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Gene-Tailored Treatments for Brain Disorders: Challenges and Opportunities

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Abstract: Brain disorders pose major challenges to medicine and treatment innovation. This is because their spectrum spans inflammatory, degenerative, traumatic/ischaemic, and neoplastic disease processes with a complex and often ill- understood aetiology. An improved genetic and genomic understanding of specific disease pathways offers new approaches to these challenges, but at present it is in its infancy. Here, we review different aspects of the challenges facing neuromedicine, give examples of where there are advances, and highlight challenges to be overcome. We see that some disorders such as Huntington's disease are the product of single gene mutations, whose discovery has been leading to the development of new targeted interventions. In the field of neurosurgery, the identification of a number of mutations allows an elaborated genetic analysis of brain tumours and opens the door to individualised therapies. Psychiatric disorders remain the area where progress is slow. Genetic analyses show that for major common disorders such as schizophrenia and depression there are no single gene alterations which offer options for targeted therapy development. However, new approaches are being developed to leverage genetic information to predict patients' responses to treatment. These recent developments hold promise for early diagnosis, follow-up with personalised treatments with adjusted therapeutic doses, predictable responses, reduced adverse drug reactions, and personal health planning. The scenario is promising but calls for increased support for curiosity-driven research into the mechanisms of normal brain functioning as well as challenging adaptations of health care and research infrastructures, encompassing legal frameworks for analysing large amounts of personal data, a flexible regulatory framework for correlating big data analyses in cooperative networks between academia and the drug development industry, and finally new strategies for brain banking in order to increase access to brain tissue samples. To make personalised medicine for brain disorders a reality, a joint effort between all relevant stakeholders - among which patients and patient organisations should play an important role - is required.

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we advance the understanding of the healthy and diseased brain
by bringing together Science & Society.

GENE TAILORED TREATMENTS FOR BRAIN DISORDERS

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Abstract

Brain disorders offer major challenges to medicine and to treatment innovation. This is because of their spectrum across inflammatory, degenerative, traumatic/ischemic and neoplastic nature and complex and often ill-understood aetiology. Genetic and genomic dissection offers new approaches to these challenges but one which is in its infancy at present. Here we review different aspects of the challenges facing neuro-medicine and give examples of where there are advances, as well as highlighting challenges to be overcome.

We see that some disorders such as Huntington's disease (HD) are the product of single gene mutations whose discovery is leading to the development of new-targeted interventions. In the field of neurosurgery, the identification of a number of mutations allows an elaborated genetic analysis of brain tumours and opens the door for individualized therapies. Psychiatric disorders remain the area where progress are left behind. Genetic analysis show that for major common disorders such as schizophrenia and depression there are no single gene alterations which offer options for targeted therapy development. However, new approaches are being developed to leverage genetic information to predict patient's response to treatment.

These recent developments hold promise for early diagnosis, follow-up by personalized treatments with adjusted therapeutic doses, predictable responses, reduced adverse drug reactions, and personal health planning. The scenario is promising but calls for challenging adaptations of health care and research infrastructures, encompassing legal frameworks for analysing large amounts of personal data, a flexible regulatory framework to correlate big data analyses in co-operative frameworks between academia and drug developing industry and finally new strategies for brain banking in order to increase the access to brain tissue.
To make personalised medicine for brain disorders a reality, a joint effort of all relevant stakeholders where patient and patient organizations should play an important role, is required.

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Introduction

Brain disorders comprise a variety of complex diseases in the nervous system, which include psychiatric, neurological and neurosurgical conditions. As whole, brain disorders represent one of the greatest threats to public health [1–3]. Across Europe, millions of people of all ages struggle with brain disorders. These are often long-term conditions, which severely affect the quality of life and are frequently associated with a considerable disability and sometimes a reduced life expectancy. As a result, they have an enormous impact on patients and their families and, more broadly, on the European economy. In Europe, the total annual cost of brain disorders was estimated at €798 billion in 2010, with an average cost per inhabitant of €5.550 [4]. As the population ages, the incidence of brain disorders increases even more and, therefore, the broad impact of brain disorders in the future is likely to be greater with important implications for the European economic growth.

