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A Report of the TASK3-WG4 Omics Working Group of the ILAE/AES Joint Translational Task Force

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SPECIAL REPORT

A companion to the preclinical common data elements for genomics, transcriptomics, and epigenomics data in rodent epilepsy models. A report of the TASK3-WG4 omics working group of the ILAE/AES joint translational TASK force

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[Correction added on 22 November 2022, after first online publication: The affiliation "Epilepsy Genetics Program, Department of Neurology, Harvard Medical School, Boston Children's Hospital, Boston, Massachusetts, USA" has been removed for Vicky Whittemore.]

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Abstract

The International League Against Epilepsy/American Epilepsy Society (ILAE/AES) Joint Translational Task Force established the TASK3 working groups to create common data elements (CDEs) for various preclinical epilepsy research disciplines. The aim of the CDEs is to improve the standardization of experimental designs across a range of epilepsy research-related methods. Here, we have generated CDE tables with key parameters and case report forms (CRFs) containing the essential contents of the study protocols for genomics, transcriptomics, and epigenomics in rodent models of epilepsy, with a specific focus on adult rats and mice. We discuss the important elements that need to be considered for genomics, transcriptomics, and epigenomics methodologies, providing a rationale for the parameters that should be collected. This is the first in a two-part series of omics papers with the second installment to cover proteomics, lipidomics, and metabolomics in adult rodents.

KEYWORDS

common data elements, mouse, omic data processing, preclinical, rat

1 | INTRODUCTION

The omics field has been largely driven by continuous and rapid technological advances which have enabled in-depth, cost-effective, and high-throughput analysis of biological molecules and systems. Omics-based approaches allow unbiased detection of biological parameters that include DNA (genomics; single and copy number variants, repeat expansions, etc), RNA (transcriptomics: mRNA, microRNAs, etc.), epigenetic profiles (epigenomics), proteins (proteomics), lipids (lipidomics), metabolites (metabolomics), and microbes (microbiomics). These approaches are particularly well-suited to improve the understanding of complex neurological diseases, including epilepsy, in which widespread molecular dysregulation is observed in numerous cell types. Applying these approaches to preclinical and human epilepsy studies allows us to build a more comprehensive understanding of pathomechanisms underlying epilepsy. Omics approaches can be hypothesis-free (untargeted) or targeted at specific biological phenomena to reveal molecular mechanisms explaining disease etiology and potentially providing novel pharmacological targets. Moreover, omics-based technologies can drive diagnostic and prognostic biomarker discovery as well as allowing us to monitor drug efficacy and/or potential side effects from specific treatments.

Although these holistic, unbiased approaches have revolutionized biological research, omics-based studies are methodologically complex and require their own unique considerations, which must be accounted for as

Key Points

- This joint ILAE/AES initiative introduces common data elements (CDEs) related to measurement of genomics, transcriptomics, and epigenomics parameters in biological samples from adult rodents.
- Case report forms (CRFs) and a companion paper discussing their use are provided for genomics, transcriptomics, and epigenomics methodologies.
- Future use of these forms is aimed at standardizing animal experiments to improve and facilitate future meta-analysis studies.

early as possible during the planning stages of the study (Figure 1).

The considerations include the following: (a) the need for suitable animal models; (b) optimization of animal environment, housing, and management; (c) preferred analytical procedures for sample collection and storage; (d) consideration of methodologies to be used (including quality control, sample preparation, and analytical workflows), often unique for a specific omics approach; (e) bioinformatics, which includes a sufficiently large sample size to achieve the desired statistical power when hundreds or thousands of different variables are compared as well as expertise in handling and analyzing large

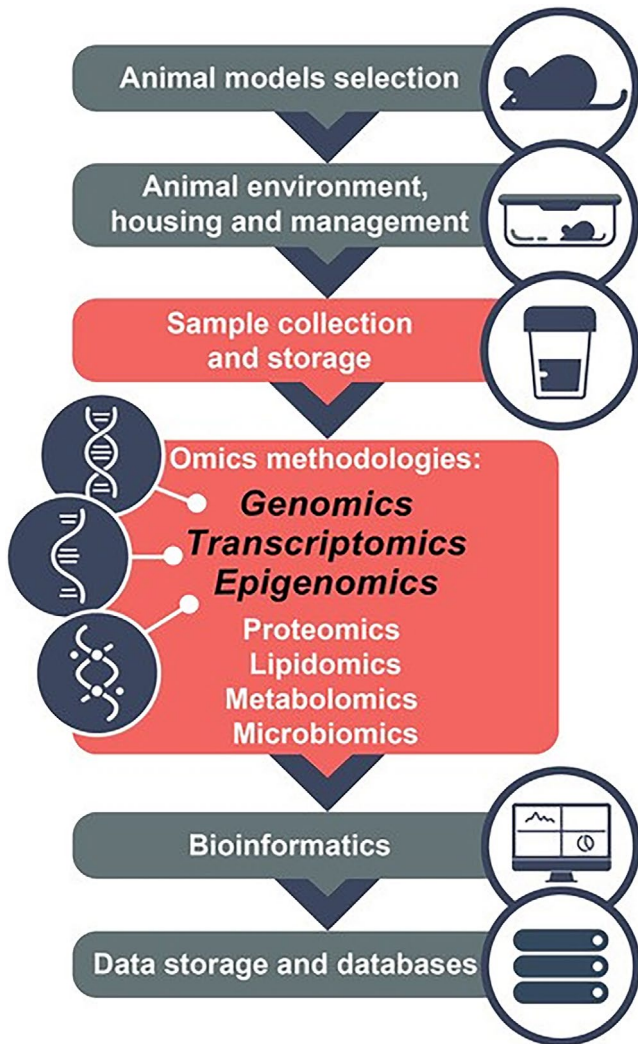


FIGURE 1 Flowchart of omics-based studies

data sets, data annotation, and cross-omic integration; and (f) specialized storage and computing capabilities.

Due to the complexity of omics-based studies, harmonization of all stages of the analytical process and adoption of common practices will not only increase the scientific rigor and reproducibility, but also ensure that data can be readily reused according to FAIR principles,¹ shared, and compared between laboratories as well as integrated with other omics-based data sets to provide a systems level understanding of epilepsy. To this end, the TASK3 Omics Working Group sought to develop common data elements (CDEs), generate case report forms (CRFs), and draft companion papers to assist with the CDE/CRF implementation.

