/or anti-CD20 antibodies remain the first-line treatment. In case of relapse or resistance, BRAF inhibitors are an option only in patients carrying the mutation (56,104). As a rare disease, gathering all eligible patients in a cohort is immensely helpful in future study design (51).

Hodgkin lymphoma. Hodgkin lymphoma consists of two distinct disease entities, classical Hodgkin lymphoma, and nodular lymphocyte-predominant Hodgkin lymphoma. The classical Hodgkin lymphoma is further subclassified into four...
subgroups: nodular sclerosis (the most common one, 90% of all Hodgkin lymphomas), mixed cellularity, lymphocyte depletion, and lymphocyte-rich Hodgkin lymphoma. Each subtype has different clinical features and outcomes. Histologically, the hallmark of classical Hodgkin lymphoma is the presence of large Hodgkin and Reed-Sternberg cells, expressing CD30 and CD15 and negative for B-cell markers, admixed with various mature non-neoplastic inflammatory cells. Nodular lymphocyte-predominant Hodgkin lymphoma is characterized by preservation of the B-cell program in the neoplastic cells. Optimal management consists of chemotherapy and autologous stem cell transplantation, but in the case of relapse the treatment approaches are limited. PM may offer new options in this setting (50,54,55,61,62,105,106).

Mantle cell lymphoma. Mantle cell lymphoma (MCL) is a relatively rare (3-10% of all non-Hodgkin lymphomas) B-cell lymphoma with poor prognosis (median survival 3-5 years). It is characterized by the t(11;14)(q13;q32) translocation, present in >95% of the cases (107). Commonly it presents with nodal disease, with the spleen, bone marrow and the gastrointestinal tract being also infiltrated. Classic presentation follows an aggressive clinical course, but other variants as leukemic non-nodal mantle cell lymphoma or in situ mantle cell lymphoma are considered indolent. Despite the improvement in response durations with currently available treatment options, patients will eventually relapse, making the need for novel therapies urgent (52,53,108).

Clinical importance. Hematologic malignancies are a group of heterogeneous diseases requiring careful histopathologic evaluation and molecular characterization that is essential for optimal therapeutic management. Hematologic tumor biobanks would contribute to the evolution of the current knowledge, hoping to benefit thousands of patients around the world. More precisely, integration of clinical as well as tissue-derived data such as molecular characteristics, can be used for detection of biomarkers, screening of patients for clinical trials, offering opportunities to refine therapeutic decision-making, foster multidisciplinary high-impact research, and ultimately improve patient outcomes. They can also promote the study of genomics in oncology through a public data sharing platform.

Sample collections: Laboratory of Biological Chemistry, Medical School, NKUA

Pediatric brain tumors. This sample collection contains 72 samples of pediatric brain tumors, of which 54 are FFPE samples and 18 are cryopreserved astrocytoma samples, stored at -80°C. Specifically, it comprises 40 astrocytomas (24 pilocytic astrocytomas, 9 astrocytomas grade II, 2 astrocytomas grade III, and 5 glioblastomas), 15 medulloblastomas, 9 ependymomas, 3 atypical teratoid/rhabdoid tumors, 3 craniopharyngiomas, 1 gangliogioma and 1 primitive neuroectodermal tumor. These tumors belong to ICD-10-CM Code C71 (malignant neoplasms of the brain). They have been molecularly characterized using RT-PCR, western immunoblotting, and immunohistochemistry for several epigenetic markers, and research data have been recently published (59,109).

Clinical importance. Due to the sensitive location of tumors within or adjacent to the brain, biobanking of brain tumor specimens in neuro-oncology is highly challenging and valuable. Pediatric brain tumor repositories are important for neuro-oncology progress and promotion of PM.

Sample collections: ‘Andreas Syggros’ Hospital of Cutaneous and Venereal Diseases. The collections of malignant skin tumors contain 97 samples. The collection of metastatic melanomas includes 11 samples of primary tumor together with 13 samples of adjacent normal skin surrounding the melanoma and 13 samples of the metastatic sites (lymph nodes, lung, brain). The second collection of metastatic cutaneous squamous cell carcinomas (cSCCs) includes 29 samples of primary tumors and 31 samples of lymph nodes with metastatic SCC deposits.

