COMMENTARY

Advancing research towards faster diagnosis, better treatment, and end of stigma in epilepsy

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Abstract

Seven large European Union (EU)-funded epilepsy-related research projects joined forces in May 2018 in Brussels, Belgium, in a unique community building event – the epiXchange conference. During this conference, 170 investigators from the projects DESIRE, EpimiRNA, EPISTOP, EpiTarget, EpiXchange, and EpiPGX as well as the European Reference Network EpiCARE, met up with key stakeholders including representatives of the European Commission, patient organisations, commercial partners and other European and International groups.

The epiXchange conference focused on sharing and reviewing the advances made by each project in the previous five years; describing the infrastructures generated; and discussing the innovations and commercial applications across five thematic areas: biomarkers, genetics, therapeutics, co-morbidities and biobanks & resources. These projects have, in fact, generated major breakthroughs including the discovery of biofluid-based molecules for diagnosis, elucidating new genetic causes of epilepsy, creating advanced new models of epilepsy and the pre-clinical development of novel compounds. Workshop-style discussions focussed on how to overcome scientific and clinical challenges for accelerating translation of research outcomes and how to increase synergies between the projects and stakeholders at a European level. The resulting advances would lead towards a measurable impact of epilepsy research through better diagnostics, treatments and quality-of-life for persons with epilepsy. In addition, epiXchange provided a unique forum for examining how the different projects could build momentum for future novel ground-breaking epilepsy research in Europe and beyond. This report includes the main recommendations which resulted from these discussions.

Introduction

Epilepsy affects over 6 million people in Europe, with an estimated annual healthcare and societal cost of 16 billion euros[1]. This condition presents as an exceptionally multifaceted cluster of diseases, which vary in semiology, aetiology, pathophysiology, progression, outcome and co-morbidities[2]. The epilepsy research community, in partnership with industry and other stakeholders, has had many successes, including the development and approval of over 20 different anti-seizure drugs which provide seizure control for two-thirds of patients[3]. However, none of these drugs prevent the development, or alters the course, of epilepsy and 30% of patients remain refractory to currently available treatment – a figure that has not changed over the last decades[2,4]. In addition, more than 30% of treated patients experience adverse events compromising their quality of life. They also suffer from concurrent cognitive, psychiatric and other co-morbidities, as well as stigma which is still widely related to this condition[5,6]. It often takes many years before a patient receives a correct diagnosis or the appropriate medication[7]. Research to elucidate molecular mechanisms of epilepsy is now reaching the clinic, with gene panels and exome/genome sequencing guiding some treatment and care pathways[8,9]. However, the majority of patients still do not receive a genetic diagnosis. Another key unmet need is that there has been a 2-3-fold increase in mortality of persons with epilepsy, with sudden unexpected death in epilepsy (SUDEP) being the major cause of premature loss of life in affected persons[10].

Together, these challenges mandate transdisciplinary expertise and coordinated actions in brain research that integrate other scientific disciplines and emerging technologies, in order to advance our understanding of the cause(s) and treatment of epilepsy. Concurrently, unique features of epilepsy as a medical condition provide invaluable opportunities for fundamental studies of brain network function, improved imaging and diagnostics, and the search for disease mechanisms and novel drug targets. This could also lead to new therapies for other conditions such neuropsychiatric disorders[11], neurodegenerative diseases[12] and autism[13]. Consequently, research into the treatment of epilepsy also provides a unique insight over the broader neuroscience field.

