BIORESOURCE PAPER

Dutch Parelsnoer Institute-Cerebrovascular Accident (CVA) Study: A Large Multicenter Clinical Biobank with Standardized Collection and Storage

H. J. A. Van Os[1], Y. M. Ruigrok[2], J. Manniën[3], E. J. Van Dijk[4], P. J. Koudstaal[5],
G. J. Luijckx[6], P. J. Nederkoorn[7], R. J. Van Oostenbrugge[8], M. C. Visser[9],
L. J. Kappelle[2], H. W. Verspaget[10], A. Algra[2,11] and M. J. H. Wermer[1]

[1] Department of Neurology, Leiden University Medical Center, Leiden, NL

[2] Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht and Utrecht University, Utrecht, NL

[3] Parelsnoer Institute, Utrecht, NL

[4] Department of Neurology, Radboud University Medical Center, Nijmegen, NL

[5] Department of Neurology, Erasmus Medical Center, Rotterdam, NL

[6] Department of Neurology, University Medical Center, Groningen, NL

[7] Department of Neurology, Academic Medical Center, Amsterdam, NL

[8] Department of Neurology, Maastricht University Medical Center, Maastricht, NL

[9] Department of Neurology, VU Medical Center, Amsterdam, NL

[10] Parelsnoer Institute, Utrecht, and Department of Biobanking, Leiden University Medical Center, NL

[11] Julius Center for Clinical Research and Patient Care, University Medical Center Utrecht and Utrecht University, Utrecht, NL

Corresponding author: H. J. A. Van Os (h.j.a.van_os@lumc.nl)

The Dutch Parelsnoer Institute-Cerebrovascular accident (CVA) Study is part of the Parelsnoer Institute (PSI), initiated in 2007 by the Netherlands Federation of University Medical Centers (NFU). PSI is a cooperation of all eight Dutch University Medical Centers (UMCs) and aims at building large prospectively collected datasets with uniformly and standardized storage of biomaterials for complex diseases. Currently, PSI covers 18 disease-specific cohorts called 'Pearls', and this number is still growing. One of these cohorts is the Stroke or CVA Pearl. For each of the cohorts, PSI offers the UMCs an infrastructure and standard procedures for storing the specific biomaterials in their certified biobanks. Clinical data are stored in a central database after being pseudonymized to ensure patient privacy. For the Parelsnoer Institute-CVA Study, blood for genetic analysis, serum and plasma are collected according to nationally agreed standards. Currently (November 2017) the Stroke Pearl has stored blood samples with prospectively obtained clinical data of around 6000 patients in all UMCs combined. Blood samples and data are available for all researchers with a methodologically valid research proposal.

(1) Overview

Project description

The Dutch Parelsnoer Institute-Cerebrovascular accident (CVA) Study is part of the Parelsnoer Institute (PSI), initiated in 2007 by the Netherlands Federation of University Medical Centers (NFU) [1]. PSI is a cooperation of all eight Dutch University Medical Centers (UMCs) and aims at building large prospectively collected datasets with uniform and standardized storage of biomaterials for complex diseases. Currently, PSI covers 18 disease-specific cohorts called 'Pearls', and this number is still growing [2–18]. PSI is centrally organized and has an executive board for operational management to ensure collective standardization strategies. Additionally, a team of PSI

experts supports researchers and the executive boards of the participating UMCs with implementing these strategies. Standardization between and within UMCs is established via multiple standard operating procedures (SOPs) regarding i) storing of biobank materials in the certified biobanks of the UMCs. These SOPs are developed by biobank coordinators from all UMCs together and cover all phases of biobanking. ii) managing the clinical database for every specific disease, hosted via a web based application (ProMISe) [1, 19] (**Figure 1**).