Metastatic melanomas. Melanoma is a malignant tumor that arises from melanocytes and primary involves the skin. Even small tumors may have a tendency to metastasize, either by the lymphatic or the hematogenous route, thus leading to a relatively unfavorable prognosis. The mean time of overall survival for metastatic melanoma patients ranges from 6 up to 9 months, with a limited five-year overall survival rate 1-2% (110). The incidence of metastasis seems to be related to the Breslow thickness, melanoma type, presence of ulceration, increased mitotic rate and intense regression. Two-thirds of metastases are originally confined to the drainage area of regional lymph nodes and can appear as: satellite metastases (defined as up to 2 cm from the primary tumor); in-transit metastases (located in the skin between 2 cm from the site of the primary tumor and the first draining lymph node); micro-metastases in the regional lymph nodes identified via sentinel lymph node biopsy (SLNB).

Clinically or radiologically recognizable regional lymph node metastases. Distant metastases can be clinically defined by the number of organs involved, presence of brain metastases, and serum levels of lactate dehydrogenase (LDH) (111). As early as 2002, the depiction of BRAFV600E mutations in melanoma set the stage for an explosion of interest for developing oncogene-directed therapy in this disease (BRAFV600E inhibitor-veumurafenib) (112). In the last decade, additional targets have been achieved, creating a new era of molecular treatment for advanced diseases. Novel agents that impact on various signaling pathways or modulate the immune system ([anti-PD-1 drugs (nivolumab, pembrolizumab) and anti-CTLA-4 antibody (ipilimumab)] hold the promise of a whole new therapeutic landscape for metastatic melanoma patients (57,58,113).

Cutaneous squamous cell carcinomas. Cutaneous squamous cell carcinoma (cSCC) originates from squamous cells of the epidermis or its appendages. The majority of cSCCs are low risk, with a 90% 5-year survival rate after surgical excision. Low-risk patients are unlikely to experience local recurrence (10%) or lymph node metastasis (5%) (114). Nevertheless, there is a subgroup of cSCC patients with an increased risk of local recurrence (10-47.2%) and metastatic spread (15-38%), which are characterized as high-risk. In this category of
patients, SLNB is encouraged for nodal staging and detecting micro-metastasis. No study yet has sufficiently assessed the impact of SLNB on the survival of these patients. As there are no solid criteria, the management of these high-risk cSCC patients, is usually in the clinician's discretion (115,116). Although early cSCC is a common tumor and totally curable with surgical excision, metastatic or advanced cSCC is relatively rare, potentially life-threatening and without established treatment options. In the past, diverse options have been used with unsatisfactory results including chemotherapy (cisplatin, fluorouracil, bleomycin, doxorubicin), 13-cis-retinoic acid, and interferon-α2a (117). Other treatments, such as epidermal growth factor receptor inhibitors have also been used with moderate success. In recent years, a better understanding of the biological behavior of cSCC, estimating clinical and histological risk factors, have led to new promising immunotherapy. These treatments include PD-1 inhibitors such as cemiplimab and pembrolizumab whose efficacy is still being tested (118).

**Clinical importance.** Metastatic melanomas and cSCCs are of great clinical interest due to their association with the high morbidity and mortality of the patients. Tissue-derived data concerning histological characteristics in correlation with clinical data should be integrated for new biomarker development, and for the elucidation of molecular tumor profiles resulting in new management guidelines for these patients, while also presenting novel treatment opportunities with the very promising immunotherapeutic approaches. High-risk cSCCs and the detection of possible micro-metastasis in sentinel lymph nodes are the new challenges in dermato-oncology. Clinical trials globally are trying to develop and provide dependable prognostic models for better nodal staging and reasonable treatment options for high-risk cSCCs.