In this first paper, we focus on genomics, transcriptomics, and epigenomics. This will be followed by a second paper on proteomics, lipidomics, and metabolomics. We hope that the use of these CDEs and CRFs will help investigators design and execute omics studies in way that facilitates harmonization and data sharing among laboratories,

thereby improving the cost-effectiveness, scientific rigor, and reproducibility of the studies performed.

2 | METHODS

The Omics Working Group consists of 12 (pre)clinical epilepsy researchers, selected on their relevant expertise who developed CDEs and CRFs for various omics modules. In this manuscript, we focus on two modules: (a) sample collection for genomics, transcriptomics, and epigenomics (Figure 2) and (b) methodologies for genomics, transcriptomics, and epigenomics (Figure 3). These modules are designed to be used together, with an investigator able to select appropriate options in both. They are also designed to be used in conjunction with published CRFs including the “core animal characteristics CRF” described in Harte-Hargrove et al² that covers general animal husbandry and “individual experimental” CRFs such as those covering EEG, physiologic data, pharmacological studies, and behavioral analysis CRFs, as appropriate.^{2–6}

The forms are analogous to previous preclinical CDEs by the TASK3 group of the ILAE/AES Joint Translational Task Force^{2–7} and by the National Institute of Neurological Disorders and Stroke (NINDS) for traumatic brain injury research.⁸ The CDEs generated by the TASK3 Physiology Working Group (Physiologic Data in Rodent Epilepsy Models),⁴ as well as by the EPITARGET consortium (Targets and Biomarkers for Antiepileptogenesis),⁹ have served as useful templates for the TASK3 Omics Working Group. The proposed recommendations originate mostly from previously published methods in rodent epilepsy model research. Within the Omics Working Group, the modules were divided among the members according to their expertise. Each subgroup prepared a draft for the CDE/CRF forms as well as the accompanying part of the manuscript, presented this to the whole group during one of the 10 Working Group meetings, and the draft was assessed and adjusted until a consensus was reached. The final version includes feedback from members of the TASK3 group and the Task Force.

The CDEs presented here apply to adult rodents, rats or mice, and are not readily applicable to immature animals, which will need specific CDEs taking into account their size, developmental stage, and ongoing acquisition of specific functions.¹⁰

3 | RESULTS

In the first CDE, we describe the sample collection and storage options specific for genomics, transcriptomics, and epigenomics followed by the second CDE outlining methodologies used to generate genomics, transcriptomics, and

Omics Studies**Case Report Form: 1 CRF Module –sample collection and storage for genomics, transcriptomics and epigenomics.docx****CRF module: Sample collection for genomics, transcriptomics and epigenomics**Date that this CRF was filled out:Name of person filling out CRF:Project name/Identifier:Animal ID:

<u>CDE Name</u>	<u>Data Collected</u>
Subject	
Species used	<input type="checkbox"/> Rat <input type="checkbox"/> Mouse <input type="checkbox"/> Other
If other, please specify	
Strain used	
Sex	<input type="checkbox"/> Male <input type="checkbox"/> Female <input type="checkbox"/> Unknown
Body weight (g)	
Model used	<input type="checkbox"/> Kainic acid <input type="checkbox"/> Pilocarpine <input type="checkbox"/> Electrical stimulation <input type="checkbox"/> Other
If other, please specify	
Date / Time of sample collection MM/DD/YYYY; hh:mm:ss	
Anesthesia	
Anesthesia	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
If anesthesia was administered, specify type	<input type="checkbox"/> Isoflurane <input type="checkbox"/> Sevoflurane <input type="checkbox"/> Ketamine/Xylazine <input type="checkbox"/> Pentobarbitone <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	
Route of administration	<input type="checkbox"/> Intramuscular <input type="checkbox"/> Intraperitoneal <input type="checkbox"/> Intravenous <input type="checkbox"/> Inhalational <input type="checkbox"/> Unknown <input type="checkbox"/> Other

FIGURE 2 Sample collection and storage case report form (CRF; see main text for details)

If other, please specify	
Isoflurane concentration induction %	
Isoflurane concentration maintenance %	
Sevoflurane concentration induction %	
Sevoflurane concentration maintenance %	
Ketamine dose mg/kg	
Xylazine dose mg/kg	
Pentobarbitone dose mg/kg	
Other anesthesia dose mg/kg	
Starting time of anesthesia in hours and minutes	
Total anesthesia duration in minutes	
Animal sacrifice (select all applicable)	<input type="checkbox"/> Decapitation <input type="checkbox"/> Cervical dislocation <input type="checkbox"/> Overdose of anesthetic <input type="checkbox"/> Unknown <input type="checkbox"/> Not sacrificed
Blood collection	
Collection modality	<input type="checkbox"/> Trunk <input type="checkbox"/> Cardiac puncture <input type="checkbox"/> Lateral saphenous vein puncture <input type="checkbox"/> Tail vein puncture <input type="checkbox"/> Cannula collection <input type="checkbox"/> Orbital plexus <input type="checkbox"/> Retromandibular plexus <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	
If cannula collection, specify blood vessel	
Blood volume collected in ml	
Blood collection container company	
Blood collection container type	
Volume of tube ml	
Anticoagulant used	<input type="checkbox"/> K ₂ EDTA ¹ <input type="checkbox"/> Heparin <input type="checkbox"/> Citrate <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	

¹ EDTA, K₂ Ethylenediaminetetraacetic acid, is recommended for RNA analysis.

