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Review

What is the role of next generation sequencing in status epilepticus?

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ABSTRACT

Status epilepticus is a life-threatening medical condition which requires immediate diagnosis and treatment. In children, it may be a recurrent manifestation in the context of heterogeneous severe developmental genetic encephalopathies, as well as the first neurological manifestation. Mutations in several genes have been consistently associated with status epilepticus despite none of them can be considered as 'pure' Mendelian status epilepticus gene. Most genetic conditions featuring status epilepticus can be assigned to specific phenotypic subgroups, including cortical dysplasias, inborn errors of metabolism, mitochondrial diseases, or epileptic encephalopathies and childhood syndromes. Next generation sequencing (NGS) has increased the number of genes associated with, and improved the turnaround time for molecular diagnosis of, status epilepticus, allowing more timely and rationale management choices for specific conditions. Next generation sequencing might become part of the standard of care in the near future for a large subset of patients with status epilepticus, especially in early life. At present, trios whole exome sequencing, with a first analysis of point and copy number variants of an *in silico* panel containing 'status epilepticus' genes might represent best choice as it would allow a rapid screening.
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1. Genetic causes of status epilepticus

Status epilepticus (SE) is an important target for genetic studies. The range of known causes of epilepsy which characteristically result in SE differs considerably from the range of genes causing genetic epilepsies in which SE is absent or an occasional feature. Status epilepticus can thus be considered not just only a more severe form of an ordinary seizure disorder but also one that may be favored by a particularly low seizure threshold, or involve different networks, pathways, biochemical or physiological processes, and mechanisms governing epileptogenesis and its self-sustaining mode [1].

Genetic mutations associated with SE have been recently listed in a comprehensive report [1] which reviewed all available literature where SE had been specifically mentioned as a consequence of the mutation in standard genetic databases, in case reports, or in review articles. Although 122 genes were identified whose mutations have been consistently associated with SE (i.e., in which SE is a characteristic, specific, or common feature), none of the genes could be considered as 'pure' Mendelian SE gene. Most genetic conditions featuring SE can be assigned to specific phenotypic subgroups, including cortical dysplasias, inborn errors of metabolism, mitochondrial diseases, or epileptic encephalopathies and childhood syndromes. Almost all the genes associated with SE are involved in infantile- or childhood-onset forms and are associated with intellectual disability. Only a minority of genes are associated with adult-onset status [1].

A relatively large number of genes cause epileptic encephalopathies or more specific epilepsy syndromes that are strongly associated with SE (Table 1). Epileptic encephalopathies are often accompanied by prolonged periods of electrographic SE in most individuals. However, the causative genes may also be associated with much less severe conditions, with clinical or electrographic signs of SE. For example, the *KCNQ2* gene was initially associated with benign familial neonatal seizures (BFNS) [5] and subsequently with a form of early-onset epileptic encephalopathy [6].

There are various genetic inborn errors of metabolism and other congenital conditions strongly associated with SE (Table 2). For some of these conditions, early diagnosis is of great importance as a specific treatment option is available. These treatable conditions include *GLUT1* deficiency; disorders of creatine and serine biosynthesis, pyridoxine metabolism, folate transport and metabolism, and nonketotic hyperglycinemia; molybdenum cofactor deficiency; Menkes disease; and Wilson disease.

Mitochondrial gene defects are frequently associated with SE (Table 3). Most patients harbor mutations in nuclear genes causing multiple respiratory chain defects as is observed in the disorders of

Abbreviations: BFNS, benign familial neonatal seizures; CGH, comparative genome hybridization; CNVs, copy number variants; HPO, human phenotype ontology; NGS, next generation sequencing; SE, status epilepticus; UTR, untranslated region; WES, whole exome sequencing; WGS, whole genome sequencing.

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Table 1
Epileptic encephalopathies and syndromes reported to be strongly associated with status epilepticus.