Despite the immense advances in the field of oncology, cancer remains one of the main causes of mortality and morbidity worldwide. Personalized medicine has evolved greatly in the current era and has significantly altered patient care and management. Biobanks are a crucial part of personalized medicine enabling a systematic way of data collection, processing, and functioning. They provide stable ground for the enhancement of cancer genomics, transcriptomics, proteomics, metabolomics and epigenomics, which form the main pillars for biomarker establishment and future drug development. Moreover, the emergence of large data collections in cancer research has clearly underlined the importance of biobanks. Biospecimens are critical fuels for human disease-oriented research; cancer biobanks that integrate clinical and tissue derived data, offer extensive opportunities to refine therapeutic decision making, to foster high impact research and to improve patient outcomes. Having carried out a thorough review of the regulations governing the creation and establishment of biobanks in the Greek landscape, we formed a pilot biobank of rare malignant neoplasms with a total of 553 samples of patients with different tumor types. By laying the groundwork with the establishment of this pilot biobank, while conforming to international guidelines and recommended governance models, we aspire that this endeavor shall assist the intricate biobanking harmonization process. This biobank aspires to further bridge the gap between translational and routine medical practice by aiding clinicians and researchers alike. Molecular profiling in precision oncology can identify the best possible treatments, while also aiding researchers for investigating potential biomarkers. The biobank's samples along with their associated data have aim to meet the rising demand of quality biosamples in cancer research. It is our belief that the future of medical research is entwined with accessible, effective, and ethical biobanking and that our project will facilitate research planning in the ‘-omic’ era by contributing high-quality samples along with their associated data.

**Acknowledgements**

This project was supported by the Hellenic Network of Precision Medicine on Cancer (HNPM). We are especially thankful to HNPM’s Coordinator, Dr Kostas Stamatopoulos, for his support and for his constructive comments.

**Funding**

This work was funded by the Hellenic Network of Precision Medicine on Cancer (HNPM).

**Availability of data and materials**

Not applicable.

**Authors’ contributions**

CP and PK shared supervision of this work. DSK coordinated the activity of all participants, and carried out the majority of manuscript writing, reviewing and bibliographic search. In addition, he provided the ethical background and analysis. AP carried out sample acquisition and data quality assessment, analysis, interpretation, and management. DMV carried out all software and database development and functionality. DSK, AP and DMV carried out the conceptualization and testing of the interface development. EAK, DNZ, ED, AK, GK, VT and EC carried out sample and data acquisition. SS, EL and PK provided their expertise as pathologists. DKS, AP, DMV, EAK, DNZ, ED, SS, EL, CP and PK carried out manuscript editing and participated in the bibliographic research. SS, EL, CP and PK revised and gave final approval of the manuscript. All authors read and approved the final manuscript for publication.

**Ethics approval and consent to participate**

The study was conducted in accordance with the Declaration of Helsinki and ethical approval was obtained for all tissue samples from the University Hospitals' Ethics Boards and/or the Bioethics Committee of the University of Athens Medical School.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.
References

1. Kuhn TS: The structure of scientific revolutions, 2nd edition, enlarged. University of Chicago Press, Chicago, IL, 1970.

2. National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease: Toward precision medicine: Building a knowledge infrastructure for biomedical research and a new taxonomy of disease. National Academies Press (US), Washington, DC, 2011.

3. American Society for Human Genetics: Biobanking in health care: Evolution and future objectives, challenges, and innovation: Overview. EPMA J 7: 173‑177, 2016.

4. Patil S, Majumdar A, Awan KH, Sarode GS, Sarode SC, Gadhari AR and Gondivkar S: Cancer oriented biobanks: A comprehensive review. Oncol Rev 12: 357, 2018.

5. Coppola D, DeSouza Y, Eliason J, Glazer B, Guadagni F, Merino-Martinez R, Norlin L, van Enckevort D, Anton G, Merino, et al: Extending the minimum information about biobank data sharing specification across Europe. Springer International Publishing, Cham, 2021.

6. Sándor J, Drakopoulou A and Bárd P: The legal regulation of biobanking in health care: Evolution and future challenges, and innovation: Overview. EPMA J 7: 173‑177, 2016.