Because of their wide range, complex and often ill-understood aetiology, brain disorders are major challenges to medicine and treatment innovation. It is now clear that brain disorders have a strong genetic component, which confers susceptibility or resistance, and influences severity and progression of the disease. The complexity of this genetic component can vary greatly across brain disorders. While some brain disorders are monogenic meaning that they result from mutations in one single gene, the prevalence of polygenic disorders resulting from the interplay of multiple genes and environmental factors is much higher. However, the distinction between these two extreme groups can be imprecise since even in the case of monogenic brain disorders co-operating genetic or epigenetic factors can alter several aspects of the disease such as onset, evolution and response to treatment [5]. In the recent years, the advent of the new genomic technologies offers the possibility to dissect the genetic or epigenetic components of brain disorders and opening the door to personalized medicine. The effective application of genomic findings to clinical practice holds the promise of determining the predisposition to disease and~~/or deliver~~

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~~The challenge to apply correctly genomic findings to clinical practice holds the promise of determining the predisposition to disease~~, to deliver timely targeted prevention and to tailor the right therapeutic strategy for the right patient at the right time. Several health care strategies integrate genomic information in the clinical research and practise as marker for diagnosis, prognosis and prevention, as well as targets for treatment [6]. In particular, the identification of genetic markers associated with disease, allows accurate diagnosis, prognosis and correlation to follow-up of the disease. Furthermore, it serves also as basis for the design of preventive strategies that minimize risk for developing the disease and of therapeutic approaches according to a person's genetic makeup. Finally, the analysis of genomic information by uncovering the biological mechanisms that causes the disease can influence the approach of developing new drugs. Thus, a genome-based personalised medicine approach should play an important role in promoting health and combating brain disorders by completely shifting the therapeutic paradigm from "one fits all patients" and "trial-and-error" prescription, to a personalized concept of treatment tailored to the specific genetic signature of the patient, "gene-tailored treatment". Potentially, this should lead to more

powered clinical trials, which are able to detect expected subgroup efficacies in new drugs, rather than being discarded as "ineffective for all".
While recent advances and issues related to personalised medicine for brain disorders are more extensively reviewed elsewhere [7–12], in this article we have chosen few examples as paradigm for neurological, neurosurgical and psychiatric conditions which emphasise the major scientific challenges facing the discipline. In addition, we also discussed on those "brain specific" practical and ethical challenges, which relate to genetic/epigenetic disease assessment, brain banking and patient involvement.

Neurological disorders: Huntington's disease

Huntington's disease (HD) is characterized by a complex phenotype including motor, cognitive and psychiatric symptoms and signs starting at different ages and steadily worsening until death after around 15-25 years[13,14].. The cause is a dynamic mutation with expansion of a CAG repeat in the Huntingtin (HTT) gene[15], which is transcribed into an abnormal protein with an elongated polyglutamine tract. Polyglutamine HTT accumulates in the affected brain [16] and protein function is changed in multifaceted ways related to the numerous roles of the normal protein[17]. One way to handle with the disturbed protein is to silence HTT gene transcription, which leads to a decrease in abnormal protein content.

Several strategies aimed at decreasing expression of the abnormal elongated allele HTT gene are the process of development in animal models with the hope that lower levels of the abnormal protein would rescue disturbed molecular pathways and decrease neuronal cell death. They include antisense oligonucleotides (ASO), interfering RNA molecules, and proteins modulating the transcription process. Decrease in HTT expression improves the symptoms and prolongs survival in HD mouse models[18,19]. Specifically HTT mRNA targeted ASO[20], induce its degradation by RNases and can be modified to be resistant to exonuclease cleavage improving their stability. After injection in the brain of HD animal models, HTT mRNA levels in the striatum are lowered without morphological damage[21]. A safety trial with intrathecally injected ASOs is underway (ClinicalTrials.gov identifier: NCT02519036). Small interfering RNA (siRNA) or micro interfering RNA (miRNA) bind to the abnormal HTT transcript, leading to its degradation by the RNA induced silencing complex with a consecutive decrease in mutated protein and this approach has been found to improve phenotype in animal models[22]. The molecule may be packaged into modified adenoviruses acting as a vector, and stereotactic injections of such constructs have been found to be safe in primates for 6 months[23]. This treatment is followed by a significant decrease in HTT mRNA as compared with controls.

