BIORESOURCE PAPER

The Parelsnoer Institute: A National Network of Standardized Clinical Biobanks in the Netherlands

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The Parelsnoer Institute (PSI) is a collaborative biobanking project of all eight University Medical Centers in the Netherlands which was launched in 2007. Basically, PSI consists of three dimensions: participating institutions, disease entities and a central organization. An executive board for operational management instigates collective strategic and tactic policies and a central team of PSI experts and advisors supports the researchers and the board in establishing and implementing standards and procedures. PSI offers researchers an infrastructure and standard procedures for the establishment, expansion and optimisation of clinical biobanks for scientific research. To ensure patient privacy clinical data is pseudomized and carefully stored in a central database. Human biomaterials are collected according to nationally agreed standards.

   Currently PSI covers fifteen large disease specific cohorts (the so-called 'Parels' or 'Pearls') and new 'Pearls' are being developed. The Parelsnoer Institute currently (December 2016) has stored more than 538,000 biospecimens with annotated clinical data of more than 30,000 patients. All these materials and data are available for anyone with a bona fide research proposal.

(1) Bioresource Overview

Project description

In 2007, the Netherlands Federation of University Medical Centers (NFU) launched the Parelsnoer Institute (PSI) [1], with the aim of facilitating medical research and innovation ultimately leading to better diagnosis, treatment or even prevention of complex disorders [2–17]. PSI is a collaborative network of all eight Dutch University Medical Centers (UMCs), also known as academic teaching hospitals. **Figure 1** describes the organization of the Parelsnoer Institute. Basically, PSI consists of three dimensions: participating institutions (the 8 UMCs), disease entities (currently 15 disease specific groups which are called 'Pearls', still expanding) and the central organization with several expert areas. An executive board for operational management (see **Figure 1**) instigates collective strategic and tactic policies. In addition, a central team of PSI experts and advisors, working in the participating UMCs, supports the researchers and the board in establishing and implementing standards and procedures.

Several standard operating procedures (SOPs), regulations and agreements constitute a framework of ready to use harmonized standards throughout the subsequent phases of the biobanking process. Templates provide tools for efficient implementation of the SOPs and use of these templates contributes to the level of standardization. Application of this framework by all UMCs yields large uniform collections and contributes to high quality at all levels.
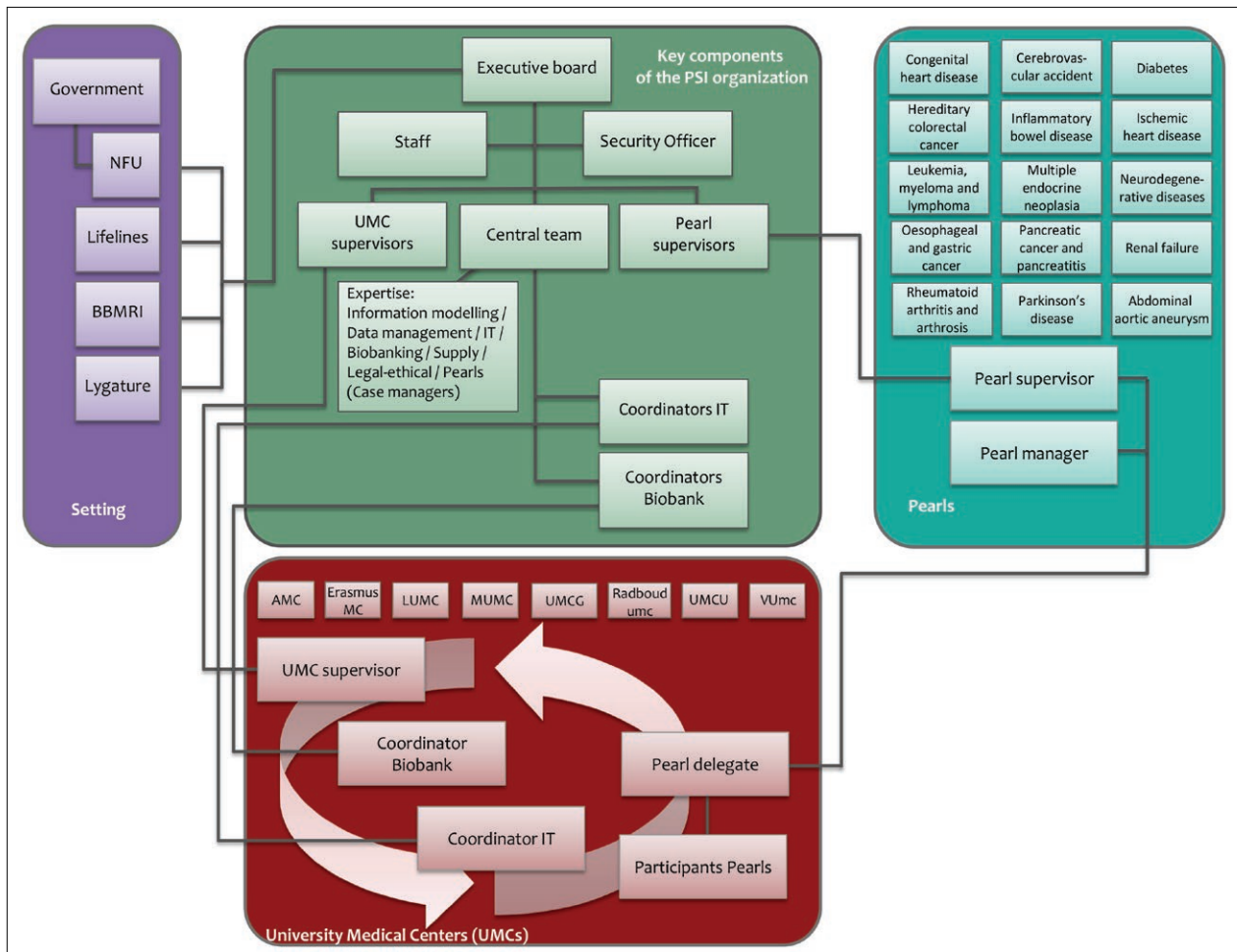
Figure 1: Organization of the Parelsnoer Institute.