Investment in epilepsy research under Framework Programme 7

There has been historical under-investment in epilepsy research relative to its disease burden[14]. Compounding this, various manufacturers of anti-seizure drugs have recently disengaged from research and development in the area of epilepsy therapeutics[15]. Tackling these challenges received a critical boost in 2013, when, after determined and successful efforts to put epilepsy on the EU research agenda, a specific call was included in the last year of Framework Programme (FP) 7, inviting large collaborative research projects to address the challenges posed by epilepsy and to advance our understanding of mechanisms, diagnosis and treatment. Projects had to be multi-disciplinary in nature, feature collaborative work by scientists and clinicians as well as other technical experts from outside the field. Lastly, each project required a significant involvement of small and medium-sized enterprises (SMEs). Four projects received funding – a total investment of approximately 50 million € - each with unique, as well as complementary, research approaches blending basic and translational science, animal models and clinical studies and trials. The projects were called DESIRE, EpimiRNA, EpiSTOP and EpiTarget. In addition, a number of other European epilepsy research projects overlapped within this same timeframe, including EpiPGX and Epixchange, which were funded by earlier funding rounds in FP7, and EpiCARE, a European Reference Network approved and funded by CHAFEA, the EU Consumers, Health, Agriculture and Food Executive Agency, to enhance and better network clinical care and research in epilepsy.

epiXchange 2018 – A unique community-building event for epilepsy research in Europe

Soon after the projects were launched, discussions began between the Project Coordinators to bring together these projects when results began to emerge. Although the epilepsy research communities in Europe and across the world meet regularly through events such as the European, International and American epilepsy congresses, the project Coordinators recognised that an event which bringing together these specific projects would be unique, focusing on the achievements, the discoveries made and the breakthroughs still to come. It would also provide a forum to identify

remaining roadblocks and challenges to progress and discuss ways to secure research funding through future European and other programmes.

The epiXchange conference was held on May 23rd 2018 in Brussels, Belgium. Altogether 170 investigators from 18 European countries and 5 non-EU countries met with several stakeholders, representatives of the European Commission, patient organisations, non-profit research institutes and other key European and international groups, to present the results from their ongoing research. The conference was organised into a series of thematic sessions, chaired by clinicians and scientists from the different projects. The thematic areas were based on shared research priorities that were specifically addressed by the EU call: biomarkers; genetics; therapeutics; co-morbidities; and databases & biobanks.

The epiXchange meeting clearly captured the scale of progress made by the different consortia. This included traditional scientific outputs such as new knowledge about the causes and treatment of epilepsy, novel genetic causes of epilepsy, diagnostic biomarkers and precision medicine approaches, transformative new in vitro and in vivo models (e.g., induced pluripotent stem cells and use of model organisms such as zebrafish), structural and functional brain imaging and new therapeutic targets moving into preclinical development. All these results and outputs were published (or in submission) in leading peer-reviewed journals (**Table 1**). The meeting also highlighted other important achievements including the infrastructure and expertise developed to date, refinements of molecular and other biomedical research technologies, establishing best research practices, expanding bio-resources such as DNA and tissue banks, creating new databases that can transform the power of pathway discovery, and significantly for future progress, the development of new inter-sectorial partnerships. There was specific attention on how these projects have helped support, and have been supported by, small and medium enterprises in Europe, a key impact metric for the FP7 projects. Each project clearly benefitted from this innovative research approach and recognised the key role of industry in accelerating translation of basic science towards actual life-changing patient care and the resulting socio-economic contribution to Europe. A number of the industry-based researchers also presented at the meeting.

Finally, the meeting provided a forum to discuss the way forward for accelerating epilepsy research in Europe and beyond. EpiXchange was both a reflection on what was achieved and what was foreseen emerging in the near future. It was (it is) a means for reinforcing the existing collaborations between projects and creating new ones that will lay the foundations for success in delivering transformative research with direct impact for the citizens of Europe with epilepsy. More information about these various research projects, presentations and videos from the conference can be found at www.epixchange2018.eu.

Overview of projects and summary of projects' achievements

Through oral presentations and posters, project coordinators and presenters at epiXchange summarised key achievements. The main highlights of these achievements are included in **Table 1**. Details of each project can be found at their various hosting websites.