For the Dutch Parelsnoer Institute-CVA Study, each UMC stores blood for genetic analysis, serum, and plasma in their own certified biobank. The creation of large stroke cohorts is currently of great importance in genetic stroke research, illustrated by genome-wide association studies (GWASs) performed in the last years [20–23]. Stroke is a heterogeneous disease consisting of several etiological subtypes with different underlying pathophysiological mechanisms. These subtypes include ischemic stroke and transient ischemic attack (TIA), cerebral venous sinus thrombosis, intracerebral hemorrhage and subarachnoid hemorrhage. Ischemic stroke mainly consists of the subtypes large vessel atherosclerosis, cardio-embolism and small vessel disease. Large etiological subtypes of intracerebral hemorrhage are small vessel disease and vascular malformations. Aneurysmal subarachnoid hemorrhage can be classified

as aneurysmal or perimesencephalic. Most subtypes are thought to have a specific genetic architecture, as GWASs have found multiple genetic loci to be subtype-specific. Future genetic stroke research may lead to management approaches more tailored to the different subtypes and novel therapeutical targets [20, 21, 24].

The aim of the Dutch Parelsnoer Institute-CVA Study is first to create a large prospective cohort of stroke patients with blood samples and DNA collected through standardized procedures and stored in an uniform way. These samples are coupled with stroke subtypes according to the TOAST classification and the ASCO system. The Trial of Org 10172 Acute Stroke Treatment (TOAST) classification distinguishes i) large-artery atherosclerosis, ii) cardio-embolism, iii) small vessel occlusion, iv) stroke of other determined etiology and v) stroke of undetermined etiology as etiological stroke subtypes [25]. The ASCO system (where A stands for atherosclerosis, S for small vessel disease, C for Cardiac source, O for other cause) classifies similar subtypes, though both classification schemes have been found to have different characteristics in practice [26, 27]. These classifications enable us to investigate associations between genetic risk loci and stroke subtypes and to enable pooling with data of other ongoing genetic stroke studies [20, 21, 25, 27]. Second, besides genetic research the Parelsnoer Institute-CVA Study population is
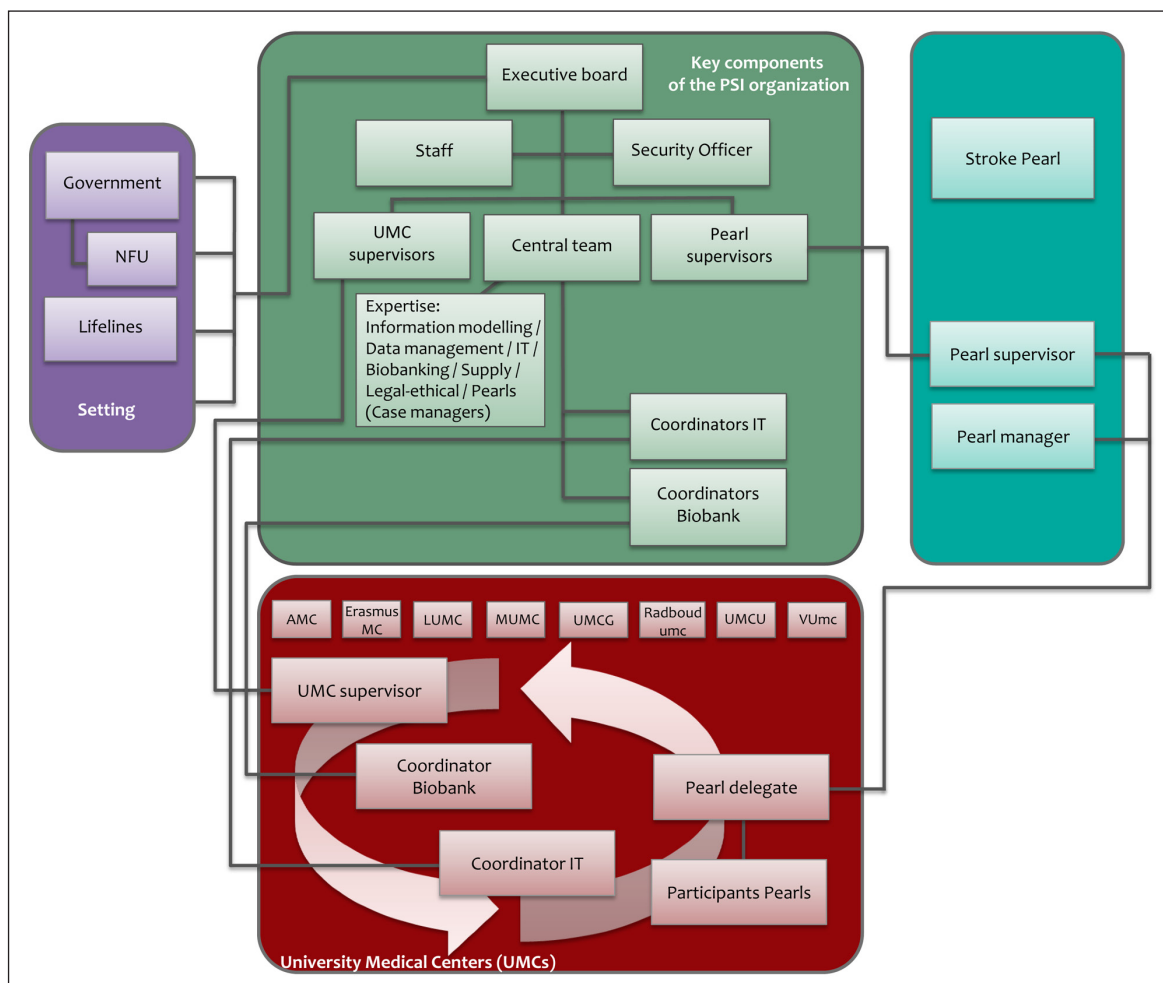