² Indicate final concentration in blood (recommended K₂EDTA about 5 mM)

FIGURE 2 (Continued)

If EDTA ^{1,2} , concentration in mM	
If Heparin ² , concentration in U/ml	
If Citrate ² , Concentration mM	
Plasma separation	
Number of centrifugation steps	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	
Centrifugation speed step 1 in g	
Centrifugation time step 1 in minutes	
Centrifugation temperature step 1 in °C	
Centrifugation speed step 2 in g	
Centrifugation time step 2 in minutes	
Centrifugation temperature step 2 in °C	
Samples kept on ice before centrifugation?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Serum separation	
Clotting time in minutes	
Clotting temperature in °C	
Centrifugation speed in g	
Centrifugation time in minutes	
Centrifugation temperature in °C	
Cerebral spinal fluid collection	
Cerebrospinal Fluid collection container company	
Cerebrospinal Fluid collection container type	
Volume of tube in ml	
Volume collected in µl	
Tissue collection	
Collected sample from tissue	<input type="checkbox"/> Brain tissue <input type="checkbox"/> Single cells <input type="checkbox"/> Selected cells <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If brain tissue, specify collected tissue	
If brain tissue, specify collected weight	

FIGURE 2 (Continued)

If single cells, specify collected cell type(s)	
If selected cells, specify collected cell type(s)	
If other, please specify	
Sample storage	
Storage temperature	<input type="checkbox"/> -20°C <input type="checkbox"/> -70°C <input type="checkbox"/> -80°C <input type="checkbox"/> Liquid nitrogen <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	
Volume per aliquot in µl	
Delay between collection and storage in minutes	
Storage time in days	
Number of freeze/thaw cycles	

Parameters

Date and time of sample collection (MM/DD/YYYY; hh:mm:ss)						
Time point after initial insult (days)						

Instructions: Please check boxes where applicable. If none of the predetermined options is appropriate use the default space to specify your answer.

This form is to be filled in for one individual animal.

FIGURE 2 (Continued)

epigenomics data. For a summary of the methods used, as well as their advantages and disadvantages, see [Table 1](#). We provide a rationale and an overview of the elements that are included in the CDEs and the corresponding CRFs. The CDE and CRF modules linked to this paper are also available as electronic files.

3.1 | Sample collection for genomics, transcriptomics, and epigenomics

CRF File name: 1. CRF Module - Sample collection and storage for genomics, transcriptomics and epigenomics.docx.

CDE File name: 1. CDE_chart - Sample collection for genomics, transcriptomics and epigenomics.xlsx ([Supporting information](#)).

3.1.1 | Rationale

For genomics and transcriptomics, samples can be collected from different sources, including blood, cerebrospinal fluid (CSF), and brain tissue. Care is required in choosing the appropriate sampling method for a given experimental goal as well as proper positive and negative controls. Adequate training in sampling techniques cannot be underestimated as this is a significant cause of variability. Whenever possible, quality control (QC) samples should be included in each run to determine sample-to-sample variability (imprecision). For a detailed explanation on the use of QC samples in biomedical laboratories, the reader is referred to several excellent resources by Westgard (see <https://www.westgard.com/>).

Omics Studies**Case Report Form: 2 CRF Module – genomics, transcriptomics and epigenomics.docx****CRF module: Genomics, transcriptomics and epigenomics**Date that this CRF was filled out:Name of person filling out CRF:Project name/Identifier:Animal ID:

<u>CDE Name</u>	<u>Data Collected</u>
Experiment type	
Omics level	<input type="checkbox"/> Genomics <input type="checkbox"/> Transcriptomics <input type="checkbox"/> Epigenomics
Input type:	<input type="checkbox"/> Bulk primary tissue <input type="checkbox"/> Selected cell-types from primary tissue <input type="checkbox"/> Cell-cultures <input type="checkbox"/> Single-cell/single nuclei
Assay type <i>For the “specify” section more details about the assay type are required. For example, if RNA-Sequencing is selected, there is a need to specify if this assay will be for bulk or single cell purposes (e.g., scRNA-Seq) and will attempt to identify regulatory regions or expression (e.g., ChIP-sequencing, Ribo-sequencing)</i>	<input type="checkbox"/> DNA-Sequencing <input type="checkbox"/> RNA-Sequencing <input type="checkbox"/> Array-based
If DNA-Sequencing, please specify	
If RNA-Sequencing, please specify	
If Array-based, please specify	
Sample preparation	
Sample preparation	<input type="checkbox"/> Genomic DNA <input type="checkbox"/> Cell free DNA <input type="checkbox"/> miRNA/RNA <input type="checkbox"/> Cell free miRNA/RNA <input type="checkbox"/> Exosomes <input type="checkbox"/> Single cell suspension <input type="checkbox"/> Unknown <input type="checkbox"/> Other

FIGURE 3 Genomics, transcriptomics, and epigenomics case report form (CRF; see main text for details)

If other, please specify	
Quality control date and time MM/DD/YYYY hh:mm:ss	
Quality control type	<input type="checkbox"/> Hemoglobin contamination <input type="checkbox"/> RNA integrity <input type="checkbox"/> Protein contamination <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	
Sample preparation date and time MM/DD/YYYY hh:mm:ss	
Extraction kit used, specify company	
Specify extraction kit used	
Specify extraction kit cat no	
Amplification of genetic material date and time MM/DD/YYYY hh:mm:ss	
Amplification of genetic material	<input type="checkbox"/> Whole genome amplification PCR-based <input type="checkbox"/> Whole genome amplification PCR-free <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	
Whole genome amplification PCR-based kit used, specify company	
Specify whole genome amplification PCR-based kit used	
Specify whole genome amplification PCR-based kit cat no	
Whole genome amplification PCR-free kit used, specify company	
Specify whole genome amplification PCR-free kit used	
Specify whole genome amplification PCR-free kit cat no	
Library preparation	
Library preparation date and time MM/DD/YYYY hh:mm:ss	
Amount of input DNA	

FIGURE 3 (Continued)

Library preparation DNA	<input type="checkbox"/> Whole genome sequencing <input type="checkbox"/> Exon sequencing <input type="checkbox"/> Targeted capture sequencing <input type="checkbox"/> Bisulfite conversion <input type="checkbox"/> Methylation array <input type="checkbox"/> Other
If other, please specify	
Library preparation DNA, specify source	
Library preparation DNA, specify company	
Library preparation DNA, specify kit name	
Library preparation DNA, specify cat no	
Amount of input RNA	
Library preparation RNA	<input type="checkbox"/> Ribosomal-depleted <input type="checkbox"/> PolyA-selected <input type="checkbox"/> Other
If other, please specify	
Library preparation RNA, specify source	
Library preparation RNA, specify company	
Library preparation RNA, specify kit name	
Library preparation RNA, specify cat no	
Number of input cells/nuclei	
Library preparation single cells/nuclei	<input type="checkbox"/> 10x Genomics <input type="checkbox"/> SMART-seq <input type="checkbox"/> Other
If other, please specify	
Library preparation single cells/nuclei, specify source	
Library preparation single cells/nuclei, specify company	
Library preparation single cells/nuclei, specify kit name	