The **DESIRE** project (http://www.epilepsydesireproject.eu/) focussed on uncovering developmental brain processes to understand the genetic mechanisms underlying epileptogenic developmental disorders (i.e. early onset epilepsies in children). The research in DESIRE comprised work packages focused on discovering mutations in such patients and understanding the mechanisms of disease. This research has added value through the development of novel diagnostics and treatment strategies where use of gene therapy and reprogramming of somatic cells into neurons was also being pursued, along with new recording and analysis tools for diagnosing epileptiform activity in patients. Another function of the project has been to continue to expand the collection of pathological brain specimens in the European Brain Bank. The project has also resulted in the launch of a multi-centre longitudinal study of Dravet Syndrome (DS) patients.

The **EpimiRNA** project (https://www.epimirna.eu/) focussed on molecules called microRNAs (miRNAs) which serve important functions in controlling gene expression. EpimiRNA's research has focused on cataloguing which miRNAs are active in animal models of epilepsy and in brain tissue from adult epilepsy patients. The project also focussed on identifying miRNAs in biofluids, such as diagnostic biomarkers, on solving the mechanisms by which miRNAs affect brain excitability, the use

of systems biology to predict miRNA-target interactions, looking for possible genetic variation in miRNAs or their targets in epilepsy patients and exploring the potential of miRNA-based treatments. The project also included clinical studies on brain stimulation and recording technologies.

EPISTOP (http://www.epistop.eu/) was the first human study aimed to prospectively identify biomarkers for epileptogenesis , beginning from its latent phase, through active epilepsy and chronic disease. (TSC). In the project risk factors and biomarkers of epilepsy development were identified in newborns and infants with tuberous sclerosis complex (TSC). A key part of the study was determining whether early preventive treatment can block or delay the onset of epilepsy and co-morbidities such as cognitive and language developmental problems. Research within the project also included investigations into the cell and molecular mechanisms by which genetic mutations cause TSC.

EpiTarget (https://www.epitarget.eu/) focused on identifying biomarkers and multiple basic mechanisms for epileptogenesis in adults, and translating these findings to the clinic by validating the biomarkers in human samples. The project focused on testing combinatorial therapeutic approaches such as combining anti-oxidant or anti-inflammatory treatments in pre-clinical models. Common data elements (CDEs) were devised to enable harmonisation of procedures between laboratories in preclinical trials. The biomarker research included identification of proteins and RNAs in biofluids as well as using imaging techniques. Finally, the project explored gene therapy approaches and advanced drug delivery tools.

In addition to the four main projects, epiXchange featured presentations from three other projects. The FP7 **EpiPGX** project (https://www.epipgx.eu/) aimed to identify genome-based biomarkers for use in clinical practice to personalise treatment of epilepsy, by stratifying patients for clinical trials, preventing relapse and reducing adverse drug reactions. **EpiXchange** (www.epixchange.eu) was an FP7-IIAPP that explored innovative cell and gene therapies for the treatment of partial epilepsies. **EpiCARE** (https://epi-care.eu/) is a DG Sanco European Reference Network focusing on rare and complex epilepsies and aims to develop and deliver highly-specialised diagnostics and clinical care in order to improve interventions and outcome in individuals with rare and complex epilepsies initiated in 2017. EpiCARE is an extension of a previously DG Sanco funded

project, E-PILEPSY (2014-2016), a pilot network of cooperation in epilepsy surgery and refractory epilepsy that continues as the surgical therapeutic arm of EpiCARE..

Altogether, the presentations and additional achievements of the various projects clearly indicated the enormous advances in our understanding of the pathogenesis, diagnosis and treatment of epilepsy. Collectively, the projects have led to dozens of new discoveries about the cellular and molecular mechanisms of epilepsy and have driven the preclinical development of dozens of potential new therapies. A wide range of diagnostic approaches are, in fact, now at various stages of validation and entering clinical testing. The impacts from these projects can thus extend beyond the scientific advances and the new technologies to patient care, including improved diagnosis, better understanding of side effects, new community resources fostering increased competitiveness of small and medium enterprises in Europe. However, in order to ensure that these achievements are of concrete benefit and reach persons with epilepsy, further research and innovation efforts are still required by the community of researchers, clinicians and industry. This collaborative effort should also involve patients, as described in the next section.

epiXchange: recommendations for the future

In addition to the presentations of the achievements of the various projects to date, the epiXchange meeting provided a new forum for a discussion about the future of epilepsy research. A series of recommendations for future research emerged, aimed at ensuring a broadening of the knowledge base and achieving the necessary impact to improve the lives of persons with epilepsy or those at risk of developing epilepsy (**Figure 1**). Particular emphasis was also made on the engagement of persons with epilepsy and their caregivers in research and innovation actions.