Such a precision treatment performed in a specific way according to gene mutation may further be personalized in order to target only the mutant gene transcript leaving the normal one untouched. This would allow expression of the normal protein with conservation of its multifaceted functions and a suggested protective function in the HD brain affected. Instead of a general silencing, such a strategy would use DNA or RNA specifically recognizing the elongated allele only in a selective (allele-specific) way, leading to the degradation of the

abnormal, elongated mRNA with a consecutive decrease in abnormal protein content. Such selectivity may be achieved by targeting single nucleotide polymorphisms found only on the abnormal allele, on top of targeting the expanded CAG repeat part. siRNA may be designed to specifically target the mutant allele in a selective way, with conservation of a normal wild type HTT expression[24]. Patients with elongated CAG repeats, a status which will eventually lead to full penetrance of the disorder, may be selected to the target therapy according to the presence of specific single nucleotides on the allele with elongated CAG repeats[25]. Only patients who are homozygous at targeted single nucleotide sequence would not be candidate for such a personalized therapy.

Since the single cause of HD is precisely known, and can be confirmed long before onset, this disorder may be considered as a paradigm for disease modifying treatment of other monogenic neurodegenerative disorders. Furthermore, there is a long presymptomatic phase, during which opportunities for a disease-modifying treatment might be tested and applied.

Neurosurgical Disorders: Brain tumours

Primary or intrinsic brain tumours, - glioma - arisinggliomas - arise from glia, are confined to the brain and carry an extremely poor prognosis which is determined by their diffusely infiltrative nature involving the whole brain precluding curative resection and precluding access to most anti-tumour drugs. The specific neurobiology of these tumours and brain physiology as such add significantly to the underlying oncological challenge. Nevertheless, apart from the underlying issue of drug delivery to the brain, a more elaborate genetic analysis of brain tumours allowed for an emerging thinking along the concepts of individualizing therapies also for brain tumour patients [26,27].

Search for gene mutations specific to gliomas has begun already at the start of cancer genomics with at first oncogenes and then tumours suppressor genes being found[28,29]. More than 20 years ago it turned out that chromosomal 1p/19q deletions described very well oligodendroglial tumours and allow for therapeutic decisions which have been proven valid in clinical trials with more than a decade of follow up [30]. Many more specific gene mutations were found thereafter with the EGF-receptor mutations[31] and IDH1/IDH2 mutations[32] being the most recent of these mutations. In addition epigenetic modifications as in the MGMT gene have shown to be relevant to the response to chemotherapeutics[33].

Very few of these molecular genetic discoveries have led to therapeutic opportunities, mostly because of lack of effective substances able to penetrate into the brain. Nevertheless, some current therapeutic developments are based on such genetic insights, such as the development of a peptide vaccination against a unique epitope of the mutated EGF-receptor, which led to a phase III trial in glioblastoma awaiting results in 2016 and likewise there is an early clinical trial effort with vaccination against a mutant IDH-1 peptide sequence. The determination of MGMT gene methylation has led to stratification of clinical trials and even categorical adaptation of temozolomide chemotherapy in elderly glioblastoma patients, a first step to personalized medicine[34].

Meanwhile several large consortia efforts have arrived at the characterization of gene expression subtypes of glioblastoma and the dynamics of shifting patterns and their relation to therapy and prognosis but have not yet translated into clinical practice. This extends also into the less aggressive earlier "low grade" lesions, which may offer an even more beneficial opportunity for therapeutic intervention since the disease has not progressed as far [35]. It is becoming evident, that there is more knowledge available than adequately analysed for its clinical implications [36] and that large databases and appropriate bioinformatics are needed to correlate outcomes and treatment efficacies with gene profiles. Most advanced in that respect, - also for the availability of targeted drugs is the pediatric neuro-oncology with the medulloblastoma field [37–39]. With effective targeted agents for distinct genetic subgroups, survival and prognosis has been dramatically diversified/personalized.