Each UMC stores biomaterials in their own certified biobank(s) according to the PSI biobanking protocol, which was developed by biobank coordinators from all UMCs together and covers all phases of biobanking. Each Pearl provides a different variety of biomaterials such as serum, plasma, DNA, faeces, urine, cerebrospinal fluid, pancreatic cyst fluid, viable cells, fresh frozen tissues and/or FFPE tissues. Metadata (e.g., type of material) from biomaterials and the unique sample code are registered in the central database together with the clinical data [18].

For each Pearl a specific information model is defined for the detailed clinical dataset including personal data and clinical data pertaining the specific disease [19]. The data are collected both via electronic and manual methods and are hosted in a validated web based application (ProMISe) that fulfills international standards for data management, quality assurance, and privacy protection using a Trusted Third Party [20, 21].

Classification (1)
Human.

Classification (2)
Biological samples and associated clinical data.

Context
Spatial coverage
Description:
All eight University Medical Centers across the Netherlands: Academic Medical Center (Amsterdam), Erasmus Medical Center (Rotterdam), Leiden University Medical Center, Maastricht University Medical Center, Radboud University Medical Center (Nijmegen), University Medical Center Groningen, University Medical Center Utrecht, VU University Medical Center (Amsterdam).
Northern boundary: +53.4647366.
Southern boundary: +50.757197.
Eastern boundary: +7.222824.
Western boundary: +3.364563.

Temporal coverage
Eight disease-specific bioresources started their collection in 2009. Five others started later and new collections will start in the (near) future. The end date might differ between the collections, however, so far no expected end date has been determined for any collection.

Temporal coverage for accessibility
The bioresources are available for use in bona fide research projects; no end date determined.

(2) Methods

Steps

For each Pearl a specific information model is defined, called PRISMA: Parelsnoer Repository for Information Specification, Modelling and Architecture. PSI adheres to the principle of reusing electronic health record (EHR) information for scientific purposes ("registration at the source", http://www.nfu.nl/programma/registratie-aan-de-bron/programma). Therefore, PRISMA is developed with reuse of information and with minimization of registration burden as prime directives, while also taking routine care procedures into account. The architecture is in compliance with (inter-)national classifications such as International Classification of Diseases and Related Health Problems (ICD-10), SNOMED CT and the Logical Observation Identifiers Names and Codes (LOINC®).

