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BIORESOURCE PAPER

The Radboud Biobank: A Central Facility for Disease-Based Biobanks to Optimise Use and Distribution of Biomaterial for Scientific Research in the Radboud University Medical Center, Nijmegen

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The Radboud Biobank offers disease-based biobanks a centralized facility to optimize the use and distribution of biomaterial for scientific research. Notably, two population biobanks are also included in this collection. All collections are professionally and sustainably maintained using high-quality and secure standardized protocols for ICT, legal-ethical aspects, sample collection, processing and storage, communication and distribution. The Radboud Biobank includes biomaterial (e.g. DNA, serum, plasma, tissue, urine and faeces – depending on the specific patient group), images, associated clinical data (patient, disease-specific and phenotypic data) and derived information (genotypic data, microarray gene expressions). Patient advocates and other relevant stakeholders are actively involved in the governance of the Radboud Biobank.

Keywords: Biobank; research-infrastructure; disease-based; biomaterial; clinical data

Funding statement: The Radboud Biobank was implemented by the Radboudumc Executive Board as part of the university research infrastructure. It is a central facility for the Radboudumc, with guaranteed central support for at least 15 years. A governing strategic board, encompassing relevant stakeholder groups, oversees the operations of the Radboud Biobank. Two patient representatives are included in this strategic board, and one holds the position of chairperson.

(1) Bioresource Overview

Project description

The Radboud Biobank was established in 2012 with the aim of providing a centralized facility within the Radboud university medical center (Radboudumc) for the collection, storage and management of biomaterial, images and the corresponding clinical data. Its infrastructure is based on the Parelsnoer Institute model (PSI; [1]), which is a unique nationally representative biobanking partnership between the eight University Medical Centers (UMCs) in the Netherlands. It is expected that this infrastructure will serve as a conduit for generating robust scientific data, leading to improved health in patients as well as reinforcing the importance of biomedical research in the Radboudumc and abroad.

The Radboud Biobank was established to promote research for both prevalent and rare diseases (de novo biobanks, secondary use biobanks, remaining material from clinical trials

and non-experimental follow-up studies). Such studies may be initiated by the founders of the sub-collection. However, biomaterial and clinical data from the Radboud Biobank are also available to other researchers with bona fide research protocols that directly or indirectly contribute to medical innovation. Each request for use of Radboud Biobank samples is reviewed by an institutional review board (IRB) and must be approved by the head of the sub-biobank.

The high requirements placed on quality, standardization and harmonization strengthen the research possibilities and both quality and quantity of the scientific output. Costs associated with patient inclusion and sample and data collection are covered by the participating department. The Radboud Biobank covers the costs of sample preparation, freezing, storage and sample management. For each issuance, investigators pay a fee to partly cover operational costs of the Radboud Biobank. The extent of the fee depends on the nature and quantity

of the samples and the affiliation of the researcher with the Radboudumc.

Classification (1)

Human.

Species

Homo sapiens.

Classification (2)

Clinical biobank: biological samples and associated data, clinical data.

Context

Spatial coverage

Latitude: 51° 49' 23.7324".

Longitude: 5° 51' 42.5046".

Temporal coverage

Start data: January 2012. End date: not applicable (the intention is to include patients as long as possible, and thus there is no temporal limit); this implies that biomaterial and associated data will be stored without any time limitation.

Temporal coverage for accessibility

N/A.

Radboud Biobank has not indicated a date for samples and data to be destroyed.

(2) Methods

Steps

Samples are collected in a routine clinical care setting. Individual clinical departments are responsible for this part of the biobanking process. Once a sample arrives at the Department of Laboratory Medicine, Human Genetics or Pathology, responsibility for the material is transferred to the Radboud Biobank.