Figure 1: Organogram of the Parelsnoer Institute.

also very well suited for epidemiological studies because of its prospective, multicenter design and large sample size [28].

Classification (1)
Human

Classification (2)
Biological samples and associated clinical data

Context
Spatial coverage
Description
All eight Dutch University Medical Centers: 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
For the Parelsnoer Institute-CVA Study, the UMCU started collecting data in 2009, the seven other UMCs started in 2010. Data collection is ongoing in five UMCs, no end date has been determined.

Temporal coverage for accessibility
The blood samples are available for researchers with a methodological valid research proposal (see *access criteria* for more information); no end date has been determined.

(2) Methods
Patients
Inclusion criteria for the Dutch Parelsnoer Institute-CVA Study are a diagnosis of TIA or stroke, presenting in one of the eight Dutch UMCs within one month after stroke onset. Stroke encompasses ischemic stroke, cerebral venous sinus thrombosis, intracerebral hemorrhage, and subarachnoid hemorrhage (both aneurysmal and perimesencephalic hemorrhage). Further inclusion criteria are age >18 years and the provision of informed consent. Informed consent is defined as written consent by the donors to collect data and biological samples in a Biobank for future scientific purposes in order to study etiopathogenesis and the clinical course of CVA. Informed consent includes the option for the donors to revoke their consent any time, after which the data and biomaterials will be removed from the CVA Biobank, except for the data and samples already included in research protocols. These very broad inclusion criteria result in the incorporation of nearly all stroke patients seen in Dutch UMCs in the Dutch Parelsnoer Institute-CVA Study database. For every patient, data on medical history, family history, vascular risk factors, medication use and exact time of stroke symptom onset are recorded. Deficits in neurological examination at baseline are recorded according to the National Institutes of Health Stroke Scale (NIHSS), a graded assessment of consciousness, eye movements, visual fields, motor and sensory impairments, ataxia, speech, cognition and inattention [29]. Ischemic stroke subtype is defined according to both the TOAST classification and the ASCO system [26, 27]. Data are collected on treatment such as intravenous thrombolysis, neurosurgical (clipping or decompressive surgery) or endovascular (coiling of aneurysms, intraarterial thrombectomy or thrombolysis) intervention, start of oral anticoagulation treatment in case of atrial fibrillation, and start of secondary prophylactic treatment. Additionally, we collect data on laboratory investigations and on imaging, i.e. brain CT and CT angiography, brain MRI and MR angiography and ultrasound investigations. After three months functional outcome is prospectively recorded via a structured telephone interview, using the modified Rankin Scale [30].