Higher throughput translational models for diagnostics and therapy target development

It is recognised that seizures are a symptom of epilepsy. Preclinical seizure models have a strong track record of delivering benefits for persons with epilepsy, having been instrumental in the

discovery of many of the currently used, effective anti-seizure drugs[16]. Recognising that these traditional models have led to somewhat blinkered approaches, however, it has become clear that we need different types of animal models. New, higher throughput models and refined “old” models will help to discover disease-modifying therapies and to de-risk failure in translation. Thus, ongoing research is resulting in the identification of several genetic and acquired *in vitro* and *in vivo* animal models of human epilepsies, leading to a better understanding of the mechanisms of development of the various epilepsies and types of seizure generation. To make faster progress and increase the translational value of preclinical research, epiXchange investigators agreed that there is an urgent need for:

- The development of new, high throughput, translational *in vitro, in vivo, and in silico* **models** through the application of innovative technologies including advanced optogenetics and chemogenetics, genome modifications (CRISPR-based), human induced pluripotent stem cells and human brain organoids.
- The refinement of the existing epilepsy models and the development of innovative preclinical and clinical study designs. Closer matching of models to human clinical *phenotypes may* help ensure more direct and immediate clinical translatability.
- Further and expanded efforts to discover new targets through hypothesis-driven and un-biased “omic” approaches using animal and human models, in order to continue to elucidate the mechanisms of epileptogenesis.

These improvements in modelling will address the urgent need for an evidence-based disease classification, integrating clinical, pathological and genetic findings in order to reduce time to diagnosis and personalised treatment.

Target-led diagnostics discovery

The rate of misdiagnosis of epilepsy remains high[17]. This does not only relate to diagnosis of epilepsy itself, but also to the recognition of the epilepsy type and aetiology, processes that may take several years. Improved diagnostic techniques may be expensive, but a more accurate diagnosis would result in prompt application of correct treatments and, therefore, would be cost effective in the long term. Long delays in accurate diagnosis could be related to a poor knowledge of epilepsy among health care professionals, lack of accurate aetiology-based diagnosis, and incomplete understanding of disease mechanisms in a patient with a given epilepsy diagnosis. Thus, target-led diagnostics discoveries will lead to:

- An increase in the mechanism-led multimodal diagnostic and prognostic tools, including **genetic, epigenetic and proteomic tests** for anti-epileptogenesis and epilepsy, possibly at bedside.
- Identifying readily accessible and easy to evaluate and interpret **biomarkers** for diagnostics, prognostics, advancement and discovery of new and personally-adapted treatment regimes.
- A better understanding of the **mechanisms of SUDEP** (Sudden Unexplained Death in Epilepsy) and the development of innovative methods for its prevention.

These activities would result in a better overall stratification of people enrolling in preclinical and clinical trials. It would thus subsequently lead to greater predictive power of possible adverse events, comorbidities (such as attention deficit hyperactivity disorder or depression), and treatment efficacy towards (faster) individualised patient-centred care.

Digitalisation and new wearable materials in epilepsy diagnostics & monitoring

We still have limited understanding of the impact of everyday events and circumstances on seizure control in the epilepsies. Environmental and other influences undoubtedly exist, but are difficult to determine and measure, since digitization of this information on a widespread scale is still missing[18]. The development of digital datasets offers the possibility of progress in this key area through the:

- Development of digital information and communications technologies in **healthcare** such as e-health and m-health technologies for personalised **diagnosis** of epileptogenesis, as well as **monitoring** of progression and treatment of epilepsy.
- Development of innovative virtual ***storage solutions*** such as Mycloud®, possibly with other neurological diseases.