Each Pearl defines its own set of biosamples to be collected and stored in the biobank. Biomaterials are preferably collected during routine clinical procedures. Samples are stored in certified UMC biobanking facilities which collectively constitute the federative PSI biobank. The biobanking protocol of PSI is implemented in all the participating institutions and covers all phases of biobanking; from collection to storage of

Sample	Volume/number	Processing	Time	Aliquoting	Storage
Serum	10 ml clotted blood	2000 × g at room temperature or 4°C for 10 minutes	Within 2–4 hours	≥ 5 × 0.5 ml	−80°C
EDTA plasma	10 ml	2000 × g at room temperature or 4°C for 10 minutes	Within 2–4 hours	≥ 5 × 0.5 ml	−80°C
Citrate plasma	9 ml	2000 × g at room temperature for 10 minutes	Within 2–4 hours	≥ 5 × 0.5 ml	−80°C
DNA (blood)	10 ml EDTA blood	Whole blood or cell pellet, to UMC specifications	Within 4 weeks (4°C) or 3 months (< −20°C)	≥ 2 stock aliquots	4°C or lower
Faeces	Not specified	Direct storage or after homogenization	Within 12 hours	≥ 5 × 5 gr	−80°C
Urine +/− antioxidants (AO)	Not specified, midstream	2000 × g at room temperature or 4°C (AO) for 10 minutes	Within 4 hours	6 aliquots 0.9 ml	−80°C
Cerebrospinal fluid	3–20 ml	2000 × g at room temperature or 4°C for 10 minutes	Within 2 hours	≥ 6 × 0.5 ml	−80°C in polypropylene tubes
Biopsy FFPE	n* per location#	Formalin fixation and paraffin embedding	Immediate fixation	Per set	Room temperature
Biopsy frozen	n* per location#	Snap frozen in isopentane	Immediate	Per set	−80°C
Resection specimen FFPE	n* per location#	Snap frozen in isopentane	At pathology	0.5 cm³ samples	Room temperature
Resection specimen frozen	n* per location#	Snap frozen in isopentane	At pathology	0.5 cm³ samples	−80°C
Pancreatic cyst fluid	≥ 0.5 ml	None	Within 2–4 hours	0.5 ml portions	−80°C
Viable cells (PBMCs or bone marrow)	20–40 ml heparinized sample	Density centrifugation at room temperature	Within 24 hours	10 × 10E6 cells per cryovial	−130°C

Table 1: Summary of procedures on collection, processing and storage of samples defined in the biobanking protocol of PSI.[†]

[†] Deviations to be registered: hemolytic, lipemic, icteric, wrong tube, volume incorrect, storage temperature deviation, longer storage time, mixing/homogenization incorrect, centrifugation process different, storage problem, other deviation as free text.

* as specified by Pearl.

for instance normal or affected or inflamed or tumor in intestinal tract or skin.

PBMCs: peripheral blood mononuclear cells.

the samples. Metadata (e.g., type of material) from bio-materials and the unique sample code are registered in the central database together with the clinical data. The detailed clinical dataset includes personal data (e.g., age, gender, education level, ethnic origin, weight, height) and clinical data pertaining the specific disease (e.g., diagnosis, lab results, complications, physical examination, (medical) treatment, questionnaires). The data are collected both via electronic and manual methods and are hosted in a validated web based application (ProMISe) [20].

PSI also provides an infrastructure and procedures to uniformly collect and store images, for instance MRI images. Standardized source images are safely stored in the local Picture Archive and Communication System (PACS) in the UMCs. After anonymization, the images are subsequently uploaded in the TraIT Bio-Medical Imaging Archive (BMIA), which is a safe and sustainable online archive [22].

Stabilization/preservation
Table 1 gives a summary of procedures on collection, processing and storage of samples defined in the biobanking protocol of PSI.

Type of long-term preservation
See **Table 1**.

Storage temperature
See **Table 1**.