Steps
For the Parelsnoer Institute-CVA Study, a specific Parelsnoer Repository for Information Specification, Modelling and Architecture (PRISMA) has been defined. PRISMA is an information model enabling us to reuse electronic health record (EHR) information for scientific purposes. This reuse of information minimizes registration burden while at the same time routine care procedures are taken into account. The architecture is in agreement with national and international classifications such as International Classification of Diseases and Related Health Problems (ICD-10), SNOMED CT and the Logical Observation Identifiers Names and Codes (LOINC®) [1]. For all stroke patients included in the Parelsnoer Institute-CVA Study, all predefined demographic and clinical variables including data on functional outcome are recorded as coded data via PRISMA and are sent to the central PSI database, a validated web based application (ProMISe) [19]. Additionally, blood for genetic analyses, serum and plasma are collected, preferably during routine clinical procedures. Blood samples are then stored in certified UMC biobanking facilities adhering to the PSI biobanking protocol. This protocol covers all phases of biobanking, from collection to storage of the samples. Metadata on blood samples and the unique sample code are registered in the central database together with the clinical data.

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**.

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

Sample	Volume/ number	Processing	Time	Aliquoting	Storage	Additional information
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	SOP deviations*
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	SOP deviations*
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	OD ratio 260/280, concentration in μg/ml*

* See the 'Quality assurance measures' section for detailed additional information.

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

Quality assurance measures
PSI uses two main strategies to guarantee uniform collection and storage of clinical data between UMCs which are i) limiting the number of collected variables to only the essentials and ii) using existing EHR infrastructure within UMCs infrastructure for recording of data.

As there is no possibility to improve quality of biomaterials afterwards, strict adherence to biobank related SOPs optimizing integrity of biomaterials is needed. Biobank coordinators from all UMCs have together developed the PSI biobanking protocol, encompassing all phases of biobanking, i.e. sample collection, pre-analysis, registration, processing and storage.

The biobanking protocol according to Biospecimen Reporting for Improved Study Quality (BRISQ) is as follows [31]. Blood collection for the CVA Biobank is performed according to the biobank SOP. EDTA blood (10 ml) and Serum blood (10 ml) are collected by venipuncture in the arm. Collection of smaller tubes and pooling of samples is not allowed. Clotting time for serum is defined at 60 minutes at room temperature. Blood is to be stored at room temperature until centrifugation. Centrifugation is to be performed at 2000 g either at room temperature or at 4°C. Aliquoting is in volumes of 0.5 ml in at least 5 quantities. Processing time from venipuncture to storage in freezer at –80°C is predefined at preferably 2 hours with a maximum of 4 hours. All samples are stored under unique identifiers without identifiable patient information. DNA samples from EDTA blood are to be processed within 4 weeks when stored at 4°C or within 3 months when stored at ≤–20°C. Processed DNA should be stored as at least 2 stock solution aliquots at ≤4°C with unique samples codes, including concentration and quality data based on the OD 260/280 ratio. All processing and quality data, including specific time points to assess processing time and track and trace of the samples are registered in a local Biobank Management Information System. Core samples data are provided to the central infrastructure of the Parelsnoer Institute CVA Biobank. In addition to the processing data deviations from the Biobank SOP per individual sample, if applicable, are also registered in the database. These SOP deviations include: hemolytic, lipemic, icteric, wrong blood tube, incomplete filling of the blood tube, temperature deviation, processing time deviation, mixing problems, centrifugation deviation, storage problems and free text remarks (**Table 1**).

Source of associated data
Data are recorded from electronic health records and laboratory reports. Each UMC has its own research IT infrastructure that delivers the data to their local database in ProMISe, a web based application. The information supplied by each UMC is first validated and then periodically uploaded to the central Parelsnoer Institute-CVA Study database in ProMISe for storage on a national level. During uploading, identifying patient data are encrypted using special software of a trusted third party (Trusted Reversible Encryption Service®, Houten, Utrecht, The Netherlands). As additional measure for protection of privacy, the identifying data are encrypted again when exported from the central database for research purposes. In specific situations, e.g. in case of incidental findings that need feedback to the patient or in case of data-linkage, de-pseudonymization can be performed by authorized personnel. The PSI IT infrastructure is in agreement with privacy and international security standards [1].