These would lead to a better understanding of the effect of environmental, lifestyle and other factors on epilepsy, and establish a Big Data discovery platform to improve the treatment and quality-of-life of persons with epilepsy and of their caregivers.

Personalised medicines and delivery systems

Despite the introduction of about 10 new anti-seizure treatments over the past 15 years, the proportion of people with poorly-controlled epilepsy has not decreased[19,20]. This could be related to an incomplete understanding of disease mechanisms in a patient with a given epilepsy diagnosis. Therefore, there is an urgent need for:

- The development of **evidence-based precision medicines**, integrating clinical,imaging, electrophysiologic, pathologic, and genetic findings for anti-epileptogenesis and epilepsy.
- The development and application of innovative **drugs**, **technologies** and preclinical and clinical **trial designs**.
- The development of new technologies for targeted **treatment delivery** such as gene therapy, oligonucleotides for targeting miRNA, siRNA, and small vesicle nanocarriers for proteins or peptides.
- Developing ***personalized*** **therapeutic monitoring** across genders and all ages, through the collection of information from the brain activity.

- The development of non-invasive applications for **multimodal monitoring of the efficacy** of treatments and epilepsy surgery.

This would lead to the development of novel personalised technologies for therapy and for monitoring the efficacy of therapy, drug delivery and compliance.

Epilepsy data ecosystem

The seven EU funded projects contributing to **epiXchange** have each individually generated a number of unique databanks, tissue biobanks and databases. The lack of harmonisation and standardisation in data collection and storage across the projects makes integration of these "banks" a complex process, hindering Big Data analysis and access from these key datasets. The new data protection GDPR regulations ensure that each person is now the steward of his/her own data. Innovative IT solutions provided by various SMEs or existing EU-funded data platforms can be used to address these requirements and will implement GDPR requirements about when and how consent is obtained and what data are stored. Therefore, epiXchange is proposing:

- The integration of these preclinical and clinical genetic, tissue, EEG, and neuroimaging banks into a virtual, controlled access **European Epilepsy Data Ecosystem**. This would lead to the development of ancillary informatics tools, Big Data analyses and mining, and mathematical modelling of large multimodal datasets. Standardisation in this field will greatly facilitate the guiding of breakthrough prospective diagnostic and therapy development studies.
- To ensure that this European Epilepsy Data Ecosystem can subsequently contribute to larger global existing databases such as the European Open Science Cloud, BBMRI (the European research infrastructure for biobanking), Human Brain Project and ELIXER (an intergovernmental organisation that brings together life science resources from across Europe). This would lead to a complete clinical-to-network-to-cell-to-molecule phenotyping of the epilepsies which takes into account life-style factors, demographics, genetics and other complex

data, and provides unprecedented opportunities for preclinical, clinical, technological, and societal research and innovation activities.

Comprehensive European and world-wide epilepsy care

In addition to addressing traditional scientific questions, the epiXchange meeting also recognised the opportunity to develop new infrastructural models which would lead to a comprehensive European and world-wide epilepsy care for all ages. There must be better access across all Europe and worldwide to diagnostic tools such as genetic testing, brain MRI, PET and MEG. While some of these issues are being addressed through the European Reference Network, EpiCARE, with an emphasis on utilisation of virtual technology, this is an area which is still very much in development, due to a lack of structured resources. We envisage:

- The creation of Virtual Epilepsy Centres would greatly help to alleviate some of these demands, and also address cognitive and behavioural comorbidities often seen in persons with epilepsy.
- The fostering of data-driven **regulatory requirements** and the harmonisation of health care regulations at a European level, providing secure patient management platforms and financial support for holistic care.