Only of late, with improving methods of detecting gene mutations as such or specific molecules derived thereof in the circulation, biomarkers have been defined [40,41] which need to be taken into the rationale for clinical trials design upfront to account for subgroup efficacy. Condensing all genetic knowledge on intrinsic brain tumours, there are a sufficient number of genetic alterations known, which would allow a gene tailored personalized treatment.

Psychiatry Disorders

Psychiatric disorders remain the area where progress is slower. One of the obvious applications for the increased genetic understanding of all the main psychiatric disorders is leveraging this knowledge to understand better a patient's likely response to treatment. However, due to the complexity of this group of diseases, success has been limited using conventional methodologies, where only small pathways around specific target genes are investigated. It is likely that even though there is a genetic contribution to psychiatric conditions, no obvious simple link will be reported between an individual gene and its polymorphisms or changes in gene expression, and treatment response. This may not be surprising in light of the complex genetic architecture of these conditions as well as the multitude of changes at the gene expression and protein level. Consequently, complementary routes addressing the question of individualizing a patient's treatment need to be considered in addition to the conventional approach. An alternative approach is to base the search on the whole genome, thereby taking advantage of the ability to make multiple tests during the search for an association. The benefit of such an approach is to allow for the additive effective of what may be individually weak signals. This seams a reasonable approach in light of what is now known about the genomic structure of for example schizophrenia which is highly heritable, but which is a polygenic burden primarily arising from rare, disruptive mutations distributed across many genes [42].

One clear lesson from the studies on genetic risk association studies has been the need to generate sufficient sample sizes to be in a position to identify significant associations. To explore the question of treatment response is also likely to require relatively large sample sizes. This has proved possible in the search for genetic variants associated with response to lithium treatment in bipolar disorder [43]. Lithium response in 2563 patients was collected

and tested for genomic association, and one locus was identified which conferred in an independent test a significantly lower rate of relapse. If this result can be confirmed the locus would represent a novel genetic biomarker for lithium response, but its relatively low frequency within the population limits its direct clinical importance. It may still prove clinically relevant if further such loci could be identified and combined in an informative manner.

Another source of potential variability in response to antipsychotic response has been reported to be associated with epigenetic changes in mGLU2 promoter activity as a potential consequence of long term treatment. Similarly, an investigation into the potential utility of DNA methylation changes in IL11 in predicting response to antidepressants in patients with Major Depressive Disorder (MDD) did show potential utility for this approach [44].

In view of the current progress that has been made and the clear scope for further improvement in the area of predicting treatment, response a number of suggestions can be made. Increase the power to detect signals through the increase of sample sizes. While is a challenge to collect large cohorts, there is a clear prospect for success based on the results achieved in the search for risk association signals [45]. For example, common polygenic variation was shown to account for at least one third of the total variation in schizophrenia risk, when 1 million SNPs are tested in more than 8,000 patients and 19,000 controls [42]. Another avenue to follow is to combine genomic datasets, that is combine genetic variation other types of –omic datasets e.g. DNA methylation status variation or proteomic data. This makes biological sense since there are many inputs into response beyond genetic. Bioinformatic techniques have been developed to allow the searching of these large datasets in an informed manner and which can uncover biologically meaningful relationships.

Another key aspect is the limited access to the brain and the need of approaches that allow to acquiring the information from the periphery. In this respect, a new opportunity to overcome the problem of tissue availability is given by the use of epigenetic markers, which while reflecting what is occurring in the brain are accessible through peripheral tissues like blood urine and saliva. Underlining the validity of such approach, the analysis of epigenetic markers from the blood of patients with MDD has recently led to the identification of a potential target for novel antidepressant treatments [31]. Likewise there has been some success in identifying blood-based biomarkers which may predict schizophrenia prior to disease onset [46]. or dysregulation in the brain in patients with autism spectrum disorder [47].

Another area that needs to be considered is the integration of comorbidities, such as suicide and suicidal behaviors. Genetic and epigenetic biomarkers are beginning to be uncovered, such as SKA2 which has been linked to suicidal behavior and anxiety and stress [48,49]. As well as being developed further for its own sake, an important question is if there is any interaction with comorbid conditions.

Overall, while important progresses have been made in beginning to build for individualized treatments for psychiatric disorders, at the same time major challenges remain along the path of moving treatments from the bench to clinical practice.