Sample handling and storage are based on standard operating procedures (SOPs). These procedures were established to ensure standardized sample collection and handling, and to guarantee a collection of samples of high and reproducible quality. Deviations from the SOPs are recorded as issues with haemolytic, lipemic, icteric, wrong tube, incorrect volume collected, deviation from time between sampling and storage, storage temperature deviation, incorrect sample handling (centrifugation, mixing/homogenization) storage problem or other deviation as free text. **Figure 1** shows the schematic workflow of the Radboud Biobank.

Stabilization/preservation

Table 1 gives an overview of procedures for collecting, processing and storing of samples defined in the Radboud Biobank's biomaterial protocol.

Type of long-term preservation

See **Table 1**.

Storage temperature

See **Table 1**.

Shipping temperature from patient/source to preservation or research use

The Radboud Biobank is directly embedded in the routine processes of the Radboudumc.

- Body fluids (DNA, plasma, serum, urine, cerebrospinal fluid): Body fluids from the clinical departments are transferred by the internal clinical transport service, a pneumatic tube system, to the Radboud Laboratory for Diagnostics (RLD). The RLD is responsible for the receipt of all samples. However, the sample handling takes place at the in-house Radboudumc expert laboratories to ensure best practices in sample handling. The samples for DNA-isolation are handled by Genome Diagnostics, Department of Human Genetics. All remaining samples are handled by the laboratory of Clinical Chemistry, Department of Laboratory Medicine.
- Fresh frozen and Formalin-Fixed Paraffin-Embedded (FFPE) tissue: Fresh frozen and FFPE tissues are directly transferred from the operating rooms to the Department of Pathology by the internal clinical transport service. The tissue should be sent in a good leak-proof, unadorned container with formalin. The volume of formalin should be at least twice as large as the tissue fragment. Until transport, tissue can best be stored at 4°C (refrigerator) or briefly at room temperature and not in (melting) ice.

Shipping temperature from storage to research use

Body fluids or materials and fresh frozen tissue samples are shipped on an excess of dry ice (−80°C) and FFPE samples at room temperature. Shipment is carried out by various certified courier services. At the moment, data loggers are not used. However, each confirmation of receipt of a shipment attests that sufficient dry ice was still present in the package.

Quality assurance measures

The sample handling is embedded in the quality management system of all cooperating laboratories, i.e. Department of Laboratory Medicine, Human Genetics or Pathology. Process control is based on the department's detailed SOPs.

Source of associated data

The Radboud Biobank requires some basic data for the catalogue, however, the department responsible for a specific disease-based biobank has defined a minimal dataset. This dataset comprises patient information collected in the context of routine daily clinical practice, among which are base-line data (patient history, physical examination, diagnostic investigations, imaging, pharmacy) and data obtained during the follow-up treatment of the patient.

To facilitate follow-up, connections to existing medical registries are actively sought. This includes, for example, links to registries for vital status, cause of death, hospitalization, cancer diagnoses and pathology records.