Integration to society and regulatory space

The enormous medical, economic and social burden of epilepsy can only be addressed through the co-ordination and integration of research among private and public partnerships. There should be a multi-stakeholder dialogue for priority setting in epilepsy research in order to define the goals/aims/opportunities for a leverage-synergy-maximal impact. This would allow patient/family participation from the outset of the mission, and would ensure that the results really address the needs of the epilepsy community. This can be achieved through multiple actions:

- **Persons with epilepsy** should have a **key role** to play in the drug-discovery process, the development of new devices, the assessment of new neurosurgical techniques and the planning of clinical trial designs. They also have a key role to play in the application of the research findings.
- The high incidence of epilepsy as a co-morbidity in various brain diseases, such as traumatic brain injury, stroke, and Alzheimer's disease, can address some of the crisis the pharmaceutical industry is presently facing, since this mission would be a unique opportunity to join forces **across various research and patient communities** in order to implement joint research initiatives.
- **Health care providers and policy makers** should also take part in the selection process of future research directions. They are key enablers, facilitating the provision of initiatives such as starter grants for SMEs and the funding of clinical trials. Health Insurance providers can be involved in the development of new models on the best and sustainable use of limited resources. This is an area which is still very much underexploited.
- Public **educational programmes** on epilepsy for patients, different sectors of society and for all stakeholders should be developed.
- **Supporting actions to facilitate and maintain interactions** between various research initiatives and between different stakeholders, e.g. through the organisation of joint events and workshops, ongoing educational activities for early stage researchers in epilepsy and the development of collaborative short- and long-term research strategies, should be established, also with the contribution of patients.
- A global **initiative for independent living** should be undertaken in a world-wide effort to reduce stigma, using validated tools and indicators, which can thus provide clear outcome measures and address discrimination.

Engagement of actors in the cross-disciplinary epilepsy mission across multiple sectors of society

The development of innovative diagnostic tools and treatments, as described above, requires not only trained and experienced clinicians, but also experts in genetics, cell biology, chemistry,

pharmacology, electrophysiology, imaging, mathematics, computer sciences, artificial intelligence, engineering, nanotechnologies, robotics, personalised drug design, and surgery. In addition to the regulatory implications of such research, the implementation of innovations furthermore mandates an entrepreneurial spirit, the involvement of (patent) lawyers, financial experts and product designers. These various actors must align and synergise cross-disciplinary research at all levels of the innovation chain for the discovery of novel diagnostic tools and therapies. This is essential if new treatments to address unmet needs are to reach the market. There are also unique opportunities for industry to leverage targets and assets which were developed for other disease areas.

In addition, it is key to recall that epilepsy can start at any age and is often a life-long condition. It affects various aspects of life, from education to employment, creating problems not only just for the person with epilepsy, but also for caregivers. These, and the wider lay community, need to be informed and educated about the condition in order to prevent misperceptions, discrimination, stigma, and bring persons with epilepsy out of the shadows. These educational programs should be conjointly designed by various actors, including persons with epilepsy themselves as well as professionals from the medical, educational and public-relation spheres.

The building and financing of comprehensive and safe epilepsy care requires the interaction of different actors: from the patient to the researcher, from the regulatory to policy makers in different sectors of the society (educational, health care, legislative). Moreover, it requires understanding of societal changes, which are leading to the greater expectation by patients for the highest possible level of epilepsy care, across borders with Europe-wide access.

Conclusions

epiXchange clearly showed that there remains an urgent need to unravel the basic molecular and cellular mechanisms of the epilepsies and integrate this information with data from population and patient cohorts. This research must continue in parallel with translational approaches in order to drive innovative solutions for therapy. The meeting acknowledged the important role of other EU funded epilepsy research projects such as E-pilepsy and ESBACE, and the two early stage

researcher training networks ECMED and EUGliaPhD in the debate. The epiXchange conference has shown how such an integrated approach can maximise the outputs and speed up the innovation process. This can be achieved through the:

- **sharing** of technologies, concepts, novel mechanisms, biomarkers and therapies;
- **sharing of common infrastructures** (e.g., Epilepsy Data Ecosystem) in a FAIR (fairness and accuracy in reporting) data management manner;
- identification of synergies with **other brain disease-**oriented programmes, where epilepsy can occur as a comorbidity, such as traumatic brain injury;
- identification of synergies in different projects to **engage patients** and caregivers into the digital development and the design of applications for R&I activities in diagnostics and monitoring, and optimizing clinical study designs;
- providing **digital applications and innovative holistic epilepsy care** models for the implementation of affordable comprehensive care.