Disorder	Gene
Migrating malignant partial seizures of infancy	*KCNT1*
Ohtahara syndrome; west syndrome other undefined early onset EE	*STXBP1*
Neonatal onset EE	*KCNQ2*
Infantile onset EE	*SCN2A*[a]
Infantile onset EE	*SCN8A*[a]
Infantile onset EE	*CDKL5*
Dravet syndrome	*SCN1A*[a]
PCDH19-related disorder	*PCDH19*
Infantile onset EE	*CHD2*
Infantile onset EE	*DNM1*
Infantile onset EE	*GABRB3*

EE = epileptic encephalopathy.
[a] Early diagnosis in these conditions may entail treatment decisions that may reduce the number of episodes of status epilepticus [2–4].

mitochondrial Deoxyribonucleic acid (DNA) maintenance because of mutations in the *POLG*, *PEO1*, *RRM2B*, and *MTTL1* genes [7].

Some genes which, when mutated, cause cortical dysplasia and other structural brain abnormalities, are strongly associated with SE (Table 4). Status epilepticus can also be caused by other genetic mechanisms including chromosomal abnormalities, such as ring chromosome 20 [8], 4p deletion, 7q11.23 deletion, 1p36 deletion, and inv dup chromosome 15 [9–11] (Table 5).

2. Next generation sequencing

The advent of next generation sequencing (NGS) has considerably increased the number of genes associated with epilepsy and, as a consequence, of those associated with SE. Several genes have been identified not only through international collaborative efforts gathering large cohorts of sporadic patients but also through the study of small cohorts. The most successful NGS studies have been performed in sporadic patients with severe epilepsies (especially the early-onset epileptic encephalopathies) using a trio analysis consisting of whole genome sequencing (WGS) or whole exome sequencing (WES), sequencing of the proband, and healthy parents [12].

The scenario of genetic diagnostic workflow has significantly changed with the application of NGS, including WGS, WES, and gene panel sequencing, making it possible to simultaneously sequence a large number of genes and to obtain, in a short time, a molecular diagnosis in an increasing number of patients. Whole genome sequencing entails the sequencing of the entire genome with a uniform coverage. Whole genome sequencing has therefore a higher chance to detect structural rearrangements and copy number variants (CNVs). Whole exome sequencing is less complex and expensive than WGS since sequencing the coding regions only reduces wet-lab, computational, and data storage costs. Whole exome sequencing is not limited to selected genes, as for gene panels, but includes the coding of almost all known human genes (about 20.000). However, although a broader clinical use of WES would be desirable, there are yet limitations that hamper its use as a clinical tool in several healthcare settings [13,14]. The WGS approach is largely confined to the research field although it is being progressively considered as a diagnostic asset [15]. While WES is now used as a diagnostic tool in many centers [16–18], gene panel sequencing represents, at present, the most widely adopted method for the clinical diagnosis of genetic disorders, offering a quicker and cost effective approach to identify mutations. Indeed, several commercial companies have developed gene panels and offer them for molecular diagnosis [19].

Table 2
Genes causing inborn errors of metabolism and other congenital conditions reported to be strongly associated with status epilepticus.

Disorder	Gene
Pyridoxal-5′-phosphate dependent epilepsies[a]	*PNPO*
Pyridoxine-dependent epilepsy[a]	*ALDH7A1*
Hyperprolinemia type II[a]	*ALDH7A1*
Folinic acid responsive epilepsy[a]	*ALDH7A1*
Folate transporter deficiency[a]	*FOLR1*
Glucose transporter 1 deficiency[a]	*SLC2A1*
Congenital disorders of serine metabolism (phosphoserine aminotransferase deficiency)[a]	*PSAT1*, *SLC1A4*
Congenital disorders of glycosylation	*PIGA, ALG3, ALG1, RFT1*
Biotin thiamine disease[a]	*SLC19A3*
Nonketotic hyperglycinemia	*AMT*, *GLDC*, *GCSH*
Neuronal ceroid lipofuscinoses types 3 and 6	*CLN3*, *CLN6*
Ornithine transcarbamylase deficiency	*OTC*
Citrullinemia type 11	*SLC25A13*
Biotinidase deficiency[a]	*BTD*
Serine biosynthesis disorders[a]	*STK11*
Glutaric acidemia type I[a]	*ETFA*, *ETFB*, *ETFDH*
Creatine synthesis defects[a]	*CT1*, *GAMT*
Urea cycle disorders[a]	*PCK1*
Menkes disease	*ATP7A*
Molybdenum cofactor deficiency[a]	*MOCS1*

[a] Treatable.