7. European Commission: Biobanking for Europe: A Challenge for Governance. Directorate-General for Research and Innovation Science in society, EUR 25302 EN, 2012.
60. Levidou G, Siakantaris M, Papadaki T, Papadavid E, Chiou Z, Giannopoulos A, Stavropoulos N, Konstantinidou I, Ross M, Thiers B, Anonymous L, Anonymous J, Anonymous K, Anonymous L, Anonymous M, Anonymous N, Anonymous O, Anonymous P, Anonymous Q, Anonymous R, Anonymous S, Anonymous T, Anonymous U, Anonymous V, Anonymous W, Anonymous X, Anonymous Y, Anonymous Z, Anonymous AA, Anonymous AB, Anonymous AC, Anonymous AD, Anonymous AE, Anonymous AF, Anonymous AG, Anonymous AH, Anonymous AI, Anonymous AJ, Anonymous AK, Anonymous AL, Anonymous AM, Anonymous AN, Anonymous AO, Anonymous AP, Anonymous AQ, Anonymous AR, Anonymous AS, Anonymous AT, Anonymous AU, Anonymous AV, Anonymous AW, Anonymous AX, Anonymous Ay, Anonymous AZ, Anonymous BA, Anonymous BB, Anonymous BC, Anonymous BD, Anonymous BE, Anonymous BF, Anonymous BG, Anonymous BH, Anonymous BI, Anonymous BJ, Anonymous BK, Anonymous BL, Anonymous BM, Anonymous BN, Anonymous BO, Anonymous BP, Anonymous BQ, Anonymous BR, Anonymous BS, Anonymous BT, Anonymous BU, Anonymous BV, Anonymous BW, Anonymous BX, Anonymous BY, Anonymous BZ, Anonymous CA, Anonymous CB, Anonymous CC, Anonymous CD, Anonymous CE, Anonymous CF, Anonymous CG, Anonymous CH, Anonymous CI, Anonymous CJ, Anonymous CK, Anonymous CL, Anonymous CM, Anonymous CN, Anonymous CO, Anonymous CP, Anonymous CQ, Anonymous CR, Anonymous CS, Anonymous CT, Anonymous CU, Anonymous CV, Anonymous CW, Anonymous CX, Anonymous CY, Anonymous CZ, Anonymous DA, Anonymous DB, Anonymous DC, Anonymous DD, Anonymous DE, Anonymous DF, Anonymous DG, Anonymous DH, Anonymous DI, Anonymous DJ, Anonymous DK, Anonymous DL, Anonymous DM, Anonymous DN, Anonymous DO, Anonymous DP, Anonymous DQ, Anonymous DR, Anonymous DS, Anonymous DT, Anonymous DU, Anonymous DV, Anonymous DW, Anonymous DX, Anonymous DY, Anonymous DZ.

59. Dimtsas GS, Georgiadi EC, Karakitsos P, Vassilakopoulos TP, Lakiotaki E, Levidou G, Angelopoulou MK, Adamopoulos C, Sachanas S, Pangalis GA, Vassilakopoulos TP, Korkolopoulou P: An update on molecular alterations in melanocytic tumors with emphasis on Spitzoid lesions. Ann Transl Med 6: 249, 2018.

58. Peet AC: Identification and characterisation of childhood lymphoid neoplasms: Clinicopathological features. Exp Dermatol 23: 931-933, 2014.

57. Giannopoulos A, Stratigos A, Soura D, Saetta A and Banfi G: Standardizing in vitro diagnostics tasks in clinical trials: A call for action. Ann Transl Med 4: 181, 2016.

56. Mendy M, Caboux E, Lawlor WT, Wright J and Wild CP: Common minimum technical standards and protocols for biobanks dedicated to cancer research. World Health Organization, International Agency for Research on Cancer, Lyon, 2017.

55. Lippi G, Simundic AM, Rodriguez-Manas L, Bossuyt P and Banfi G: Standardizing in vitro diagnostics tasks in clinical trials: A call for action. Ann Transl Med 4: 181, 2016.

54. Levidou G, Siakantaris M, Papadaki T, Papadavid E, Vasilakopoulos TP, Angelopoulos MK, Marinos L, Nikolau V, Economou D, Antoniou C, et al.: A comprehensive immunohistochemical approach of AKT/mTOR pathway and p-STAT3 in mycosis fungoides. J Am Acad Dermatol 69: 375-384, 2013.