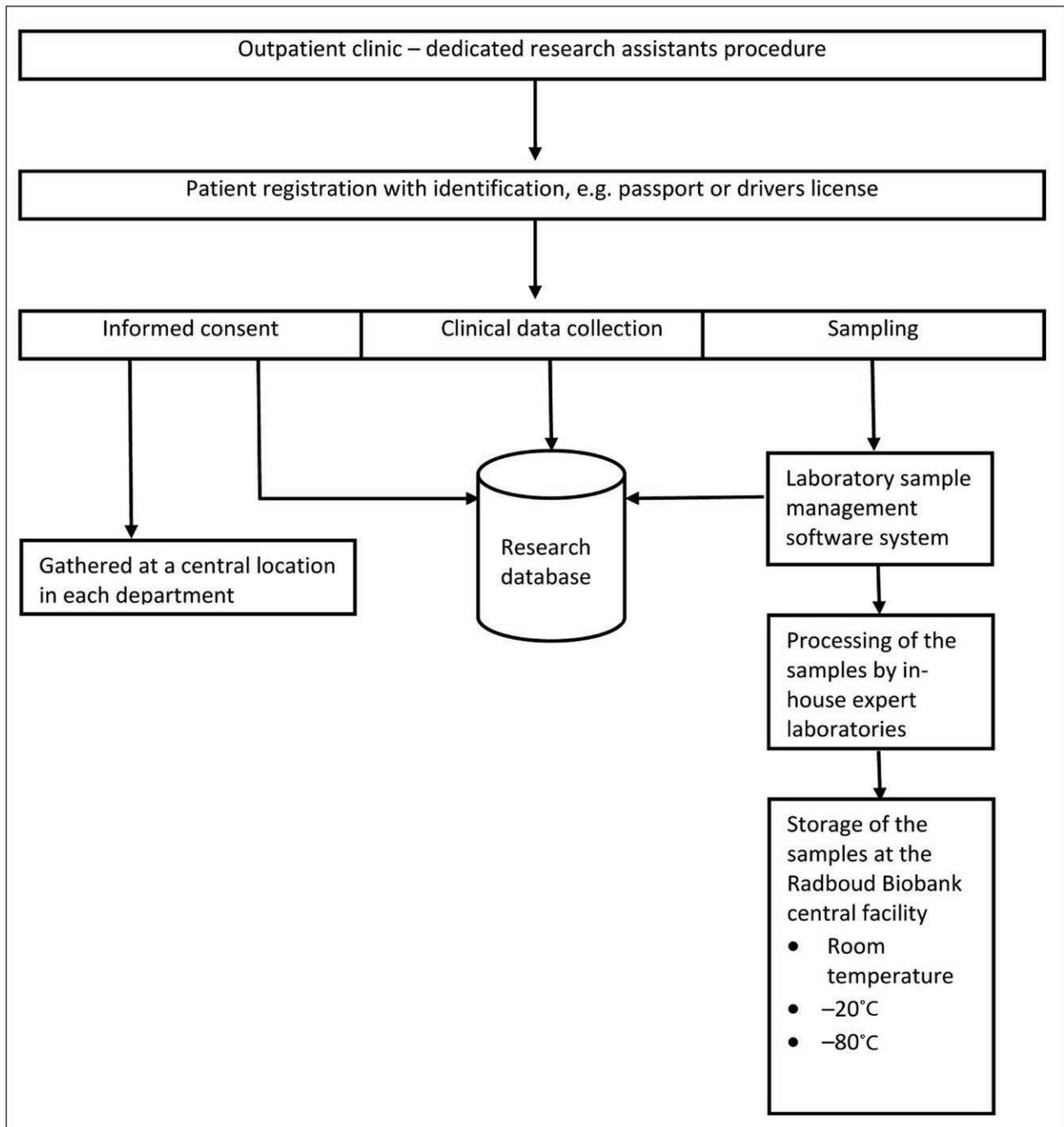


Figure 1: The flow of biomaterial and associated clinical data of a sub-biobank for the Radboud Biobank.

The Radboud Biobank guarantees the privacy of the participants. Biomaterial and associated clinical data are stored using unique codes. The key connecting these codes to patient identifiers is kept by the owner of the specific disease-based biobank. The software package for the research database produces the unique code also noted on the application form accompanying the biomaterial. The Radboud Biobank laboratory technician enters the same code in the laboratory sample management software system. Each month, the Radboud Biobank functional manager synchronizes the research database and the sample management system using study numbers. Pseudonymisation is mandatory since hospital patient identifiers do not adequately protect

patient privacy. In situations of external use, Radboud Biobank identifiers are encrypted by a Trusted Third Party using TRES (Trusted Reversible Encryption Services).

Ethics Statement

All new biobank initiatives are assessed by the IRB. This board also evaluates each specific request for use of the biomaterial and accompanying data in subsequent research proposals. The IRB handles ethical assessment of biobank-related issues with consideration given to both quality (i.e. principles of Good Research Practice) and efficiency (i.e. high frequency of meetings, digital procedure). A positive assessment is followed by an immediate authoritative decision and fast delivery of the material to

Table 1: Overview of procedures on collection, processing and storage of samples defined in the Radboud Biobank biomaterial protocol.