FIGURE 3 (Continued)

Library preparation single cells/nuclei, specify cat no	
Sequencing/Array	
Sequencing/Array date and time MM/DD/YYYY hh:mm:ss	
Sequencing/Array platform (e.g Illumina HiSeq 4000)	
If sequencing was performed, please list sequencing configuration	<input type="checkbox"/> Paired-end <input type="checkbox"/> Single-read <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	
Sequencing read length in nts	
Sequencing configuration read depth or coverage	
Data processing (Please include version numbers)#	
Read quality control	
Alignment software	
Reference genome used	
Reference annotation used	
Count of aligned reads	
Variant calling	
Other	
Data analysis	
Genomics	<input type="checkbox"/> Variant analysis <input type="checkbox"/> Copy number variation <input type="checkbox"/> Loss of heterozygosity <input type="checkbox"/> Polygenic risk score <input type="checkbox"/> Genome Wide Association Study <input type="checkbox"/> Population databases <input type="checkbox"/> In silico prediction tools

FIGURE 3 (Continued)

	<input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	
Transcriptomics	<input type="checkbox"/> Differential expression <input type="checkbox"/> Gene co-expression analysis <input type="checkbox"/> Gene ontology/Pathway analysis <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	
Epigenomics	<input type="checkbox"/> Differential expression <input type="checkbox"/> Gene ontology/Pathway analysis <input type="checkbox"/> Transcription factor enrichment <input type="checkbox"/> Copy number variation <input type="checkbox"/> Loss of heterozygosity <input type="checkbox"/> Chromosomal abnormalities <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	
Specify software and workflow used for data analysis (Please include version numbers)	1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____
Validation of -omics data	
DNA	<input type="checkbox"/> Sanger Sequencing <input type="checkbox"/> Droplet digital PCR <input type="checkbox"/> Southern blot <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	

FIGURE 3 (Continued)

RNA	<input type="checkbox"/> Droplet digital PCR <input type="checkbox"/> Real-time PCR <input type="checkbox"/> In situ hybridization <input type="checkbox"/> Northern blot <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	
Epigenomics	<input type="checkbox"/> Bisulfite Sequencing <input type="checkbox"/> Unknown <input type="checkbox"/> Other
If other, please specify	
Data availability	
Data availability	<input type="checkbox"/> No <input type="checkbox"/> On request <input type="checkbox"/> Publicly available
If on request, please provide contact details	
If publicly available please specify data storage site	
If publicly available please specify accession number	
Data provided according to FAIR principles	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unknown

Instructions: Please check boxes where applicable. If none of the predetermined options is appropriate use the default space to specify your answer.
This form is to be filled in for one individual animal.

The available tools for data processing are vast and varied and are dependent on the type of -omics analysis performed, the platform being used, and the specific research question. Here, the most important steps in data processing are listed, space is provided to specify the tool used.

FIGURE 3 (Continued)

3.1.2 | Measurements

Blood sampling can be performed repeatedly from the same animal to collect longitudinal information for omics studies. The researcher should pay attention to the maximum volume that can be collected as per

institutional regulatory guidelines and also see <https://www.nc3rs.org.uk/our-resources/blood-sampling>. CSF collection is often performed during a terminal experiment, but it can also be performed multiple times from the same animal. Longitudinal collection requires surgical implantation of a cannula in the cisterna magna.¹¹

TABLE 1 Overview of methods used for omic studies

Method	Advantages	Disadvantages
Blood collection	Fast, simple, repeated sampling possible	Small volume, low number of cells, not sure if obtained information is brain specific
Cerebrospinal fluid collection	CNS-specific information can be obtained	Very small volume, difficult to perform, sample can easily be contaminated with blood
Brain tissue collection	Subregion/cell-specific information can be obtained	Lethal experiment
Genomics	Relatively easy to perform, genetic information can be obtained including introns, exons, promotor, high-throughput screening, high accuracy	Difficult to determine the final biological effects due to posttranscriptional and posttranslational changes and epigenetics
Transcriptomics	Information of the transcriptome can be obtained including splice variants, noncoding RNAs, high sensitivity	Posttranslational modifications can influence protein expression, expensive, information processing is cumbersome
Epigenomics	Information of gene regulation can be obtained	Challenge to link to gene expression as multiple processes can influence the transcription

Brain samples are typically collected after decapitation of the animal.

3.1.3 | Equipment

For the collection of blood and CSF samples, needles or cannulas are needed, as well as specific collection tubes. To separate plasma, a centrifuge is needed. For the collection of brain tissue, dissection tools are needed.

3.1.4 | Procedures

Blood collection

For the procedures of blood collection, we used the information that is available from the TASK3 Physiology Working Group.⁴ If the animal will be sacrificed immediately before or after the blood collection, trunk blood can be collected directly after decapitation (up to 2–6 ml of whole blood for an adult rat, up to 1 ml for an adult mouse), without touching the animal with the collection tube. This approach allows collecting large amounts of whole blood, but blood may be mixed with tissue fluids. Alternatively, a cardiac puncture can be performed to collect blood directly from the heart (up to 2–6 ml of whole blood for a rat, up to 1 ml for a mouse). If the animal will not be sacrificed after the blood collection, several methods can be used:

Lateral saphenous vein withdrawal (anesthesia optional as per institutional ethical guidelines): For a rat, up to 200 μ l may be taken for a single sample, and for a mouse, up to 150 μ l ml, which can usually be repeated at 2-week intervals without disturbances to the hematological status. Alternatively, multiple smaller samples (e.g., rat 20 μ l

daily and mouse 10 μ l daily) may be drawn, taking into account the limits on total sample volume. There should not be more than three attempts to collect blood. Continuous sampling should be avoided and collecting more than four samples in a day (24-h period) is not advised. Shave the back of the hind limb with an electric trimmer until the saphenous vein is visible. Hair removal cream can also be used. Restrain the animal manually or use a suitable animal restrainer. Immobilize the hind leg and apply slight pressure above the knee joint. Puncture the vein using a 20G needle and collect blood with a capillary tube or a needle attached to a syringe. Compress the punctured site to stop the bleeding. A local anesthetic cream may be applied at the collection site.

