



## Minireview

# Cognitive, neurophysiological, neurological and psychosocial outcomes in early-treated PKU-patients: A start toward standardized outcome measurement across development

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## ABSTRACT

The aim of this paper is to provide a concise summary of findings from outcome studies in early-treated phenylketonuria (PKU). The paper should not be considered as an extensive review of the many different outcome measures that have been used in PKU-research, but as an attempt to integrate such findings so that they will be of additional value for day to day monitoring of PKU-patients and may direct future research to fill the present gaps of knowledge. Neurological, neuropsychological, neurophysiological, neuroimaging, quality of life, and psychosocial findings will be discussed in the context of their potential contributions to lifelong follow-up and treatment of PKU-patients being summarized in statements.

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**Abbreviations:** ANT, Amsterdam Neuropsychological Tasks; BAEP, brainstem auditory evoked potentials; BRIEF, Behavior Rating Inventory of Executive Function; CANTAB, Cambridge Neuropsychological Test Automated Battery; EEG, electroencephalography; EF, executive functioning; EP, Evoked Potentials; ERP, Event-Related Potentials; HRQoL, Health related quality of life; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PKU, phenylketonuria; PET, positron emission tomography; VEP, Visual Evoked Potentials; WM, white matter.

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## 1. Introduction

For Phenylketonuria (PKU; MIM# 261600), past decades have shown important progress in treatment strategies and outcome [1]. This journal has recently published a comprehensive review about psychological and neuropathological findings in PKU-patients [2]. The focus of the papers in that special issue of *Molecular Genetics and Metabolism* was a description of the many different outcomes

measured in PKU. Studies generally focused on only one or two specific outcome measurements. The focus of the present paper is a first step toward integration of the different findings of studies using different outcome measures. The ultimate goal is to develop a standardized set of instruments that can be used in day to day clinical practice to monitor cognitive and social functioning throughout development of children into adulthood in relation to treatment parameters. We realize that, with the present state of knowledge, which is derived from studies using very different samples, designs and methodologies, this is a very ambitious goal. Therefore, a number of the statements at the end of this paper concern theoretical reflections, or are meant to draw attention to gaps in the current knowledge, rather than concrete recommendations for long-term monitoring of PKU-patients. In this paper we will focus on neurocognitive outcome, with an emphasis on studies into executive control, and on psychiatric and behavioral outcomes, emphasizing quality of life. Furthermore, attention will be paid to studies that have used more direct measures of brain functioning in PKU, including clinical neurological issues and measures those that have used electroencephalography (EEG), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET). All these issues will be discussed in relation to (dietary) treatment parameters.

## 2. Neurocognitive outcome

Studies on IQ are relatively simple, relatively uniform, and reference data are widely available. It is already clear from many studies that the earlier the start of the diet, the better the outcome. Studies compared IQ data in patients who started treatment before 3 weeks with patients who started treatment between 3 and 6 weeks up to 3 months, and found higher IQ-scores for those who had started earlier, indicating the importance of taking into account the time of start of treatment when studying neurocognitive outcomes in PKU [3,4]. Both the duration of high Phe concentrations before treatment and the absolute Phe concentrations during that time may be important.

From data on IQ, we cannot decide on the exact Phe concentration that is safe not to treat [5], or the age at which treatment can be safely stopped. There are data supporting the idea that IQ does not deteriorate when treatment is stopped after 8, 10, and 12 years of age and Phe is within target range until that age [6–8], while the study of Koch et al. indicates that treatment cannot be stopped too early to prevent clinical problems in adults [9]. However, results of the Koch et al. study are not entirely comparable with the results of the other studies showing no deterioration, as this study compared patients who had stopped dietary treatment at 6 years with patients that had not stopped at all [9]. Thus, based on these data, the question as to whether IQ is a suitable measurement to determine whether treatment should be continued until or beyond 10–12 years of age cannot be answered [10]. A recent meta-analysis by Waisbren et al. showed that until 18 years there is a negative effect of high blood Phe concentrations on IQ [11], indicating that treatment should at least be continued until the end of adolescence.