"Brain specific" Challenges for Personalized Medicine

The ultimate goal in personalized medicine for brain disorders is to improve current patient care and accelerate future drug therapies. We have discussed some of the recent developments in this discipline that hold promise for personalized treatments with early diagnosis, adjusted therapeutic doses, predictable responses, reduced adverse drug reactions, and personal health planning. The scenario is exciting, but at the same time, this new approach faces crucial scientific, policy and ethical issues that need to be addressed in order to translate responsibly the scientific discoveries into clinical applications for the benefit of the patients.

While many of those issues do not differ significantly between brain disorders and other therapeutic areas such as cancer, the limited access to the brain and the scarce availability of brain tissue is surely of utmost importance. By strictly speaking, brain tumours are part of the cancer field, and accordingly, the tiny advances made towards personalized medicine rely on the availability of tissue which has been easiest with leukemias which are consequently the most successfully treated oncological conditions. For many brain diseases, mostly degenerative or psychiatric, the acquisition of brain specimens is solely possible through brain banking once patients have succumbed to their disease.

Thus, the access to human brain tissue is crucial to progress further our knowledge on the associations between particular genes and brain disorders, which is paramount to develop personalised therapies. Brain banks have been indispensable for the understanding of the pathology of many brain disorders, including Alzheimer's and Parkinson's [50] and they remains a powerful resource for brain research. However, brain banking faces a set of challenges that hampers the advance in this area. Brain banks are challenged with a decline in the clinical autopsy rate and scarcity of brain donors. That is because the current legal regulations pose obstacles to brain autopsies and many clinicians have lost clinical interest for brain autopsy or are reluctant to talk about post-mortem organ donation with their patients and relatives. To overcome this problem, donor programmes may be particularly effective to raise awareness among the public and to foster a dialogue with patients leading to an increase in autopsies and brain donations. The decrease in autopsy rates and in brain donations necessitates collaboration across national and state borders with establishment of brain network such as BrainNet Europe (http://www.brainnet-europe.org). This allows access to larger numbers of shared control cases and brains from patients with brain disorders. However, efficient networking requires the standardization of protocols, diagnostic procedures, and data acquisition so that samples and data are comparable. Although several recommendations for the operating of brain banks have been delivered, a globally accepted standard protocol or regulations for banking brain tissues are still missing.

From an ethical point of view, a premortem written informed consent for brain donation is the undisputable way to respect the autonomous decision of potential donors. However, when patients or other persons die without preparing a written informed consent, it is conventional in most countries to request from relatives (next of kin) the presumptive will for a clinical autopsy or brain donation of the deceased. Because ethical and legal conditions vary

between countries, and because many countries that lack legal regulations act by customary rights, a code of conduct that satisfies the requirements of all members must be established in brain bank networks that collect brains from multiple countries or states. Moreover, particular ethical considerations are required for banking the brains of patients with psychiatric disorders, especially of consent issues. In these cases, potential donors should be encouraged to take time to make the decision to ensure that people with fluctuating decision-making capacity are not acting on impulse.

Finally, brain banks have the possibility to obtain more support from the public if they would successfully convey the advantages of their work. This may be achieved by publicizing the notion that brain banking is indispensable for the progress of medicine, as well as making brain bank procedures more transparent to the public. This awareness campaign will have to address problems of autopsy acceptability, misconceptions regarding the research that can be performed with human post-mortem tissues, the need to obtain support for brain banks from government sources or the private sector, as well as the need to increase the number of brain tissue donors.

A large number of challenges must be addressed before personalised medicine for brain disorders can become a reality. Each of these challenges must be dealt with not by a single person or group, but by all of the stakeholders that are affected by it. In this respect, patients and patient organizations represent an important stakeholder in the whole process of Personalised Medicine. But to ensure an effective and responsible involvement of patients crucial information has to be provided. The most paramount being a clear, comprehensible explanation of the term Personalised Medicine, together with the possibilities, limitations, risks and consequences of this innovative approach.
Relating to the issue of brain banking, patient organisations and specific disease focus groups must realize that once correlations can be made between genomic information that allows disease sub-classification as for “dementia” biomarkers might be developed which may reflect the disease in any bio-specimen taken alive. If an epigenetic change or a mutation happens only in the diseased brain, an awareness must be built that the adequate “personalized therapeutic decision” can only be made tissue based, requiring a biopsy. With exosomal analysis technology there is a hope that many diseases can be defined in the future from “liquid biopsies” but until that becomes available, much correlative work has to be performed between patients, academic consortional genomics or even “..omics” and pharma industry to personalize medicine as much as possible.