Sample	Volume/number	Processing	Time between sampling and storage	Aliquoting	Storage
DNA (blood)	6 ml EDTA blood	Standard DNA isolation from EDTA in clinical routine of the Department of Human Genetics	Within 4 weeks (4°C) or 3 months (<-20°C)	Stock solution, after first issuance: normalized fraction 100 ng/μL	-20°C ¹
Serum	10 ml, addition of a clot activator	2,000 × g at room temperature for 10 minutes	Within 2–4 hours	Maximum of six aliquots (0.5 ml)	-80°C ²
EDTA plasma	10 ml	2,000 × g at room temperature for 10 minutes	Within 2–4 hours	Maximum of six aliquots (0.5 ml)	-80°C ²
Heparin plasma	10 ml	2,000 × g at room temperature for 10 minutes	Within 2–4 hours	Maximum of six aliquots (0.5 ml)	-80°C ²
Citrate plasma	9 ml	2,000 × g at room temperature for 10 minutes	Within 2–4 hours	Maximum of six aliquots (0.5 ml)	-80°C ²
Cerebrospinal fluid (CSF) +/- cell count (CC)	3–20 ml	2,000 × g or 850 × g (CC) at 4°C or at room temperature (CC) for 10 minutes or 5 minutes (CC)	Within 2 hours	Maximum of six aliquots (0.5 ml)	-80°C ²
Urine	Not specified, midstream	2,000 × g at 4°C for 10 minutes	Within 4 hours	Maximum of six aliquots (0.9 ml)	-80°C ²
Faeces	Not specified	Direct storage or after homogenization	Within 12 hours	Maximum of six aliquots (5 gram)	-80°C ²
Fresh frozen tissue	Sample of affected and unaffected tissue	Immediately frozen after collecting the sample	Immediate	0.5 cm ³ samples	-80°C ²
FFPE tissue ³	Sample of affected and unaffected tissue	Immediately stored in formalin after collecting the sample (0.5 cm ³), afterwards embedded in paraffin	Immediate fixation	0.5 cm ³ samples	Room temperature

¹ -20°C in a fully automated storage system.

² -80°C in a manual storage system.

³ FFPE = Formalin-Fixed Paraffin-Embedded.

the researcher. The head of a sub-biobank must also agree to the intended delivery.

In general, patients are asked to give broad consent. The biomaterial and associated clinical data that have been stored in the Radboud Biobank are released for research purposes only, after being approved by the IRB.

Constraints

Geographical: the Radboud Biobank collects biomaterial primarily collected at the Radboudumc, a tertiary care hospital with a catchment area predominantly, though not exclusively, from the eastern part of the Netherlands.

(3) Bioresource description

Object name

Radboud Biobank, Radboudumc, Nijmegen, the Netherlands.

Bioresource name

Radboud Biobank.

Bioresource location

The Radboud Biobank is the central biobanking facility at the Radboudumc, Nijmegen, the Netherlands. The Radboud Biobank was implemented by the Radboudumc Executive Board as part of the university research infrastructure. The

Radboud Institute of Health Sciences (www.radboudumc.nl/en/radboud-institute-for-health-sciences) hosts the Radboud Biobank as a separate entity, servicing all departments of the university medical center.

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Bioresource contact

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Bioresource URL

www.radboudumc.nl/en/research/technology-centers/radboud-biobank

Identifier used

N/A.

Bioresource type

The Radboud Biobank is a hospital integrated biobank, i.e. all disease groups and clinical departments are represented. It stores all types of disease samples (see Table 1). Table 2 gives an overview of the disease categories that are included (as of July 2017). The Radboud Biobank catalogue provides real time information about the content of the Radboud Biobank.