Ethics Statement
The Parelsnoer Institute-CVA Study Group uses a patient information brochure, regulations and a consent form, approved by the local Medical Ethical Committees (MECs) of all UMCs. Subsequently, both MECs and Board of Directors of the remaining participating UMCs approved local implementation of the biobanking activities [1]. The study is performed according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act and codes on 'good use' of clinical data and biological samples as developed by the Dutch Federation of Medical Scientific Societies

[32, 33]. All patients should give written informed consent prior to inclusion.

Constraints
Only patients who have provided written informed consent are included. The PSI does not include healthy controls. After inclusion, patients may withdraw their consent at any time. 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.

(3) Bioresource description

Object name
The Parelsnoer Institute-CVA Study

Bioresource name
The Parelsnoer Institute-CVA Study

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/Parels?mod[Parelsnoer_Module_Pearl][n]=23

Identifier used
N/A

Bioresource type
For the Dutch Parelsnoer Institute-CVA Study blood for genetic analysis, serum and plasma are collected and stored (**Table 1**).

Type of sampling
The Dutch Parelsnoer Institute-CVA Study is a disease based cohort with longitudinal collections, sampled in clinical care.

Anatomical site
The brain and cerebral vasculature, including cervical vessels.

Clinical characteristics of patients/source
For the Dutch Parelsnoer Institute-CVA Study, a full clinical characterization, including extensive diagnostics, demographics, therapeutics and clinical follow-up is specified.

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

Clinical diagnosis of patients/source
Ischemic stroke and transient ischemic attack (TIA), cerebral venous sinus thrombosis, intracerebral hemorrhage, and subarachnoid hemorrhage (both aneurysmal and perimesencephalic hemorrhage).

Pathology diagnosis
N/A

Control samples
The Parelsnoer Institute does not collect control samples from healthy individuals.

Biospecimen type
For the Dutch Parelsnoer Institute-CVA Study blood samples for genetic analysis, serum and plasma are collected and stored. **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
As of November 3rd 2017, clinical data of 6074 and blood samples of 5769 patients were available in the Dutch Parelsnoer Institute-CVA Study. Of all patients with clinical data, 4390 had a final diagnosis of ischemic stroke (72%), 786 of subarachnoid hemorrhage (13%),

599 of intracerebral hemorrhage (10%), 114 of cerebral venous sinus thrombosis (2%). Further, 48 patients (1%) had another final stroke diagnosis and of 137 patients (2%) final diagnosis was missing. PSI has no end date.

Release date
Data and samples of the Dutch Parelsnoer Institute-CVA Study are currently available. Regarding all disease cohorts, the research projects based on PSI data and samples have led to several scientific publications [2–16, 18].

Access criteria
PSI has an online open access catalogue with up-to-date information about the content of the Dutch Parelsnoer Institute-CVA Study, providing insight for researchers worldwide and offering them the opportunity to submit a research proposal to the Dutch Parelsnoer Institute-CVA Study and request its data and blood samples [17]. These proposals are reviewed by the scientific committee of the Dutch Parelsnoer Institute-CVA Study, consisting of representatives of the Pearl and independent scientific experts. This committee judges whether the proposed study is relevant, methodologically valid, compliant with the scientific aims of the Dutch Parelsnoer Institute-CVA Study Group and with the privacy protection rules. In addition to this scientific committee, the Research Ethical Committee of the coordinating UMC and several other participating centers have to grant permission according to local policy. When the proposal is accepted by all committees, data from the central PSI facilities will be delivered by the PSI data manager to the researcher. Requested biomaterials will be delivered by the biobank coordinators of the UMCs. If the subsequent research project results in new individual data on the biosamples, PSI demands these newly acquired data to be made publicly available for future research purposes. For researchers using PSI data, costs are involved. These costs include direct costs for retrieval of the samples from the UMC biobanks and shipment of the samples. In addition, depending on the defined collaboration with external researchers, consortia or industrial partners additional costs will be negotiated for the Biobank related acquisition costs, sample and data collection, research project costs and contribution to the sustainability of the Parelsnoer Institute CVA-Biobank.