Shipping temperature from patient/source to preservation or research use
See **Table 1**.

Shipping temperature from storage to research use
−80°C (on dry ice).

Quality assurance measures
Quality of data and quality of stored biomaterials are by no means self-evident. In PSI, the two most important critical success factors for adequate data quality are: to limit the number of elements in the information model to what is necessary for future research and to fully integrate the collection of data in the routine of the EHR. Other essential elements for adequate quality are: use international standards (Detailed Clinical Models), develop simple and logical instructions for data collection and registration, mandate and authorize dedicated research employees, and perform regular quality checks.

For biomaterials there is no possibility to improve quality afterwards. Only a strict adherence to the biobank protocol and related SOPs can assure quality of material available for research. This is under the assumption that SOPs describe (either evidence or consensus based) what is optimal for integrity of the biomaterials. In PSI, biobank coordinators from all UMCs together have developed the PSI biobanking protocol and revise them every two years. This involvement of all biobank coordinators in establishing the protocol enhances adherence to the described procedures. The PSI biobanking protocol covers all phases of biobanking: collection, pre-analysis, registration, processing and storage of the samples (**Table 1**).

Source of associated data
The associated data are mainly coming from electronic health records, laboratory reports, and questionnaires. Each UMC has its own research IT infrastructure that
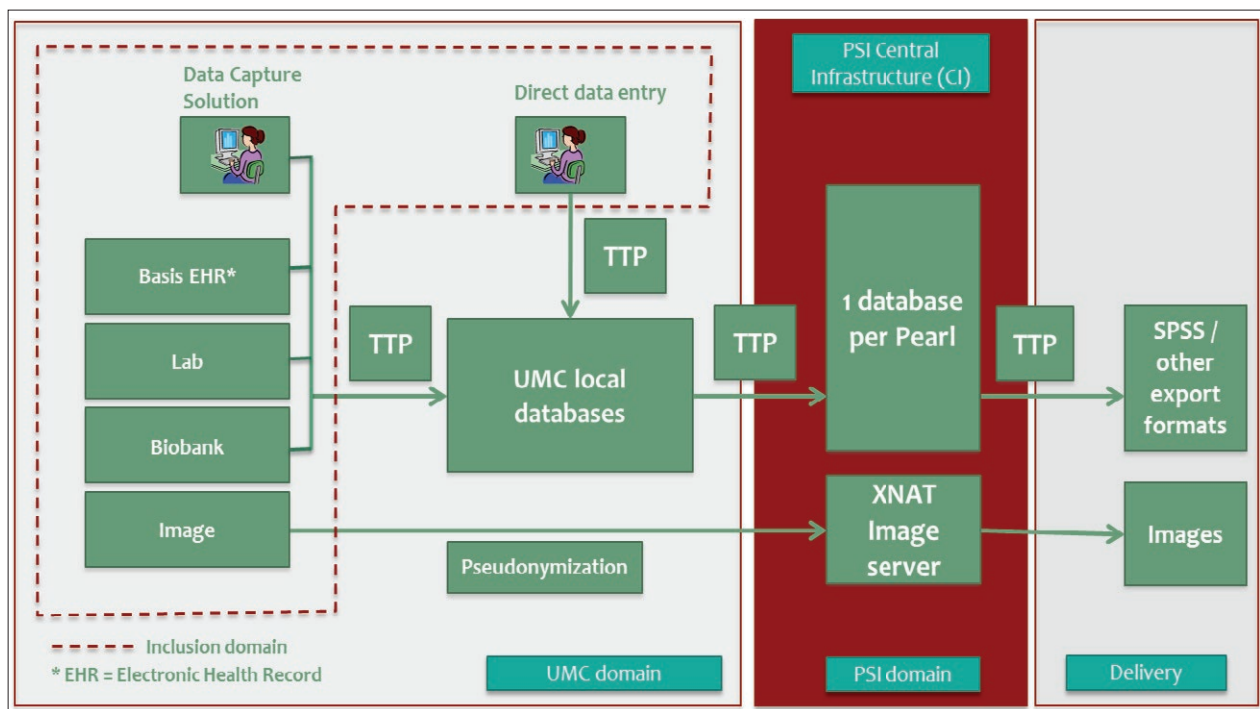