Tail-vein withdrawal (anesthesia optional as per institutional ethical guidelines): For a rat, 0.1–2 ml of whole blood, and for a mouse, 50–200 μ l of whole blood can be collected repeatedly with long intervals (hours-days-weeks). No more than eight blood samples should be taken per session and in any 24-h period. One or two blood samples can be taken per session and in any 24-h period, depending on sample volume. Restrain the animal in a cylinder or anesthetize the animal. Warm up the tail with a heating lamp or in warm water to dilate the blood vessels. Visualize a sampling site on the lateral tail vein in the distal third of the tail. While extending the tail, insert a 25G needle with syringe and collect the blood.

Vessel cannulation: For a rat, usually 100–200 μ l can be taken per sample without anesthesia, and depending on the sample volume and scientific justification, up to six samples over a 2-h period or up to 20 samples over a 24-h period may be taken. For a mouse, 10–20 μ l of blood can be taken and, depending on the sample volume and scientific justification up to six samples may be taken in a 24-h period. For additional details, see Gorter et al.⁴

Retro-orbital blood collection: Usually before sampling, a local anesthetic is dropped into the eye (e.g., 2% tetracaine). For a rat, up to 4 ml blood can be collected with recovery; 4–10 ml nonrecovery. It is recommended that only one sample be taken. For a mouse, up to 200 μ l blood can be collected with recovery; up to 500 μ l nonrecovery. It is recommended that only one sample be taken. For additional details, see Gorter et al.⁴

Lateral canthus: Pick up the animal and restrain it in one hand. Insert a small diameter glass capillary tube or Pasteur pipette into the lateral canthus. The tube should be at about a 30 degrees angle to the side of the head.

Medial canthus: Place the animal on a table or cage lid on its side. The body of the animal is restrained against the table with the palm of the hand. The thumb and forefingers of the same hand restrain the animal and gently open the eyelids to expose the eye. Insert the tube into the medial canthus and hold it at a 30 degrees angle to the nose.

Retro-mandibular venous plexus: This procedure allows collecting up to 300 μ l of whole blood in mice, and care needs to be taken to limit as much as possible the volume to the allowed amounts described above. Please note that it can be difficult to restrict the blood flow especially if the mouse is conscious and if more than 500 μ l of blood is withdrawn in a mouse, euthanasia must be considered. For additional details, see Gorter et al.⁴

For RNA or DNA analysis, whole blood can be separated into its plasma or serum components. Centrifuge the blood sample to separate plasma from whole blood within 1 h of whole blood collection using the following recommended parameters: 1300–1500 g for 10 min at 4°C without using the break. Plasma has to be removed with caution to avoid disruption of the buffy coat. For serum collection, let blood clot at room temperature for 1 h and centrifuge at 1300–1500 g for 10 min at 4°C without using the brake. Transfer the upper-phase into a new tube. To prevent platelet contamination, a second centrifuge step is needed (3000 g, 10 min, 4°C) before freezing. Freeze samples on dry ice and store aliquots at –70 or –80°C. The essential difference between plasma and serum is the presence or absence of fibrinogen and clotting factors, respectively. For small noncoding RNAs (including microRNAs), plasma is preferred over serum to (a) avoid procedural variation in clotting and coagulation process and (b) release of small RNAs from blood cells (platelets, white and red blood cells) into serum during coagulation process.¹² The type of anticoagulant used in plasma collection tubes is also important to consider. Whereas K₂ ethylenediaminetetraacetic acid (EDTA) is an acceptable anticoagulant for downstream analysis using quantitative PCR, the use of heparin or trisodium citrate as an anticoagulant potentially inhibits subsequent PCR.¹²

Cerebrospinal fluid collection

CSF is mainly CNS derived and contains none, or only a very small number of red and white blood cells, a low concentration of plasma proteins, and various levels of electrolytes and other small molecules (e.g., glucose and amino acids). Because the CSF is thought to equilibrate with the extracellular (intersitial) compartment of the brain, analysis of CSF is thought to provide more direct information about the brain microenvironment than analysis of blood. The collection of CSF from rodents is not commonly done, probably due to the difficulty of obtaining high-quality samples with significant quantity given the CSF volume is low in rodents and can be easily contaminated with blood. The cisterna magna (the opening between the cerebellum and dorsal surface of the medulla oblongata) has the largest volume of CSF in the adult rat, and is therefore often used for withdrawal. After anesthesia, the rat is placed in a stereotaxic frame and a puncture is made into the cisterna magna using a 23G needle that is connected to tubing and a collection syringe.¹³ About 100–120 μ l of CSF can be obtained at each collection. For mice, a glass capillary connected to tubing can be used to puncture the cisterna magna and about 10–15 μ l of CSF can be collected.¹⁴

For repeated CSF collection, a cannula (a 20G gauge hypodermic needle with a fitting stainless-steel wire as stylet) is inserted into the cisterna magna. The correct placement of the cannula can be checked by carefully removing the stylet from the cannula. Thereafter, the cannula is fixed to the skull by applying dental cement around the cannula itself and over anchoring screws in the skull. After recovery, CSF can be collected repeatedly without anesthesia using a collection needle that is connected to tubing.^{11,15}

Tissue collection

We recommend that fresh brain tissue samples are preserved with snap-freezing in liquid nitrogen within 10 min after decapitation.¹² The delay between decapitation and tissue preservation should be monitored and reported.

3.1.5 | Sample storage

Samples, as well as extracted DNA and RNA, if packaged properly, can be stored at –70°C to –80°C or in liquid nitrogen for more than a year.^{16–18} Although they are quite stable, it is obvious that the optimal approach is to process the sample as quickly as possible and to match case and control specimens with respect to duration of storage as much as possible. Avoid multiple freeze–thaw cycles by freezing collected samples immediately in smaller aliquots using dry ice.¹⁹ The use of preserving liquids such as RNAlater can be used when immediate freezing or processing of tissue samples is not an option.

3.1.6 | Analysis and interpretation

Select the appropriate method to handle the sample according to the method that will be used. Typically, the DNA or RNA yield is measured and quality controls are performed. See following paragraphs.