Coordination of an open access Epilepsy Data Ecosystem on a global level would also greatly increase the impact of efforts both within and outside Europe, and provide unprecedented opportunities for international co-operation. Only such a cohesive framework of knowledge acquisition and sharing with regulatory, policy, infrastructural and other supportive activities can lead to tangible innovative results within the mandate of the timeframe indicated. Facilitating synergies between existing European and international research infrastructures and consortia will leverage European research in this area. This would thus ensure a global role for EU epilepsy research in the worldwide research arena by 2030. In addition, these solutions will have a much wider global impact since they can also be used to address the unmet needs of other neurological conditions.

Therefore, the epiXchange meeting recommended the following immediate lines of action:

- Providing continuity in resources needed for the most promising innovations so as to ensure their efficient development from discovery to market and patient care.
- Supporting and aligning national strategies (e.g., exit funding) to further develop the research and innovation initiated by the Horizon Europe funding programme.
- Creating funding instruments which will ensure the continuation of the most successful projects and/or their confluence into other neuroscience projects/SMEs with potential to expand the impact of innovation.
- Synergise research funding activities in Europe with global initiatives to facilitate international collaboration and thus maximal impact of its research outputs.

This message will be all the more powerful if the whole epilepsy community works beyond our traditional remits in clinics, labs and support organizations, so as to engage those key players who are in a position to provide financial support and investment in research. All this can only be achieved if we remain bold and inspirational with a wide societal relevance, yet, at the same time, focussing on the wellbeing of persons with epilepsy.

Disclosure of Conflicts of Interest

JHC has been an investigator in clinical trials sponsored by GW Pharma, Zogenix, Vitaflo, Takeda and Marinius. She has participated in advisory boards for GW Pharma, Zogenix and Nutricia. She has been a speaker in events sponsored by GW Pharma, Zogenix, and Nutricia. All renumeration has been paid to her department. DCH holds US patent No. US 9,803,200 B2 “Inhibition of microRNA-134 for the treatment of seizure-related disorders and neurologic injuries”. DCH received funding for research described in the review article (European Union’s FP7 (602130)). He was co-organiser of the EpiXchange conference. AP received funding for research described in the review article (European Union’s FP7 (602102)). SS is the Chair of the Epilepsy Advisory Group of the Association of British Neurologists, UK and Lead of the Clinical Genetics Testing Task Force

of the International League Against Epilepsy. JM is Member of the Epilepsy Advocacy Europe and Member of the International Bureau for Epilepsy, International League against Epilepsy.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affim that this report is consistent with those guidelines

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Legend to Figure

Figure 1. “Solving the Epilepsies” – better diagnosis, treatments and end of stigma is the epiXchange-proposed Epilepsy mission for the 9th Framework Programme Horizon Europe. The goal will be to reduce the time to the correct and accurate diagnosis to less than 1 year by 2025, to present the first disease-modifying treatment in clinic by 2030, to have 80% of persons with epilepsy seizure free by 2030, to have equal quality of life for persons with epilepsy by 2030, and stop the epilepsy-related stigma by 2028. In order to achieve the goals of the Epilepsy Mission, there is a need to facilitate the dialogue between patients/families - clinicians - researchers – health care providers – educators – pharma. In parallel, to engage stakeholders in various sectors of society to interdisciplinary actions, including medical and information technology (IT) or technology sectors; small and medium-sized enterprises (SMEs), multinational enterprises (MNEs), and industry; designer sector for consumer goods and medical devices. The research and innovation projects are summarised in blue circles and described in detail in the text.