It is disputable, however, whether IQ is the most informative measure to assess neurocognitive outcome in PKU, as an IQ-score is made up of scores on several different tasks, measuring different cognitive domains, and good or above-average scores on some tasks can mask poor or below-average scores on other tasks. Although it could simply be argued to focus on subtest-performance then, evidence indicates that specific impairments are present in treated PKU that go beyond what can be picked up by IQ-tests. For PKU, especially processing speed and cognitive control/executive functioning (EF) appear to be affected [12–14]. EF refers to regulatory higher-order cognitive abilities allowing integration and processing of information across a range of cognitive domains, sensory modalities, and response modalities. One test for processing speed and one for EF, which are repeatable across different ages, may thus appear a possible solution in light of

continuous monitoring of cognitive outcome. However, matters are somewhat more complicated, mainly because it is difficult to separate processing speed and EF in most neuropsychological tasks: a processing speed deficit becomes more evident when a task becomes more complex (i.e. when more executive control is required) because of the requirement of more brain regions communicating with each other (and of more communication between neurons within brain regions). If Phe has affected white matter integrity [15], it is unlikely this has happened in one specific area of the brain, and therefore, there will be additional slowing of task performance with each new brain region involved. Involvement of many different brain regions is typical of executive function (EF-) tasks. For example, performance of a task requiring inhibitory control generally involves dorsolateral prefrontal cortex, the occipital cortex (for perception of the stimuli), and a number of motor areas (e.g. primary and premotor cortex); a working memory task also involves these areas, as well as parietal regions [16–18]. EF-tasks which also incorporate a motivational or emotional component additionally involve temporal, orbitofrontal and subcortical regions [19]. If a white-matter related processing speed deficit underlies cognitive dysfunction in treated PKU, one would thus expect much greater processing speed deficits when EF are required than when they are not. Consequently, it will be insufficient for monitoring of PKU-patients to have them perform simple processing speed tasks, as many problems will only become apparent when there is a demand for (integration of) multiple aspects of cognition.

Historically, the prefrontal cortex has been put at the center of all EF [20], and although this notion has become slightly dated with the increasing knowledge of brain networks, it is still a very important structure for EF, a structure that is always involved in executive operations, a structure containing dopaminergic neurons that appear to be more sensitive to dopamine precursor reductions than those elsewhere in the brain [21,22], and the brain structure that matures the latest of all brain regions [23–25], thereby prolonging the period throughout which it is likely to be sensitive to higher Phe levels and lower monoamine levels. Thus, evidence appears to favor regular EF-assessments in order to monitor cognitive development and functioning. As a dependent measure, one might opt to use reaction times/processing speed, but this would be sufficiently informative only in EF-tasks with multiple levels of complexity.

### 2.1. Characterizing the EF-deficit in treated PKU

EF has generally been used as an umbrella term encompassing a wide range of (combinations of) abilities such as planning, organization, strategy use, cognitive flexibility, inhibitory control, and working memory [14]. A number of efforts have been made to model or define the EF-deficit that is typical of PKU-patients [13,14]. Such approaches have been very useful in that they narrowed down findings from a myriad of EF-tasks to a number of core concepts, some of them impaired in treated PKU and others intact. In general, inhibitory control of prepotent responding and the manipulation- and monitoring aspect of working memory appear to be the most strongly affected executive functions in treated PKU, particularly when they are required simultaneously [26–29]. It should be noted, however, that the characterization of EF-deficits in PKU within theoretical frameworks has particularly been based on studies with children who were on diet at the time of neuropsychological testing. Studies with adolescents and adults show mixed results. Some appear to indicate that PKU-control differences are smaller for older on-diet groups [30], but others indicate more serious EF-problems for the older groups [31]. The main complicating factor in finding out whether deficits increase or decrease with age, and whether the abovementioned theoretical frameworks also apply to EF in older PKU-populations, is that these patients often have discontinued or at least relaxed dietary treatment regimens. Therefore, when the goal is the assemble a compendium of instruments to monitor PKU patients across different ages, one

of the first steps would have to be neuropsychological testing of older patients who have maintained strict treatment after entering adolescence. This neuropsychological testing should be performed using the same conceptually informed instruments that have been used for child studies. Another consideration before deciding upon which tests should be used for longitudinal monitoring of cognitive outcome, is that there is evidence for non-EF deficits in treated PKU as well. For instance, studies have shown abnormalities in perceptual processing, vigilance and sustained attention deficits, motor control, and visual-spatial abilities (for an overview, see [32]). Although there are studies showing that such deficits become much more evident when there is also an executive component involved [33], this might indicate that either working memory or inhibitory control could also be combined with non-executive demands in follow-up/monitoring tasks.