3.2 | Genomics, transcriptomics, and epigenomics

CRF File name: 2 CRF Module - Genomics, transcriptomics and epigenomics.docx

CDE File name: 2. CDE_chart - Genomics, transcriptomics and epigenomics.xlsx ([Supporting information](#))

3.2.1 | Rationale

Genomics, transcriptomics, and epigenomics are performed to assess an animal's genotype or epigenotype during an experiment, including exogenously introduced genetic or epigenetic variants and the endogenous genetic or epigenetic background. The evaluation of genes, gene expression, or epigenetic changes is an essential part of an omics-based molecular analysis. It provides readily available information about the structure or expression of genes or epigenetic modifications in animal models. It helps to understand the molecular consequences of introduced genetic or epigenetic variants on the animal's basal genotypic parameters. Genomics and transcriptomics analyses can be performed in a targeted fashion which has inherent bias. Alternatively, genome- or transcriptome-wide analysis can be conducted through sequencing or array-based methods to interrogate gene variants, gene expression, epigenetic modifications, or noncoding RNAs. The genotype or epigenotype of an animal model can be a reliable indicator of general health and well-being, or a disease state.^{20,21} Phenotyping (i.e., behavioral testing) of the animal model can then be correlated with known genotypes or epigenotypes. Because some behaviors are based on subjective criteria, and can reflect unconscious bias, behavioral testing should be performed by highly trained personnel and blinded whenever possible ([Supporting information](#)).

3.2.2 | Measurements

Quality control steps on collected samples should be completed prior to sample preparation to avoid or reduce bias in the downstream sequencing or array-based analyses.

The high level of hemoglobin messenger RNA (mRNA) in blood can confound downstream RNA sequencing analyses, meaning depletion is recommended and hemoglobin measurements need to be performed. An appropriate method for this is to measure the absorbance of the sample at 414 nm and use a cut-off absorbance value of 0.20–0.25 to indicate low hemoglobin. The integrity of the RNA is also a critical consideration as RNA degradation will influence transcript quantitation.²² Protein contamination, routinely measured by spectrophotometry (e.g., 260/230 ratio), can also reduce the quality of downstream applications, meaning purification of nucleic acids should be considered.²³ While, a NanoDrop spectrophotometer or Qubit Fluorometer with nucleotide-binding dyes can be used for DNA or RNA measurements, the gold-standard approach is to use a highly sensitive, chip-based assay such as a Bioanalyzer, (Agilent Technologies) or a Fragment Analyzer™ (formerly Advanced Analytical Technologies, now Agilent Technologies).

3.2.3 | Equipment

For each procedure, specific equipment is needed, see the following paragraphs. Typically, a sequencer or array platform, and a PCR apparatus are needed.

3.2.4 | Approaches

Genotyping and epigenotyping techniques for the detection of genomic, transcript, and epigenetic variants in animal models of epilepsy or seizures can be classified as unbiased screens or targeted assays. Unbiased screens are more comprehensive, as they permit hypothesis-free genome-wide analysis and identification of novel genotypes or epigenotypes associated with a given seizure or epilepsy type, but they are prone to the identification of false-positive findings and variants of uncertain significance. Targeted assays are more specific, involving interrogation of a single or relatively small number of genes or gene variants, transcripts or epigenetic sites, permitting higher-depth and sensitivity, but screening only a limited number of targets.

Unbiased screening tools

Next-generation sequencing (NGS) technologies including whole-genome sequencing (WGS), whole-exome sequencing (WES), RNA sequencing (RNAseq), and whole-genome bisulfite sequencing (WGBS) have substantially accelerated genetic and epigenetic discovery. Conventional NGS approaches typically target a population of cells from a bulk tissue. Newer single-cell

sequencing enables genome-wide screening of single cells at high resolution.^{24,25} Single-nuclei sequencing has been rapidly developed and applied to reveal germline and somatic mutations, and it has great potential to revolutionize future studies of brain-specific mutations in rodent epilepsy models. WGBS was developed more recently and has been successfully applied to determine genome-wide methylation patterns in mouse brain,²⁶ although it has not yet been applied to epilepsy models. Chromosomal, expression, and methylation arrays also have utility in epilepsy and seizure animal models for detecting genome-scale copy number variants,²⁷ differentially expressed genes,²⁸ or DNA methylation,^{29,30} respectively.

Targeted screening tools

Targeted NGS investigates particular genomic, transcript, or epigenetic regions of interest, and is cost-effective for screening large numbers of animals.³¹ There are different PCR-based methods for target-enrichment including hybridization of DNA, RNA, or protein baits such as molecular inversion probes (MIPs). MIPs have been successfully applied in targeted sequencing panels for germline and somatic mutations in human epileptic encephalopathies, epileptic spasms, and focal epilepsies,^{32–37} and can be used to study rodent models of these disorders. Other targeted methods can detect individual genetic variants with high sensitivity such as droplet digital PCR (ddPCR). This technique provides absolute quantification of DNA molecules at the single copy or allele level and a detection limit typically below 1% allele frequency,^{38,39} permitting detection of even very low level somatic mutations in rodent models.⁴⁰ Quantitative real-time PCR with fluorescent probes or DNA-binding dyes is a targeted method to confirm differential expression of specific genes in tissues of rodent models of epilepsy.⁴¹ Bisulfite sequencing can be used to confirm preferential sites for DNA methylation such as CpG islands in promoter regions that have been associated with epileptogenesis in mouse models.⁴²

3.2.5 | Procedures

Sample preparation

Sample preparation can include extraction of nucleic acids, isolation of exosomes for RNA analyses, or single-cell separation. Standard kits are generally used for extraction of nucleic acids.²³ In recent years, analysis of cell-free DNA and RNA from exosomes has become popular for identifying biomarkers of epileptic seizures.⁴³ Global expression profiling⁴⁴ and single-cell sequencing⁴⁵ rely on RNA, exosomes or single-cell separation, and are used for animal models of epilepsy and human tissues.

Amplification of genetic material

Amplification using PCR or PCR-free approaches is sometimes necessary because the amount of tissue available from an animal model provides insufficient genetic material for genome- or epigenome-wide approaches.⁴⁶

Library preparation for DNA

Library preparation depends on the downstream application, and options are summarized in a recent review by Dunn et al,⁴⁶ specifically focused on epilepsy. A variety of capture approaches are commercially available for gene panels and whole exomes which vary depending on the number of genes targeted and whether 5' or 3' untranslated regions, microRNAs or other noncoding RNAs are also included in the capture. As a consequence, the size of the genomic regions captured can differ considerably between kits.