Table 3
Mitochondrial defects strongly associated with status epilepticus.

Disorder	Gene
Mitochondrial disorder due to nuclear gene defects including Alpers syndrome, often manifesting as epilepsia partialis continua	*ADCK3*, *COX10*, *GTPBP3*, *PDHX*, *PDSS2*, *PEO1*, *POLG*, *RRM2B*, *SLC25A13*, *SLC25A22*
Disorders due to mitochondrial gene defects including MELAS and MERRF, often manifesting as epilepsia partialis continua	*MTCO1*, *MTND4*, *MTND4*, *MTTF*, *MTTK*, *MTTH*, *MTTL1*, *MTTS1*, *MTTS2*

MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF = myoclonic epilepsy associated with ragged-red fibers.

2.1. NGS panels

The composition of custom-designed gene panels is largely variable, both in the number of genes (from a dozen to several hundred) and in the choice of targeted genes, according to whether they have been developed to study more specific phenotypes or broader disease categories. Of note, large panels may comprise genes with highly disparate clinical presentations, and therefore be of use even in cohorts where phenotypic characterization is scanty, but would be similar in cost to, and not much different in turnaround times from, smaller panels. The main advantage of custom panels resides in the possibility of designing them to achieve complete control and the flexibility on the selection of both genes and regions of interest to be sequenced, such as coding sequences, untranslated regions (UTRs), promoter region, etc.

Prior to requesting a panel, a clinician should be aware of the panel's performance statistics so that this can be reviewed with the patient and family. In addition, many commercial panels will include NGS-based testing for exon-level deletions and duplications. However, CNVs detection is not feasible with all platforms and protocols, and the clinician should be aware of the benefits and weaknesses of the various methods. A positive correlation exists between the number of genes included in

Table 4
Genes causing cortical dysplasia and other cerebral structural abnormalities strongly associated with status epilepticus.

Disorder	Gene
Disorders associated with structural brain abnormalities including hemimegalencephaly, cortical dysplasia, tuberous sclerosis	*ADAR*, *AKT3*, *ARX*, *COL4A*, *FOXG1*, *mTOR*, *PNKP*, *QARS*, *SPTAN1*, *SRPX2*, *ST3GAL5*, *TBC1D24*, *TSC1*, *TSC2*, *GATOR1* complex genes

Table 5
Other genetic mechanisms associated with status epilepticus.

Ring chromosome 20
1p36 del syndrome
4p- syndrome
Angelmann syndrome
Inv dup chromosome 15

an NGS panel and its diagnostic yield. However, as the number of sequenced genes increases, that of the identified variants scales up too, resulting in higher complexity of both the bioinformatic filtering process and genotype–phenotype interpretation [20]. This increasingly laborious interpretation process may represent a major drawback when a specific result may influence treatment choices or carry prognostic implications, as it may be the case in some patients with SE.

Many targeted panels can provide 100% coverage of coding regions. If the nucleotides are not completely covered, the laboratory may Sanger "back-fill" the missing sequence to ensure full coverage. In other instances, the coverage may not be 100% (although usually quite close ≫97%), and the missing sequences cannot be interrogated. This may still be an acceptable approach in relation to the specific clinical queries and resources available. While some panels have a targeted set of genes that are enriched prior to sequencing, others may analyze only the genes of interest sequenced by exome sequencing, and the laboratory will analyze only the selected genes. This option might be particularly applicable to conditions with SE for example. While an exome may also have less than complete coverage, should the targeted genes be mutation-negative, there may be a benefit to reanalyze the entire exome on a research basis for novel gene discoveries [21]. A possible strategy is to perform WES followed by a flexible *in silico* gene-panel definition based on the human phenotype ontology terms (HPO terms) observed in the patients [22,23]. However, exome sequencing usually results in only 90–95% of the targeted exons having sufficient depth of coverage to accurately call variants [24]. A well-developed custom gene panel would offer a better coverage of the targeted genes of, or near to, 100%, and this outweighs, at present, WES potential benefits in a diagnostic setting [25]. The different coverage that a targeted panel or WES can provide should also be taken into account for management purposes. For example, a gene panel with a limited number of "actionable or treatable" genes (Table 2) covered at 100% might represent the first choice for critically ill patients manifesting severe and potentially progressive complex phenotypes, including SE, and requiring rapid decision-making or benefiting even indirectly from crucial management choices (Table 1). Should this panel fail to provide useful information, a larger panel, or a WES approach, would be the subsequent option.