Figure 2: IT Infrastructure of PSI.

delivers the data to their local database in ProMISe, which is a web based application. In some UMCs data are entered manually into the local database (mostly by research nurses and/or clinicians) while other UMCs benefit from automatic data capture directly from the EHR resources. The information supplied by each UMC is periodically uploaded, after validation, to the central database in ProMISe (one database per Pearl, which is the combination of the 8 local UMC Pearl databases) for storage on a national level (**Figure 2**). During upload of data to the local and central databases, identifying data are encrypted by special software of a Trusted Third Party (Trusted Reversible Encryption Service®, Houten, Utrecht, The Netherlands). As to further protect the privacy of the patients, the identifying data are encrypted again when exported from the central database for delivery to the researchers. In specific situations, e.g., in case of incidental findings that need feedback to the patient or necessary data-linkage, depseudonymization is possible by authorized personnel only. The PSI IT infrastructure is compliant with international security and privacy standards.

(3) Bioresource description

Object name
The Parelsnoer Institute.

Bioresource name
The Parelsnoer Institute (PSI).

Bioresource location
All eight University Medical Centers across the Netherlands participate in PSI:

1. Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
2. Erasmus Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
3. Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands
4. Maastricht University Medical Center, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands
5. Radboud University Medical Center, Geert Grooteplein-Zuid 10, 6525 GA Nijmegen, The Netherlands
6. University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
7. University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
8. VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

Bioresource contact
Parelsnoer Institute, Jaarbeursplein 6, 3521 Al Utrecht, The Netherlands.
Email: info@parelsnoer.org

Bioresource URL
http://parelsnoer.org/page/en/Home.

Identifier used
N/A.

Bioresource type
PSI is a collaborative clinical biobank, comprising a number of disease specific national bioresources (the Pearls). All types of pathology and disease samples are stored (see **Table 1**). To date (October 2016) the following fifteen disease categories are included:

– Abdominal aortic aneurysm
– Congenital heart disease
– Cerebrovascular accident
– Diabetes
– Hereditary colorectal cancer
– Inflammatory bowel disease
– Ischemic heart disease
– Leukemia, myeloma and lymphoma
– Multiple endocrine neoplasia
– Neurodegenerative diseases
– Oesophageal and gastric cancer
– Pancreatic cancer and pancreatitis
– Renal failure
– Rheumatoid arthritis and arthrosis
– Parkinson's disease

Type of sampling
PSI consists of disease based cohorts with longitudinal collections, sampled in clinical care.

Anatomical site
The fifteen Pearls cover several anatomical sites of the human body.

Disease status of patients/source
See the fifteen Pearls/diseases mentioned above.

Clinical characteristics of patients/source
A full clinical characterization, including extensive diagnostics, demographics, therapeutics and clinical follow-up is specified for each disease specific bioresource.

Vital state of patients/source
All patients are alive at inclusion.

Clinical diagnosis of patients/source
PSI covers several significant diseases, presently fifteen: Abdominal aortic aneurysm, Congenital heart disease, Cerebrovascular accident, Diabetes, Hereditary colorectal cancer, Inflammatory bowel disease, Ischemic heart disease, Leukemia, myeloma and lymphoma, Multiple endocrine neoplasia, Neurodegenerative diseases, Oesophageal and gastric cancer, Pancreatic cancer and pancreatitis, Renal failure, Rheumatoid arthritis and arthrosis, Parkinson's disease.

Pathology diagnosis
The architecture is in compliance with (inter-)national classifications such as International Classification of Diseases and Related Health Problems (ICD-10), SNOMED

Pearl[†]	Number of patients with clinical data	Number of patients with biomaterials
Congenital heart disease	5400	5400
Cerebrovascular accident	5815	5374
Diabetes	6673	6226
Hereditary colorectal cancer	1853	1534
Inflammatory bowel disease	4642	4139
Ischemic heart disease	632	412
Leukemia, myeloma and lymphoma	1755	1596
Neurodegenerative disease	1213	1122
Esophageal and gastric cancer	122	93
Pancreatic cancer and pancreatitis	318	282
Renal failure	1991	1963
Rheumatoid arthritis and arthrosis	2277	2190

Table 2: The number of included patients per Pearl.*
* dd December 12, 2016.
[†] Three Pearls (i.e., Multiple Endocrine Neoplasia, Abdominal Aortic Aneurysm and Parkinson's Disease) started recently and to date (December 2016) have not yet included patients.