(4) Reuse potential
Samples from the same donor may be used for multiple projects. The researcher may only receive samples and data on two conditions: i) they share their scientific findings with PSI and provide PSI with a copy of the published paper, and ii) they acknowledge the Dutch Parelsnoer Institute-CVA Study Group in all publications of studies using PSI data and samples.

Competing Interests
The authors have no competing interests to declare.

Author Roles
Hendrikus J. A. van Os: drafting of the manuscript.
Ynte M. Ruigrok: Chair of the Stroke Pearl management board, critical revision of the manuscript for important intellectual content.
Judith Manniën: National PSI Data Manager, critical revision of the manuscript for important intellectual content.
Ewoud J. van Dijk: Stroke Pearl manager Radboud UMC.
Peter J. Koudstaal: Stroke Pearl manager Erasmus MC.
Gert-Jan Luijckx: Stroke Pearl manager UMC Groningen.
Paul J. Nederkoorn: Stroke Pearl manager AMC.
Robert J. van Oostenbrugge: Stroke Pearl manager Maastricht UMC.
Marieke C. Visser: Stroke Pearl manager VUMc.
L. Jaap Kappelle: Stroke Pearl manager UMC Utrecht.
Hein W. Verspaget: National PSI Biobank coordinator, critical revision of the manuscript for important intellectual content.
Ale Algra: Issuance Coordinator, member of the scientific committee of the Dutch Parelsnoer Institute-CVA Study.
Marieke J. H. Wermer: Stroke Pearl manager LUMC, supervision of lead author, critical revision of the manuscript for important intellectual content.

References
1. **Manniën, J, Ledderhof, T, Verspaget, HW,** et al. 2017. The parelsnoer institute: A national network of standardized clinical biobanks in the netherlands. *Open Journal of Bioresources*, 4.
2. **Aalten, P, Ramakers, IHGB, Biessels, GJ, de Deyn, PP, Koek, HL, OldeRikkert, MGM,** et al. 2014. The dutch parelsnoer institute – neurodegenerative diseases; methods, design and baseline results. *BMC Neurol.*, 14.
3. **Hauer, AJ, Pulit, SL, van den Berg, LH, de Bakker, PIW, Veldink, JH, Ruigrok, YM,** et al. 2017. A replication study of genetic risk loci for ischemic stroke in a dutch population: A case-control study. *Sci. Rep.*, 7: 12175. DOI: https://doi.org/10.1038/s41598-017-07404-4
4. **Haverkamp, L, Parry, K, Henegouwen, MIV, van Laarhoven, HW, Bonenkamp, JJ, Bisseling, TM,** et al. 2016. Esophageal and gastric cancer pearl: A nationwide clinical biobanking project in the netherlands. *Dis. Esophagus*, 29: 435–441. DOI: https://doi.org/10.1111/dote.12347
5. **Koyak, Z, Kroon, B, de Groot, JR, Wagenaar, LJ, van Dijk, AP, Mulder, BA,** et al. 2013. Efficacy of antiarrhythmic drugs in adults with congenital heart disease and supraventricular tachycardias. *Am. J. Cardiol.*, 112: 1461–1467. DOI: https://doi.org/10.1016/j.amjcard.2013.07.029
6. **Kuijpers, JM, van der Bom, T, van Riel, AC, Meijboom, FJ, van Dijk, AP, Pieper, PG,** et al. 2015. Secundum atrial septal defect is associated with reduced survival in adult men. *Eur. Heart J*, 36: 2079–2086. DOI: https://doi.org/10.1093/eurheartj/ehv097
7. **Luijendijk, P, Lu, H, Heynneman, FB, Huijgen, R, de Groot, EE, Vriend, JW,** et al. 2014. Increased carotid intima-media thickness predicts

cardiovascular events in aortic coarctation. *Int. J. Cardiol.,* 176: 776–781. DOI: https://doi.org/10.1016/j.ijcard.2014.07.090