53. Rassidakis GZ, Medeiros LJ, Vasilakopoulos TP, Viviani S, Bonfante V, Nadali G, Herling M, Angelopoulos MK, Giardini R, Chloussis M, et al.: BCL-2 expression in Hodgkin and Reed-Sternberg cells of classical Hodgkin disease predicts a poorer prognosis in patients treated with ABVD or equivalent regimens. Blood 100: 3935-3941, 2002.
81. Council of Europe: Data Protection Directive. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004L0023. Accessed January 16, 2021.

82. Council of Europe: Recommendation CM/Rec(2016)6 of the Committee of Ministers to member States on research on biological materials of human origin. https://search.coe.int/cm/Pages/result_details.aspx?ObjectID=09000016806468f8#globalcontainer. Accessed January 15, 2021.

83. United Nations: Universal declaration of human rights. https://www.un.org/en/universal-declaration-human-rights/. Accessed January 15, 2021.

84. Council of Europe: Setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human cells and tissues, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A321995L0046. Accessed January 16, 2021.

85. World Medical Association: The declaration of Helsinki - Ethical principles for medical research involving human subjects (Last amended 2013). https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed June 13, 2021.

86. World Medical Association: The declaration of Taipei on Ethical considerations regarding health databases and biobanks (Last revised 2016). https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-consid-erations-regarding-health-databases-and-biobanks/. Accessed June 13, 2021.

87. National Bioethics Commission: On banks of biological material of human origin (biobanks) in biomedical research. http://www.bioethics.gov.gr/images/pdf/ENGLISH/OPINIONS_REPORTS/biobanks_recomm_eng.pdf. Accessed December 27, 2020.

88. Daemen J and Rijmen V: The block cipher rijndael. Lecture Notes in Computer Science. Vol 1820. Springer-Verlag, Berlin, pp277-284, 2000.

89. Neczwatal J, Barker E, Bassham L, Burr W, Dworkin M, Foti J, Advani R, Ghielmini M, Salles GA, Zelenetz AD and Jaffe ES: The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127: 2375-2390, 2016.

90. Jain P and Wang M: Mantle cell lymphoma: 2019 Update on the diagnosis, pathogenesis, prognostication, and management. Am J Hematol 94: 710-725, 2019.

91. Klonou A, Korpokoloopoulou P, Gargalionis AN, Kanakoglou DS, Katifeli G, Gazouli M, Chlamydas S, Mitios S, Kalamantanis T, Stranulis G, et al: Histone mark profiling in pediatric astrocytomomas reveals prognostic significance of H3K9 trimethylation and histone methyltransferase SUV39H1. Neurotherapeutics 18: 2073-2090, 2021.

92. Treisman J and Garlie N: Systemic therapy for cutaneous melanoma. Clin Plast Surg 37: 127-146, 2010.

93. Garbe C, Amral T, Peris K, Hauschild A, Arenberger P, Bastholt L, Bataille V, Del Marmol V, Dreno B, Fargnoli MC, et al: European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment-update 2019. Eur J Cancer 126: 159-177, 2020.

94. Nikolau VA, Stratigos AJ, Flaherty KT and Tsao H: Melanoma: New insights and new therapies. J Invest Dermatol 132: 854-863, 2012.

95. Lugowska I, Teterycz P and Rutkowski P: Immunotherapy of melanoma. Contemp Oncol (Pozn) 22: 61-67, 2018.

96. Karia PS, Han J and Schmults CD: Cutaneous squamous cell carcinoma: Estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol 68: 957-966, 2013.

97. Stratigos AJ, Garbe C, Dessinioti C, Lebbe C, Bataille V, Bastholt L, Dreno B, Fargnoli MC, Forsea AM, Frednard C, et al: European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 1. Epidemiology, diagnostics and prevention. Eur J Cancer 128: 60-82, 2020.

98. Parikh SA, Patel VA and Ratner D: Advances in the management of cutaneous squamous cell carcinoma. F1000Prime Rep 6: 70, 2014.

99. Cranmer LD, Engelhardt C and Morgan SS: Treatment of unresectable and metastatic cutaneous squamous cell carcinoma. Oncologist 15: 1320-1328, 2010.

100. Soua E, Gagari E and Stratigos A: Advanced cutaneous squamous cell carcinoma: How is it defined and what new therapeutic approaches are available? Curr Opin Oncol 31: 461-468, 2019.

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