National information points have to be implemented to assist patients in taking decision on their health plan or complaints. This will both protect the patients and preserve their patient rights, whilst also benefitting the progress made in the area. These information points should be organised at national level and monitored at the European level, making it possible for anyone to acquire the correct information in their own language but with trust, transparency and quality control present at all times. Relevant stakeholders should have access to appropriate information, to evaluate and enhance their techniques, care pathways, diagnostics, treatments, etc. which can then benefit all Member States, giving everyone access to the same personalised quality diagnosis and treatment. In the case of brain

disorders, areas such as medical devices [Deep Brain stimulation (DBS), Focused Ultrasound (FUS)], diagnostic imaging [MRI, fMRI, SPECT, PET, qEEG], should be included in neurological and psychiatric diagnostics and treatments.

Patient organisations, at European and national level, are a huge asset with their extensive patient expertise. Their close partnership with patients puts them in a unique position in the whole process. Patient organisations build on trust, making it possible to gather large amounts of disease-specific data, inform patients about their disease, treatment, everyday life and give patients a voice by representing them and providing patient-centred information to all stakeholders. When involving patient organisations at European and national (regional) level, funding and recognition should be considered to support them in this role. Properly informed patients and patient organisations are proven beneficial to researchers and other stakeholders and involving them at the beginning of the process saves precious time and money.

Conclusions

The rapid development of genome-based technologies holds promise of an effective application of genetic information to the development of individualized therapies for patient with brain conditions.

We are just at beginning of paradigm shift and a large number of scientific, policy and ethical challenges must be addressed before gene tailored treatments for brain disorders become a reality. Changing paradigm requires challenging adaptations of health care and research infrastructures, encompassing legal frameworks for analysing large amounts of personal data, a flexible regulatory framework to correlate big data analyses in co-operative frameworks between academia and drug developing industry and finally new strategies for brain banking in order to increase the access to brain tissue.

A joint effort of all relevant stakeholders is required to overcome these challenges and make gene tailored treatment for brain disorders a reality. In this respect, patients and patient organisations represent an important stakeholder and should be involved at an early stage in the process and resourced to do so. Raising awareness for brain disorders and Personalised Medicine can stimulate potential healthy participants and focuses on brain disorders in a wider sense. An open dialogue with all stakeholders coordinated at an EU-level needs to take place as we try to put a framework for Personalised Medicine in place which allows scope for ethical questions to be addressed.

References

1. WHO: Neurological disorders: a public health approach. Neurol Disord public Heal challenges 2006;41–176.
2. WHO regional office Europe: Access to new medicines in Europe : technical review of policy initiatives and opportunities for collaboration and research. 2015.
3. Global Burden of Neurological and Mental Disorders - BrainFacts.org [Internet] [cited 2016 Feb 22];Available from: http://www.brainfacts.org/policymakers/global-burden-of-neurological-and-mental-disorders/
4. Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al.: Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011 Oct;21:718–79.
5. Badano JL, Katsanis N: Beyond Mendel: an evolving view of human genetic disease transmission. Nat Rev Genet 2002;3:779–789.
6. Zhang L, Hong H: Genomic Discoveries and Personalized Medicine in Neurological Diseases. Pharmaceutics 2015;7:542–553.
7. Han G, Sun J, Wang J, Bai Z, Song F, Lei H: Genomics in Neurological Disorders. Genomics, Proteomics Bioinforma 2014;12:156–163.
8. Nicolaidis S: Personalized medicine in neurosurgery. Metabolism 2013;62:S45–S48.
9. Gutmann DH: Eliminating barriers to personalized medicine: Learning from neurofibromatosis type 1. Neurology 2014;83:463–471.
10. Evers K: Personalized medicine in psychiatry: Ethical challenges and opportunities. Dialogues Clin Neurosci 2009;11:427–434.
11. Ozomaro U, Wahlestedt C, Nemeroff CB: Personalized medicine in psychiatry: problems and promises. BMC Med 2013;11:132.
12. Robeson RH, Siegel AM, Dunckley T: Genomic and Proteomic Biomarker Discovery in Neurological Disease. [Internet]. . Biomark Insights 2008;3:73–86.
13. Kim SD, Fung VSC: An update on Huntington's disease: from the gene to the clinic. Curr Opin Neurol 2014 Aug;27:477–83.
14. Burgunder J-M: Recent advances in the management of choreas. Ther Adv Neurol Disord 2013 Mar;6:117–27.
15. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research