Library preparation for RNA

Library preparation for RNA targets the whole transcriptome and has been used in animal models to study molecular signatures of epileptogenesis⁴⁷ and RNA editing.⁴⁸ Whole transcriptome RNA may be enriched by ribosomal depletion or polyA-selection prior to expression array or sequencing.⁴⁹ Selection of RNA fragments of a specific size can be performed prior to library preparation to enrich for a small RNAs (e.g., miRNAs).⁵⁰

Library preparation for epigenetics

This involves bisulfite treatment of single-stranded DNA prior to library enrichment for downstream methylation arrays or next-generation sequencing analysis.⁵¹ Techniques to analyze genome-wide histone modifications or transcription factor binding tend to follow standard library preparation techniques optimized for low-input DNA following the immunoprecipitation step.

Library preparation for single cells

This comprises physical separation or disaggregation of cells from tissue into single-cell suspension including optional enrichment for or exclusion of specific cell types.⁵² Single cells are then captured in wells or droplets prior to lysis to release RNA.⁵²

DNA screening

For most experiments, this involves short-read sequencing of bulk tissue DNAs; however, single-cell⁴⁵ and long-read⁵³ sequencing are increasingly being used on epileptic cell and tissue DNAs. Chromosomal microarrays and ChIP-seq are still frequently used to identify and characterize chromosomal abnormalities, best exemplified by studies of animal models and patients with epilepsy due

to variants in the chromodomain helicase DNA-binding (CHD) family of proteins, including *CHD2*, that modulate gene expression.⁵⁴

RNA screening

RNA screening is frequently conducted on animal models using RNA sequencing of bulk tissue RNAs although single-cell RNA (scRNA) sequencing is increasingly being adopted.⁵² Expression arrays still have utility for epilepsy animal models where fresh-frozen tissue is available. In humans, there are methodological challenges as the available specimen for analysis is often formalin-fixed and paraffin-embedded.⁵⁵

Epigenetic screening

Epigenetic screening to identify methylated and demethylated regions, particularly around promoters and CpG islands, can reveal modifications associated with epilepsy in animal models and humans.⁵⁶ Noncoding RNAs, including miRNAs, are a specific area of interest for experimental and human epilepsies. miRNAs are also emerging as biomarkers and potential treatment targets for status epilepticus.

3.2.6 | Analysis and interpretation

Data processing and data analysis

Over the past decade, the production of raw DNA and RNA omics data has become rather standardized, predominately due to the large market share held by specific companies (e.g., Illumina); however, no optimal or standard data processing or analysis pipeline exists. This issue is further confounded by a large body of literature outlining a variety of pipelines and analytic techniques, each purporting to offer a more accurate representation of the genome or transcriptome.^{57–60} Ultimately, the processing pipeline chosen is dependent on the biological question being asked, the profiling technique being used and the personal preference of the bioinformatician analyzing the data. As strategies vary greatly between laboratories, each utilizing a different combination of commercial and in-house algorithms and pipelines specific analysis details will not be listed here.

As with data processing, the possibilities for data analysis are wide and varied and again depend in the specific research question being asked. For WGS or WES, a straightforward approach such as variant analysis may be carried out utilizing the standards and guidelines established by the American College of Medical Genetics for interpretation of clinical sequence variants in known genes.⁶¹ As for gene expression, data produced from RNA-sequencing, differential expressed genes, or

miRNAs can be identified, alternatively more advanced techniques such as weighted-gene coexpression network analysis or various machine learning techniques can be applied.

Regardless of the processing or analysis pipeline chosen, it is important that each step (e.g., quality control, removal of low-quality reads, mapping to the genome, and analysis) is well documented and includes the algorithm used, the settings chosen, along with any assumptions made when analyzing the data. Keeping appropriate records not only facilitates the interpretation of the data and allows for reproducible workflows, but also enables efficient data sharing across the scientific community, allowing for different data sets produced at different times to be combined in large-scale meta-analyses, or to be re-analyzed using different pipelines. Furthermore, for the reuse data, it is important that metadata and data are well-described according to FAIR principles¹ so that they can be replicated and/or combined in different settings.

4 | DISCUSSION

4.1 | Target confirmation and validation

The unbiased nature of the omics approach is a strength, potentially highlighting novel pathogenic molecular targets. However, it is still important that identified targets are confirmed and validated. To confirm these targets, an independent methodology is commonly applied, with the same samples used in the omics approach. However, target confirmation also includes the use of an independent cohort and, ideally, also other epilepsy models. Ultimately, after target confirmation, target validation has to be performed in which the role of a specific target in (the development of) epilepsy is investigated.

Human genomics approaches have been very successful in identifying new epilepsy genes, and are being employed to unravel the genetic architecture of different epilepsies.⁶² A number of model systems have been successfully developed to characterize and in some cases provide additional validation of the pathogenic nature of a given variant.⁶³ This includes in vitro expression systems that allow the impact of a variant to be studied in isolation, the introduction of variants into neurons rederived from pluripotent stem cells and the engineering of knock-in rodent models based on the genetic lesion.⁶³ As an aside, the human stem cell and rodent knock-in models provide disease relevant starting points on which to apply omics aimed at identifying emerging biomarkers of disease pathology.

For variants identified using genomic approaches in rodent models, in vitro functional analysis and potentially

stem cell models can be used to validate any finding and provide insight into pathogenic mechanisms.⁶⁴ Congenic strains can also be developed to probe the pathogenicity of a given variant. These paradigms work well in the context of monogenic causes of pathology.²⁰ However, modeling polygenic causes of disease remains difficult and as a consequence validating such variants remains problematic, both in rodents and in humans. A similar issue arises when probing epigenetic changes. By their nature, epigenetic alterations can have wide ranging impact on transcription across all developmental periods.^{51,56} Modeling this is difficult and validation relies on consistency in changes across different rodent models of the same disease or correlation with epigenetic changes observed in humans. Transcriptomic, and more recently proteomic, analysis of rodent models has been used to identify a number of novel disease targets in epilepsy.⁴⁸ Here, the impact of a given protein can be probed using knockout, knockdown, and overexpression approaches.⁶⁵ Targeted knockdown or overexpression approaches can model brain-region-specific impacts. However, rarely, if ever, do transcripts or proteins change in isolation. Therefore, pathogenicity is likely due to a “concert” effect where multiple proteins contribute which is clearly difficult to model.