There are some instances in which the patient's phenotype appears to be associated with a specific gene. For example, the major contribution of *SCN1A* to Dravet syndrome, and the syndrome's actual genetic homogeneity, should still suggest that in patients with a convincing phenotype, this gene be involved even when genetic testing proved negative, especially if it was performed some time ago. It is therefore likely that considering the improved yield of *SCN1A*-related diagnostic procedures, which have evolved from mutation screening methods to NGS [26], the contribution of genomic rearrangements [27], somatic mosaicism [28], and poison exon mutations [29], we are not far from detecting *SCN1A* abnormalities in all patients with the core Dravet syndrome phenotype. This end goal can only be achieved using a diagnostic approach suitable for revealing the molecular mechanisms mentioned above.

2.2. Whole exome sequencing and whole genome sequencing

The diagnostic yield of WES for suspected monogenic diseases ranges from 22 to 31% but depends on several factors including phenotype (with early age of onset, consanguinity, or recurrence in sibling considerably raising the rate of positive findings) and the sequencing strategy used (trios analysis for *de novo* mutations; quartets analysis for recessive or compound heterozygous conditions) [30]. In the epilepsies of suspected genetic origin, the yield of WES ranges from 17% to 72% [12].

The costs of WES and WGS continue to decrease, making access to these approaches available to a wider population. Studies on cost effectiveness of comparative genome hybridization (CGH)-array, WES versus panel testing, and single gene testing show that trio-WES has a higher diagnostic rate and is best performed early in the diagnostic odyssey [31,32].

In the near future, the routine use of WES would be expected to transition to the routine use of WGS. There are definite advantages to WGS, including CNVs detection, a more uniform coverage across the genome and, with advancing technologies, a deeper coverage to detect mosaicism.

Both WES and WGS have proven highly useful in the early diagnosis of severe infantile neurodevelopmental disorders. In particular, studies conducted by different groups in neonatal intensive care units in newborn infants with severe conditions, some of which featuring SE or severe seizures, have shown that rapid WES or WGS can provide a diagnosis for as many as half of acutely ill infants informing management and reducing costs in around 50% of those to whom a diagnosis is returned [33–37].

3. Conclusions

Considering how relevant health and cost issues implications are for early SE and how frequently genetic etiologies underlie it, it is to be expected that NGS methodologies will become part of the standard of care in the near future for this category of patients. The ideal would be to conduct a pilot study capable of producing an exact measure of the costs/benefit balance when SE is a main presenting manifestation and in relation to the specific NGS methodology used. Trios WES, with a first analysis of point and CNVs of an *in silico* panel containing the 'status epilepticus' genes indicated in Tables 1 to 4, represents, in our opinion, the best choice at present as it would allow a rapid screening of known genes. Subsequently, the analysis will be extended to genes not usually associated with SE, if necessary.

Conflict of Interest

RG, EP, CM and DM have no conflicts of interest related to the contents of this paper.

References

[1] Bhatnagar M, Shorvon S. Genetic mutations associated with status epilepticus. Epilepsy Behav 2015;49:104–10. https://doi.org/10.1016/j.yebeh.2015.04.013.
[2] Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. Lancet 2000;356:1638–42. https://doi.org/10.1016/S0140-6736(00)03157-3.
[3] Wolff M, Johannesen KM, Hedrich UBS, Masnada S, Rubboli G, Gardella E, et al. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. Brain 2017;140:1316–36. https://doi.org/10.1093/brain/awx054.
[4] Boerma RS, Braun KP, van den Broek MP, van Berkestijn FM, Swinkels ME, Hagebeuk EO, et al. Remarkable phenytoin sensitivity in 4 children with SCN8A-related epilepsy: a molecular neuropharmacological approach. Neurotherapeutics 2016;13:192–7. https://doi.org/10.1007/s13311-015-0372-8.
[5] Biervert C, Schroeder BC, Kubisch C, Berkovic SF, Propping P, Jentsch TJ, et al. A potassium channel mutation in neonatal human epilepsy. Science 1998;279:403–6. https://doi.org/10.1126/science.279.5349.403.
[6] Weckhuysen S, Ivanovic V, Hendrickx R, Van Coster R, Hjalgrim H, Møller RS, et al. Extending the KCNQ2 encephalopathy spectrum: clinical and neuroimaging findings in 17 patients. Neurology 2013;81:1697–703. https://doi.org/10.1212/01.wnl.0000435296.72400.a1.
[7] Bindoff LA. Mitochondrial function and pathology in status epilepticus. Epilepsia 2011;52(Suppl. 8):6–7. https://doi.org/10.1016/j.mito.2016.03.003.