CT and the Logical Observation Identifiers Names and Codes (LOINC®).

Control samples
The Parelsnoer Institute does not collect control samples from healthy individuals. If needed controls can be obtained from LifeLines, a national longitudinal population biobank in the Netherlands [24].

Biospecimen type
Each Pearl provides a different variety of biomaterials such as serum, plasma, DNA, RNA, faeces, urine, cerebrospinal fluid, pancreatic cyst fluid, viable cells, fresh frozen tissues and/or FFPE tissues. **Table 1** gives a summary of procedures on collection, processing and storage of samples defined in the biobanking protocol of PSI.

Size of the bioresource
In total, clinical data of more than 32,000 patients and 538,000 biospecimens of more than 30,000 patients are available. PSI has no end date. The current number of included patients per Pearl is shown in **Table 2**.

Release date
Data and samples are currently available. PSI releases data and samples to research projects on a regular basis. Thus far, the research projects have led to many scientific publications [3–17].

Access criteria
A catalogue, i.e., an open access searchable database on the internet, provides up-to-date information about the content of all PSI collections [18]. This gives researchers the opportunity to discover for what type of patients which type and amount of data and biomaterials are available. Every researcher worldwide may submit a study proposal to the Pearl and request data, biomaterials and/or images.

A scientific committee of the Pearl (consisting of representatives of the Pearl and independent scientific experts) judges whether the proposed study is relevant, compliant with the scientific aims of the Pearl, methodologically sound, compliant with privacy protection rules and feasible in relation to the amount of biomaterial requested. In addition, permission from the Research Ethical Committee of the coordinating UMC has to be obtained and from some other participating centers according to local policy. When permissions have been granted and request forms are completed, the PSI data manager will deliver the data (and images if needed) from the central PSI facilities to the researcher. The biobank coordinators of the UMCs will deliver the requested biomaterials. If scientific analyses in research projects yield new data, PSI demands these newly acquired (individual) data to be made available for future research purposes.

Costs vary depending on the type and amount of samples. An economic quotation is sent covering shipping costs and partially costs for biobanking-related services (sample handling, consumables).

(4) Reuse potential
Samples from the same donor may be used in several different projects. As a condition of supply of material, the recipient of samples and/or data must agree to return findings to PSI on conclusion of the research purpose. These newly acquired (individual) data are then available for future research purposes. Besides, the applicant must

acknowledge PSI in all publications resulting from the use of these data and samples and provide a copy of the published paper to PSI.

Ethics Statement

PSI provides a regulatory framework in which ethical guidelines, in accordance with (inter-)national legislation and rules, are described [23]. Supported by a member of the PSI Central Team, each Pearl composes a patient information brochure, a consent form and regulations. These documents together with the strategic plan of the Pearl are reviewed by the Medical Ethical Committee of the coordinating UMC. Subsequently, Medical Ethical Committees and Board of Directors of the remaining participating UMCs have to approve local implementation of the Pearl's biobanking activities. Patients included in the Pearl give written informed consent prior to inclusion.

Constraints

Only patients who provided written informed consent are included, no healthy controls. Participants may withdraw their consent at all times. The patient can express the wish to withdraw to his/her doctor, in which case the doctor will ensure that data and materials are destroyed unless needed for validation of earlier issuance.

Competing Interests

The authors have no competing interests to declare.

Author Roles

Judith Manniën: PSI Data Manager
Tessa Ledderhof: PSI Operational Manager
Hein Verspaget: PSI Bioresource Manager
Roger Snijder: PSI Information Architect
Erik Flikkenschild: PSI ICT Coordinator and Privacy-Security Officer
Nicole van Scherrenburg: PSI Management Assistant
Ronald Stolk: member of PSI Board
Gerhard Zielhuis: PSI Managing Director

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