Group. [Internet]. . Cell 1993 Mar 26 [cited 2015 Sep 20];72:971–83.

16. Perevozchikova T, Stanley CB, McWilliams-Koeppen HP, Rowe EL, Berthelier V: Investigating the structural impact of the glutamine repeat in huntingtin assembly. Biophys J 2014 Jul 15;107:411–21.

17. Munoz-Sanjuan I, Bates GP: The importance of integrating basic and clinical research toward the development of new therapies for Huntington disease. J Clin Invest 2011 Feb;121:476–83.

18. Harper SQ, Staber PD, He X, Eliason SL, Martins IH, Mao Q, et al.: RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model. Proc Natl Acad Sci U S A 2005 Apr 19;102:5820–5.

19. Boudreau RL, McBride JL, Martins I, Shen S, Xing Y, Carter BJ, et al.: Nonallele-specific silencing of mutant and wild-type huntingtin demonstrates therapeutic efficacy in Huntington's disease mice. Mol Ther 2009 Jun;17:1053–63.

20. Sah DWY, Aronin N: Oligonucleotide therapeutic approaches for Huntington disease. J Clin Invest 2011 Feb;121:500–7.

21. Kordasiewicz HB, Stanek LM, Wancewicz E V, Mazur C, McAlonis MM, Pytel KA, et al.: Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis. Neuron 2012 Jun 21;74:1031–44.

22. DiFiglia M, Sena-Esteves M, Chase K, Sapp E, Pfister E, Sass M, et al.: Therapeutic silencing of mutant huntingtin with siRNA attenuates striatal and cortical neuropathology and behavioral deficits. Proc Natl Acad Sci U S A 2007 Oct 23;104:17204–9.

23. Grondin R, Kaytor MD, Ai Y, Nelson PT, Thakker DR, Heisel J, et al.: Six-month partial suppression of Huntingtin is well tolerated in the adult rhesus striatum. Brain 2012 Apr;135:1197–209.

24. Pfister EL, Kennington L, Straubhaar J, Wagh S, Liu W, DiFiglia M, et al.: Five siRNAs targeting three SNPs may provide therapy for three-quarters of Huntington's disease patients. Curr Biol 2009 May 12;19:774–8.

25. Kay C, Skotte NH, Southwell AL, Hayden MR: Personalized gene silencing therapeutics for Huntington disease. Clin Genet 2014 Jul;86:29–36.

26. Wick W, Hau P: [Personalized therapy for gliomas]. Nervenarzt 2015 Jun;86:692, 694–6, 698–700.

27. Weller M, Stupp R, Hegi M, Wick W: Individualized targeted therapy for glioblastoma: fact or fiction? Cancer J Jan;18:40–4.

28. Collins VP, James CD: Molecular genetics of primary intracranial tumors [Internet]. . Curr-Opin-Oncol 1990 Aug [cited 2016 Feb 8];2:666–8746.

29. Bigner SH, Vogelstein B: Cytogenetics and molecular genetics of malignant gliomas and medulloblastoma. [Internet]. . Brain Pathol 1990 Sep [cited 2016 Feb 8];1:12–8.

30. Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte H, et al.: Glioma Groups Based on 1p/19q, IDH, and TERT Promoter Mutations in Tumors. N Engl J Med 2015 Jun 25;372:2499–508.

31. Lorimer IA, Wikstrand CJ, Batra SK, Bigner DD, Pastan I: Immunotoxins that target an oncogenic mutant epidermal growth factor receptor expressed in human tumors. [Internet]. . Clin Cancer Res 1995 Aug [cited 2016 Feb 8];1:859–64.

32. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al.: IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009 Feb 19;360:765–73.

33. Hegi ME, Diserens A-C, Gorlia T, Hamou M-F, de Tribolet N, Weller M, et al.: MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005 Mar 10;352:997–1003.

34. Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon M, et al.: Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol 2012 Jul;13:707–15.

35. Brat DJ, Verhaak RGW, Aldape KD, Yung WKA, Salama SR, Cooper LAD, et al.: Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med 2015 Jun 10;372:2481–98.

36. Frattini V, Trifonov V, Chan JM, Castano A, Lia M, Abate F, et al.: The integrated landscape of driver genomic alterations in glioblastoma. Nat Genet 2013 Oct;45:1141–9.

37. Pfister SM, Korshunov A, Kool M, Hasselblatt M, Eberhart C, Taylor MD: Molecular diagnostics of CNS embryonal tumors. Acta Neuropathol 2010 Nov;120:553–66.

38. Northcott PA, Pfister SM, Jones DTW: Next-generation (epi)genetic drivers of childhood brain tumors and the outlook for targeted therapies. Lancet Oncol 2015 Jun;16:e293–302.

39. Northcott PA, Shih DJH, Peacock J, Garzia L, Morrissy AS, Zichner T, et al.: Subgroup-specific structural variation across 1,000 medulloblastoma genomes. Nature 2012 Aug 2;488:49–56.

40. Weller M, Wick W, Hegi ME, Stupp R, Tabatabai G: Should biomarkers be used to design personalized medicine for the treatment of glioblastoma? Future Oncol 2010

Sep;6:1407–14.

41. Westphal M, Lamszus K: Circulating biomarkers for gliomas. Nat Rev Neurol 2015 Oct;11:556–66.

42. Ripke S, Neale BM, Corvin A, Walters JTR, Farh K-H, Holmans PA, et al.: Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014 Jul 22;511:421–7.

43. Hou L, Heilbronner U, Degenhardt F, Adli M, Akiyama K, Akula N, et al.: Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study. Lancet (London, England) 2016 Jan 21; DOI: 10.1016/S0140-6736(16)00143-4

44. Powell TR, Smith RG, Hackinger S, Schalkwyk LC, Uher R, McGuffin P, et al.: DNA methylation in interleukin-11 predicts clinical response to antidepressants in GENDEP. Transl Psychiatry 2013 Jan;3:e300.

45. Takahashi S, Glatt SJ, Uchiyama M, Faraone S V, Tsuang MT: Meta-analysis of data from the Psychiatric Genomics Consortium and additional samples supports association of CACNA1C with risk for schizophrenia. Schizophr Res 2015 Oct;168:429–33.

46. Chan MK, Krebs M-O, Cox D, Guest PC, Yolken RH, Rahmoune H, et al.: Development of a blood-based molecular biomarker test for identification of schizophrenia before disease onset. Transl Psychiatry 2015 Jan;5:e601.

47. Diaz-Beltran L, Esteban FJ, Wall DP: A common molecular signature in ASD gene expression: following Root 66 to autism. Transl Psychiatry 2016 Jan;6:e705.

48. Guintivano J, Brown T, Newcomer A, Jones M, Cox O, Maher BS, et al.: Identification and replication of a combined epigenetic and genetic biomarker predicting suicide and suicidal behaviors. Am J Psychiatry 2014 Dec 1;171:1287–96.

49. Kaminsky Z, Wilcox HC, Eaton WW, Van Eck K, Kilaru V, Jovanovic T, et al.: Epigenetic and genetic variation at SKA2 predict suicidal behavior and post-traumatic stress disorder. Transl Psychiatry 2015 Jan;5:e627.

50. Wharton SB, Minett T, Drew D, Forster G, Matthews F, Brayne C, et al.: Epidemiological pathology of Tau in the ageing brain: application of staging for neuropil threads (BrainNet Europe protocol) to the MRC cognitive function and ageing brain study. Acta Neuropathol Commun 2016 Jan;4:11.

To improve the lives of those living with brain disorders,
we advance the understanding of the healthy and diseased brain
by bringing together Science & Society.

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