[8] Vignoli A, Bisulli F, Darra F, Mastrangelo M, Barba C, Giordano L, et al. Epilepsy in ring chromosome 20 syndrome. Epilepsy Res 2016;128:83–93. https://doi.org/10.1016/j.eplepsyres.2016.10.004.
[9] Battaglia A, Filippi T, South ST, Carey JC. Spectrum of epilepsy and electroencephalogram patterns in Wolf-Hirschhorn syndrome: experience with 87 patients. Dev Med Child Neurol 2009;51:373–80. https://doi.org/10.1111/j.1469-8749.2008.03233.x.
[10] Kanabar G, Boyd S, Schugal A, Bhate S. Multiple causes of apnea in 1p36 deletion syndrome include seizures. Seizure 2012;21:402–6. https://doi.org/10.1016/j.seizure.2012.02.004.
[11] Verrotti A, Sertorio F, Matricardi S, Ferrara P, Striano P. Electroclinical features of epilepsy in patients with InvDup(15). Seizure 2017;47:87–91. https://doi.org/10.1016/j.seizure.2017.03.006.
[12] Mei D, Parrini E, Marini C, Guerrini R. The impact of next-generation sequencing on the diagnosis and treatment of epilepsy in paediatric patients. Mol Diagn Ther 2017;21:357–73. https://doi.org/10.1007/s40291-017-0257-0.
[13] Chakradhar S. Insurance companies are slow to cover next-generation sequencing. Nat Med 2015;21:204–5. https://doi.org/10.1038/nm0315-204.
[14] Deverka PA, Kaufman D, McGuire AL. Overcoming the reimbursement barriers for clinical sequencing. JAMA 2014;312:1857–8. https://doi.org/10.1001/jama.2014.14915.
[15] Belkadi A, Bolze A, Itan Y, Cobat A, Vincent QB, Antipenko A, et al. Whole-genome sequencing is more powerful than whole-exome sequencing for detecting exome variants. Proc Natl Acad Sci U S A 2015;112:5473–8. https://doi.org/10.1073/pnas.1418631112.
[16] Helbig KL, Farwell Hagman KD, Shinde DN, Mroske C, Powis Z, Li S, et al. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. Genet Med 2016;18:898–905. https://doi.org/10.1038/gim.2015.186.
[17] Dyment DA, Tétreault M, Beaulieu CL, Hartley T, Ferreira P, Chardon JW, et al. Whole-exome sequencing broadens the phenotypic spectrum of rare pediatric epilepsy: a retrospective study. Clin Genet 2015;88:34–40. https://doi.org/10.1111/cge.12464.
[18] Allen NM, Conroy J, Shahwan A, Lynch B, Correa RG, Pena SDJ, et al. Unexplained early onset epileptic encephalopathy: exome screening and phenotype expansion. Epilepsia 2016;57:e12–7. https://doi.org/10.1111/epi.13250.
[19] Chambers C, Jansen LA, Dhamija R. Review of commercially available epilepsy genetic panels. J Genet Couns 2016;25:213–7. https://doi.org/10.1007/s10897-015-9906-9.
[20] Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–23. https://doi.org/10.1038/gim.2015.30.
[21] Wenger AM, Guturu H, Bernstein JA, Bejerano G. Systematic reanalysis of clinical exome data yields additional diagnoses: implications for providers. Genet Med 2017;19:209–14. https://doi.org/10.1038/gim.2016.88.
[22] Köhler S, Vasilevsky NA, Engelstad M, Foster E, McMurry J, Aymé S, et al. The human phenotype ontology in 2017. Nucleic Acids Res 2017;45:D865–76. https://doi.org/10.1093/nar/gkw1039.
[23] Bone WP, Washington NL, Buske OJ, Adams DR, Davis J, Draper D, et al. Computational evaluation of exome sequence data using human and model organism phenotypes improves diagnostic efficiency. Genet Med 2016;18:608–17. https://doi.org/10.1038/gim.2015.137.