8. **Navis, GJ, Blankestijn, PJ, Deegens, J, De Fijter, JW, van der Heide, JJH, Rabelink, T,** et al. 2014. The biobank of nephrological diseases in the netherlands cohort: The string of pearls initiative collaboration on chronic kidney disease in the university medical centers in the netherlands. *Nephrol Dial Transpl.,* 29: 1145–1150. DOI: https://doi.org/10.1093/ndt/gft307

9. **Schoormans, D, Sprangers, MA, van Melle, JP, Pieper, PG, van Dijk, AP, Sieswerda, GT,** et al. 2016. Clinical and psychological characteristics predict future healthcare use in adults with congenital heart disease. *Eur. J. Cardiovasc. Nurs.,* 15: 72–81. DOI: https://doi.org/10.1177/1474515114555819

10. **Sluman, MA, Apers, S, Bouma, BJ, van Melle, JP, Peels, CH, Post, MC,** et al. 2015. Uncertainties in insurances for adults with congenital heart disease. *Int. J. Cardiol.,* 186: 93–95. DOI: https://doi.org/10.1016/j.ijcard.2015.03.208

11. **van der Velde, ET, Vriend, JW, Mannens, MM, Uiterwaal, CS, Brand, R** and **Mulder, BJ.** 2005. Concor, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the netherlands: Rationale, design, and first results. *Eur. J. Epidemiol.,* 20: 549–557. DOI: https://doi.org/10.1007/s10654-005-4264-9

12. **van Slooten, YJ, Freling, HG, van Melle, JP, Mulder, BJ, Jongbloed, MR, Ebels, T,** et al. 2014. Long-term tricuspid valve prosthesis-related complications in patients with congenital heart disease. *Eur. J. Cardiothorac. Surg.,* 45: 83–89. DOI: https://doi.org/10.1093/ejcts/ezt259

13. **Van Wier, MF, Huizinga, TWJ, Brouwer, E,** et al. 2016. The rheumatoid arthritis and arthrosis pearl: The biobank for early arthritis patients of the dutch umcs. *Ned Tijdschr Reumatol.,* 2: 32–39.

14. **van't Riet, E, Schram, MT, Abbink, EJ, Admiraal, WM, Dijk-Schaap, MW, Holleman, F,** et al. 2012. The diabetes pearl: Diabetes biobanking in the netherlands. *BMC Public Health,* 12. DOI: https://doi.org/10.1186/1471-2458-12-949

15. **Visschedijk, MC, Alberts, R, Mucha, S, Deelen, P, de Jong, DJ, Pierik, M,** et al. 2016. Pooled resequencing of 122 ulcerative colitis genes in a large dutch cohort suggests population-specific associations of rare variants in muc2. *PLoS One,* 11. DOI: https://doi.org/10.1371/journal.pone.0159609

16. **Vriend, JW, van der Velde, ET** and **Mulder, BJ.** 2004. [national registry and DNA-bank of patients with congenital heart disease: The concor-project]. *Ned. Tijdschr. Geneeskd.,* 148: 1646–1647.

17. **Catalogue of the Parelsnoer Institute.** 2017. www.parelsnoer.org/page/en/Catalogue (accessed October 5, 2017).

18. **Hauer, AJ, Ruigrok, YM, Algra, A, van Dijk, EJ, Koudstaal, PJ, Luijckx, GJ,** et al. 2017. Age-specific vascular risk factor profiles according to stroke subtype. *J Am Heart Assoc.,* 6. DOI: https://doi.org/10.1161/JAHA.116.005090

19. **Promise (project manager internet service).** 2017. https://www.msbi.nl/promise/ (accessed October 5, 2017).