For transcriptomics and epigenomics, target confirmation is commonly performed using ddPCR or RT-PCR, and bisulfite sequencing, respectively. For target validation, *in silico* analysis can be used to select pharmacological tools to modulate the RNA or methylation targets themselves, or identify regulatory noncoding RNAs (e.g., miRNAs and siRNAs) or methylation enzymes (e.g., histone or DNA methyltransferases or demethylases) to manipulate. Following these approaches, a variety of *in vitro* or *in vivo* experiments could be performed in animal models or human brain tissue or bodily fluids.

Consistency across rodent models and humans is key for validation of pathogenicity or relevance as a biomarker of disease. Across the omics, more advanced bioinformatics approaches that include biological clusters may help in reducing the noise and allowing easier cross-model and human comparisons.

There is increasing recognition for the need of standardization across laboratories involved in “omics” research. In this respect, recent large multicenter collaborations such as EpiCare, EpiPGX, Epixchange, DESIRE, EpimiRNA EPISTOP, EPITARGET, Epibios4Rx, Epi25 Collaborative, Epi4K, EuroEPINOMICS, and EpiGen that use standardized approaches are very important, as well as knowledge sharing during specialized conferences such as epiXchange, organized by seven large European Union-funded projects in Brussels in 2018 (see www.epixchange2018.eu). A recent paper³¹ demonstrates the power of large-scale multiomics platforms to yield cutting edge

findings that may facilitate development of novel therapeutic strategies, and stresses the importance of collaboration, standardization, and data-sharing. While these large-scale efforts are beginning to yield fruit, the harmonization procedures are in their infancy and continue to evolve. Although preclinical omics studies are providing insights into disease mechanisms, these ultimately need to be related back to the human condition. Therefore, care should be taken when translating findings in animal models to patients. Standardization facilitates comparisons between omics studies in animal models and patients with epilepsy, and also helps to determine how well animal studies reproduce the human disease.

4.2 | Novel developments

An emerging Omics technology is third-generation sequencing (TGS), which refers to long-read sequencing at the single DNA^{53,66} or RNA⁶⁷ molecule level. The average read-length of long-read sequencing is more than 1000 bp.^{68,69} The longer read-length makes this approach superior for interrogating complex DNA structural variants and repeat elements, and their effect on gene expression at the bulk tissue or single-cell level.^{70–72} TGS has not yet been used to study these type of gene variants in epilepsy models, but has demonstrated utility in human epilepsies.^{53,66}

Increasingly, single-cell sequencing methods (DNA or RNA) are allowing dissection of the complex genetic architecture of individual neurons in the context of natural or disease processes,⁷³ including epilepsy.^{74,75} Very recently, the power of running these deep sequencing approaches in parallel on different human neuronal cell types to distinguish cell-type-specific lineage patterns during human brain development has been demonstrated.⁷⁶ The obvious extension to this approach is to combine DNA and RNA sequencing with proteomic analysis (the subject of the upcoming second part companion paper in this series, and a recent review⁶⁷) to capture the complex cellular architecture of neural progenitors or neurons involved in normal brain development or epileptogenic processes. In addition to single-cell transcriptomics, spatial transcriptomics is another emerging technology to characterize expression profiles while retaining information of the spatial tissue context.^{77,78} Another recent development is single-molecule transcriptomics. Unlike conventional sequencing approaches, single-molecule long-read sequencing can render a full-length transcript sequence without depending on the error-prone, computational step of assembly. Therefore, it has much better precision in detecting alternative or novel variants.⁷⁹ Further refinements in epigenomic analyses are consistently emerging. Cut

and Run sequencing can be used to map global protein-DNA binding sites, and requires less sequencing depth due to less signal to noise ratio. Single-cell epigenomic techniques such as single-cell ATAC-Seq are also offering the possibility to interrogate chromatin conformation and gene expression at the single-cell level, although this approach has not yet been applied to epilepsy.

Finally, as recently outlined,⁶⁵ targeted genetic manipulation using CRISPR-Cas9 technology (both to insert a genetic variant of interest and subsequently to revert this genotype back to wild-type) has the potential to improve our understanding of what happens when the proliferation or differentiation of neuronal progenitors, or function of mature neurons, is perturbed in animal models of epilepsy.

5 | CONCLUSION

Genomic, transcriptomic, and epigenomic approaches are powerful strategies to understand disease underpinnings and have already contributed to elucidate pathophysiological mechanisms of epilepsy. The first epilepsy gene (*CHRNA4*) was identified in 1995⁸⁰; since then, many gene discoveries have been made, particularly following the advent of NGS in the mid 2000s.⁶² These discoveries have “solved” many rare monogenic forms of epilepsy, benefitting patients worldwide in terms of diagnosis (in many cases, ending a diagnostic odyssey) and clinical management.⁶² The identification of many novel epilepsy genes has fueled interest in drug repurposing—the discovery of new indications for approved drugs—as a strategy to improve the outcomes of epilepsy treatment.⁸¹ Driven by the development of new bioinformatics approaches and the assembly of large patient cohorts through international collaborations, the genetic architecture of the common polygenic epilepsies is also starting to be revealed.⁶² Progress in this field, for example, by determining polygenic risk scores, may also soon translate to the clinic and ultimately allow development of more effective therapies.

Considering their potential to identify novel disease biomarkers and therapeutic targets, transcriptomic and epigenomic approaches are likely to be increasingly used in epilepsy research, including those studies involving animal models, in the near future. These applications promise to improve our understanding of gene–environment interactions in epilepsies due to acquired brain insults. “Big data” approaches combining multiple data sets from a range of omics techniques are also gaining traction. The importance of standardization across laboratories and across techniques is therefore critical. The CRFs and CDEs presented in this paper provide useful tools to improve the standardization of experimental designs across a range of epilepsy research-related methods.

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CONFLICTS OF INTEREST

MP and PP are Associate Editors for *Epilepsia Open*. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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