A number of biobanks have recently received approval from the IRB and will start including data in the near future; these new biobanks include Hemangioma and congenital vascular malformations [7], Multiple Endocrine Neoplasia (MEN) [1], Pancreas cancer and pancreatitis [1], Esophagus and gastric cancer [1] and PTEN hamartoma tumor syndrome (PHTS).

Type of sampling

The Radboud Biobank is a central biobanking facility for both common and rare diseases and comprises all types of collections, thus defined:

- De novo biobanks: after careful appraisal of the scientific ambitions and the consequences for the choice of specific patient categories, prospective inclusion of new patients with explicit consent to donate additional biomaterial and associated data, on top of that obtained for diagnostics, for future research purposes;
- Secondary use biobanks: left over material obtained in the diagnostic or therapeutic process, for which the patients did not object to secondary use for purposes of future research;
- Clinical trials and non-experimental follow-up studies: material of patients participating with full informed consent in studies with a specific research purpose; after completion of the trial, consent may be requested to keep the remaining material for future research.

Anatomical site

The disease-based biobanks that are part of the Radboud Biobank (see Table 2) cover several anatomic sites of the human body.

Disease status of patients/source

See Table 2.

Clinical characteristics of patients/source

A full clinical characterisation, including patient history, physical examination, diagnostic investigations, imaging, pharmacy and follow-up is specified for each disease-based biobank.

Vital state of patients/source

All patients are alive at inclusion.

Size of the bioresource

Currently, the Radboud Biobank has more than 350,000 aliquots comprising different biomaterials (e.g. DNA, plasma, serum, urine, CSF, faeces and tissue) from over 32,000 participants. The current number of unique patients included per disease-based biobank is shown in Table 2.

Clinical diagnosis of patients/source

The disease-based biobanks that are part of the Radboud Biobank (see Table 2) cover various clinical diagnoses.

Pathology diagnosis

The clinical diagnosis is registered using standard vocabulary (e.g. ICD-10 or SNOMED CT).

Control samples

The Radboud Biobank also has samples available from the general population ($n = 6,737$ – Nijmegen Biomedical Study [8] and $n = 535$ from the human functional genomics project [5]). The Nijmegen Biomedical Study [8] is a population-based survey conducted by the Department for Health Evidence and the Department of Laboratory Medicine at the Radboudumc. This population biobank consists of questionnaire data plus serum and DNA samples. The aim of the human functional genomics project is to characterise the interaction between the genetic background of the host and the consequences on an array of physiological functions and, in a subgroup of individuals, the cognitive function of the brain [5]. One section of the project investigates these relationships in healthy individuals ($n = 535$), while the second part of the project will assess the disturbance of this balance in specific cohorts of patients (see Table 2).

Biospecimen type

Currently, a variety of biomaterials are stored in the Radboud Biobank. DNA is sampled and stored in almost all instances (96.6%), but the specific collection of other materials depends on the category of disease.

Release date

Biomaterial and the matching clinical data are currently available.

Access criteria

Biomaterial and clinical data from the Radboud Biobank are available to researchers worldwide. Each research application is reviewed by the IRB. Criteria used by the IRB for approval of

Table 2: Disease-based biobanks included in the Radboud Biobank.