20. **Network NSG, International Stroke Genetics C.** 2016. Loci associated with ischaemic stroke and its subtypes (sign): A genome-wide association study. *Lancet Neurol.,* 15: 174–184. DOI: https://doi.org/10.1016/S1474-4422(15)00338-5

21. **Traylor, M, Farrall, M, Holliday, EG, Sudlow, C, Hopewell, JC, Cheng, YC,** et al. 2012. Genetic risk factors for ischaemic stroke and its subtypes (the metastroke collaboration): A meta-analysis of genome-wide association studies. *Lancet Neurol.,* 11: 951–962. DOI: https://doi.org/10.1016/S1474-4422(12)70234-X

22. **Debette, S, Kamatani, Y, Metso, TM, Kloss, M, Chauhan, G, Engelter, ST,** et al. 2015. Common variation in phactr1 is associated with susceptibility to cervical artery dissection. *Nat. Genet.,* 47: 78–83. DOI: https://doi.org/10.1038/ng.3154

23. **Psaty, BM** and **Sitlani, C.** 2013. The cohorts for heart and aging research in genomic epidemiology (charge) consortium as a model of collaborative science. *Epidemiology,* 24: 346–348. DOI: https://doi.org/10.1097/EDE.0b013e31828b2cbb

24. **Falcone, GJ, Malik, R, Dichgans, M** and **Rosand, J.** 2014. Current concepts and clinical applications of stroke genetics. *Lancet Neurol.,* 13: 405–418. DOI: https://doi.org/10.1016/S1474-4422(14)70029-8

25. **Adams, HP, Jr., Bendixen, BH, Kappelle, LJ, Biller, J, Love, BB, Gordon, DL,** et al. 1993. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of org 10172 in acute stroke treatment. *Stroke,* 24: 35–41. DOI: https://doi.org/10.1161/01.STR.24.1.35

26. **Desai, JA, Abuzinadah, AR, Imoukhuede, O, Bernbaum, ML, Modi, J, Demchuk, AM,** et al. 2014. Etiologic classification of tia and minor stroke by a-s-c-o and causative classification system as compared to toast reduces the proportion of patients categorized as cause undetermined. *Cerebrovasc. Dis.,* 38: 121–126. DOI: https://doi.org/10.1159/000365500

27. **Amarenco, P, Bogousslavsky, J, Caplan, LR, Donnan, GA, Wolf, ME** and **Hennerici, MG.** 2013. The ascod phenotyping of ischemic stroke (updated asco phenotyping). *Cerebrovasc. Dis.,* 36: 1–5. DOI: https://doi.org/10.1159/000352050

28. **Nederkoorn, PJ, van Dijk, EJ, Koudstaal, PJ, Luijckx, GJ, van Oostenbrugge, RJ, Visser, MC,** et al. 2015. The dutch string-of-pearls stroke study: Protocol of a large prospective multicenter genetic cohort study. *Int. J. Stroke,* 10: 120–122. DOI: https://doi.org/10.1111/ijs.12359

29. **Meyer, BC** and **Lyden, PD.** 2009. The modified national institutes of health stroke scale: Its time has come. *Int. J. Stroke,* 4: 267–273. DOI: https://doi.org/10.1111/j.1747-4949.2009.00294.x

30. **Banks, JL** and **Marotta, CA.** 2007. Outcomes validity and reliability of the modified rankin scale:

Implications for stroke clinical trials: A literature review and synthesis. *Stroke*, 38: 1091–1096. DOI: https://doi.org/10.1161/01.STR.0000258355.23810.c6

31. **Moore, HM, Kelly, AB, Jewell, SD, McShane, LM, Clark, DP, Greenspan, R,** et al. 2011. Biospecimen reporting for improved study quality (brisq). *J. Proteome Res.*, 10: 3429–3438. DOI: https://doi.org/10.1021/pr200021n

32. **Association WM.** 2013. Wma declaration of helsinki – ethical principles for medical research involving human subjects. http://www.wma.net/en/10home/index.html (accessed 4 August 2014).

33. **Societies FDFoBS.** Code of conduct for responsible use of clinical data and biological samples. www.federa.org/sites/default/files/digital_version_first_part_code_of_conduct_in_uk_2011_12092012.pdf (accessed October 27, 2017).