[24] O'Donnell-Luria AH, Miller DT. A clinician's perspective on clinical exome sequencing. Hum Genet 2016;135:643–54. https://doi.org/10.1007/s40291-017-0257-0.
[25] Trump N, McTague A, Brittain H, Papandreou A, Meyer E, Ngoh A, et al. Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis. J Med Genet 2016;53:310–7. https://doi.org/10.1136/jmedgenet-2015-103263.
[26] Djémié T, Weckhuysen S, von Spiczak S, Carvill GL, Jaehn J, Anttonen AK, et al. Pitfalls in genetic testing: the story of missed SCN1A mutations. Mol Genet Genomic Med 2016;4:457–64. https://doi.org/10.1002/mgg3.217.
[27] Marini C, Scheffer IE, Nabbout R, Mei D, Cox K, Dibbens LM, et al. SCN1A duplications and deletions detected in Dravet syndrome: implications for molecular diagnosis. Epilepsia 2009;50:1670–8. https://doi.org/10.1111/j.1528-1167.2009.02013.
[28] de Lange IM, Koudijs MJ, van 't Slot R, Gunning B, Sonsma ACM, van Gemert LJJM, et al. Mosaicism of de novo pathogenic SCN1A variants in epilepsy is a frequent phenomenon that correlates with variable phenotypes. Epilepsia 2018;59:690–703. https://doi.org/10.1111/epi.14021.
[29] Carvill GL, Engel KL, Ramamurthy A, Cochran JN, Roovers J, Stamberger H, et al. Aberrant inclusion of a poison exon causes Dravet syndrome and related SCN1A-associated genetic epilepsies. Am J Hum Genet 2018;103:1022–9. https://doi.org/10.1016/j.ajhg.2018.10.023.
[30] Warman Chardon J, Beaulieu C, Hartley T, Boycott KM, Dyment DA. Axons to exons: the molecular diagnosis of rare neurological diseases by next-generation sequencing. Curr Neurol Neurosci Rep 2015;15(64). https://doi.org/10.1007/s11910-015-0584-7.
[31] Palmer EE, Schofield D, Shrestha R, Kandula T, Macintosh R, Lawson JA, et al. Integrating exome sequencing into a diagnostic pathway for epileptic encephalopathy: evidence of clinical utility and cost effectiveness. Mol Genet Genomic Med 2018;6:186–99. https://doi.org/10.1002/mgg3.355.
[32] Stark Z, Schofield D, Alam K, Wilson W, Mupfeki N, Macciocca I, et al. Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement. Genet Med 2017;19:867–74. https://doi.org/10.1038/gim.2016.221.
[33] Saunders CJ, Miller NA, Soden SE, Dinwiddie DL, Noll A, Alnadi NA, et al. Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. Sci Transl Med 2012;4:154ra135. https://doi.org/10.1126/scitranslmed.3004041.
[34] Willig LK, Petrikin JE, Smith LD, Saunders CJ, Thiffault I, Miller NA, et al. Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. Lancet Respir Med 2015;3:377–87. https://doi.org/10.1016/S2213-2600(15)00139-3.
[35] Meng L, Pammi M, Saronwala A, Magoulas P, Ghazi AR, Vetrini F, et al. Use of exome sequencing for infants in intensive care units: ascertainment of severe single-gene disorders and effect on medical management. JAMA Pediatr 2017;171:e173438. https://doi.org/10.1001/jamapediatrics.2017.3438.
[36] Farnaes L, Hildreth A, Sweeney NM, Clark MM, Chowdhury S, Nahas S, et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. NPJ Genom Med 2018;3(10). https://doi.org/10.1038/s41525-018-0049-4.
[37] Shendure J, Findlay GM, Snyder MW. Genomic medicine-progress, pitfalls, and promise. Cell 2019;177:45–57. https://doi.org/10.1016/j.cell.2019.02.003.