Disease-based biobanks	Number of unique patients July 2017 – n = 32,587 (%)
Confirmed form/increased risk of colorectal cancer ¹	494 (1.5)
Cerebrovascular infarct/cerebral haemorrhage/venous thrombosis ¹	733 (2.5)
Rheumatoid arthritis and arthrosis ² [2]	5,274 (16.2)
Neurodegenerative disorders (e.g. Alzheimer's) ¹	124 (0.4)
Chronic (progressive) renal failure ²	1,377 (4.2)
Crohn's disease/ulcerative colitis ¹	382 (1.2)
Leukaemia, myeloma, lymphoma ¹	215 (0.7)
Type II diabetes ¹	400 (1.2)
Cerebrovascular vascular accident (18–50 years)	570 (1.7)
Ischaemic heart disease ¹	162 (0.5)
Anomalies in children (e.g. malformations of the kidneys and urinary tract, intestines and anus, lip and palate, and the heart, childhood cancers; [3])	4,592 (14.1)
Parkinson's disease	1,230 (3.8)
Facioscapulohumeral muscular dystrophy (FSHD)	233 (0.7)
Infantile facioscapulohumeral muscular dystrophy (iFSHD)	45 (0.1)
Intellectual Disability	639 (2.0)
Breast Cancer	170 (0.5)
Asymptomatic women invited for breast cancer screening (50–75 years; [4])	5,674 (17.4)
Immune responses and microbiome [5]	
– Overweight patients (BMI>27)	302 (0.9)
– Recurrent Vulvovaginal Candidiasis	6 (<0.1)
– HIV-infected patients	216 (0.7)
– Type I diabetes	176 (0.5)
– Healthy controls	535 (1.6)
Cancer – breast, prostate, bladder, kidney, ovarian, melanoma, lung, testis	6,700 (20.7)
Autoinflammatory diseases	21 (0.1)
Familial bladder cancer	43 (0.1)
Myositis	30 (0.1)
Endocrine diseases	49 (0.2)
Urology	1,312 (4.0)
Hereditary prostate cancer	587 (1.8)
Congenital myopathy	9 (<0.1)
Gynaecological oncology	53 (0.2)
Systemic Sclerosis	222 (0.7)
Rhabdomyolyse	1 (<0.1)
Iron disorders [6]	11 (<0.1)

¹ Parelinoer Institute participant [1].

² Both Parelinoer Institute participant and department based biobank.

applications are listed in **Table 3**. Access is open for investigators from the department that initiated the disease-based biobank and for investigators who seek cooperation with them. Cooperation with external researchers, including those working in the health industry, is encouraged.

After the IRB has approved the research application and the head of a sub-biobank also agrees to the intended

delivery, the Radboud Biobank delivers the data and requested biomaterials to the researchers. Prior to the release, a standard Material (or Data) Transfer Agreement must be signed, which states that the biomaterial will not be used for other purposes than the original agreement, will not be delivered to third parties, remaining biomaterial will be destroyed, and that feedback will be

Table 3: Criteria used by the institutional review board to review applications for the use of biobank material and the accompanying clinical data.

-
1. Scientific and clinical relevance of the study.
 2. Proposal that fits the original aim (and informed consent) of the collection.
 3. Validity of the study design and proposed analyses.
 4. Relevance of the requested material (type, volume, numbers) for this study.
 5. Expertise of the applicant and the organisation for this study.
 6. Appropriate measures for privacy protection.
-

provided regarding the findings, profits and publications. Furthermore, new information that becomes available through scientific analyses will be added to the Radboud Biobank database.

Researchers using the samples and clinical data pay a fee per sample, which is based on the nature and quantity of the requested samples, and on the affiliation of the applicants. In addition, a fixed administrative fee is charged for each delivery. All revenues are used as return of investment.

(4) Reuse potential

Biomaterial and clinical data are provided to researchers on a non-exclusive basis, therefore samples from the same participant may be used in several different projects.

Any new research data generated by the delivered biomaterial will be shared with the Radboud Biobank. This new information from scientific analyses will be added to the Radboud Biobank database to make it available for future non-commercial clinical, research and educational purposes.

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Competing Interests

The authors have no competing interests to declare.

Author Roles

Peggy Manders: Radboud Biobank Manager.

Jennifer Lutomski: Radboud Biobank ICT Coordinator.

Cees Smit: Chairman of the Radboud Biobank Advisory Council.

Dorine Swinkels: Radboud Biobank Bioresource Manager.

Gerhard Zielhuis: Radboud Biobank Director.

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