## 2.2. Assessment of EF in PKU

Whereas it may be argued that IQ-tests also reflect several EF or EF in combination with other cognitive abilities, it appears that several computerized test batteries such as the Amsterdam Neuropsychological Tasks (ANT) [34] and Cambridge Neuropsychological Test Automated Battery (CANTAB) [35,36] include tasks that more clearly measure inhibitory control, working memory, a combination of both, and a combination of either with specific other cognitive abilities. The test battery that has been used most frequently in PKU-research is the ANT [37], but recently studies have appeared using the CANTAB [38]. Performance by PKU-patients of ANT-tasks has consistently been related to different indices of dietary control. Such data is not yet available for the CANTAB, although there are some indications that largely the same cognitive domains are affected and that there are differences between Phe high and Phe low subjects [38]. More research is necessary on outcomes from both batteries in relation to clinical parameters and in relation to each other, before a decision can be made on which tests could be used to continuously monitor cognitive outcome in PKU-patients. If tests from both batteries are indeed strongly related, indicating they measure the same cognitive abilities, it would be preferable to use only one of the batteries across centers, as some subtle differences will undoubtedly remain present. Moreover, there is still a need for comparable tests that can be administered to the youngest PKU patients (aged 0–5 years old), and there is no clarity yet on the validity of the computerized tasks in relation to day-to-day life EF.

In recent years, a number of questionnaires have been developed measuring EF in daily life, with the Behavior Rating Inventory of Executive Function (BRIEF) [39] as their best-known exponent. It has been suggested that this questionnaire could be used in regular assessments throughout development and during adult life of PKU-patients [40]. The BRIEF is a standardized informant report with versions for 2–5 year-olds (five scales: Inhibit, Shift, Emotional Control, Working Memory, Plan/Organization), 5–18 year-olds (eight scales: the five scales also present for the youngest group plus Initiate, Organization of Materials, and Monitor), and for adults (nine scales: Monitor from the BRIEF for 5–18 year olds is divided into Self-Monitor and Task Monitor). An overall composite score can be generated from all lists, as well as a number of broader EF-indices: for 2–5: Inhibitory Self-Control, Flexibility, and Emergent Metacognition, and for 5–18 year-olds and adults Behavioral Regulation and Metacognition. To date not many PKU-studies have incorporated the BRIEF, and unfortunately, results have not been very consistent. Whereas one might expect the most pronounced differences with controls in the inhibitory control and working memory domains, Anderson et al. identified impairment on subscales shifting (which may be considered a combination of inhibitory control and working memory) and monitoring [41], while Sharman et al. reported impairments on a number of subscales: initiation, working memory, planning, organization, and monitoring [42]. Antshel and Waisbren reported that

children with early-treated PKU had significantly lower Metacognition Index scores than healthy controls [43]. Moreover, there is a lack of evidence showing associations between the BRIEF-domains and laboratory measurements of EF [14]. Many operations in day-to-day life appear to require multiple EF simultaneously or EF in combination with other cognitive abilities, and this appears to be reflected in the type of questions asked in the BRIEF. Therefore, the BRIEF can, at present, not replace (computerized) neuropsychological tasks in long-term monitoring of PKU-patients. It may, however, serve as an additional measure in this monitoring process, as it likely to represent problems in daily life better than laboratory tests.

Despite its shortcomings, there are advantages as well. One such advantage is that it also has an Emotional Control-scale. EF in daily life will often contain some emotional, motivational, or affective components. This type of EF can again be investigated using questionnaires and laboratory tasks, both of which have hardly been done in PKU. Empirically-validated dual-pathway models, comprising both cognitive and emotional control (and for which neuroanatomical and neurobiological underpinnings have been identified) could be the best possible theoretical framework to capture all functional deficits observed in PKU [44,45].

## 3. Neurological outcome

In contrast with the poor neurological outcome in untreated PKU patients especially with spasticity and epilepsy, there are very few reports on neurological issues in early and continuously treated PKU patients. Problems observed in early treated PKU patients are brisk reflexes and tremor that may develop in poorly treated as well as well-treated PKU patients especially after adolescence [56], and more severe neurological problems seem to be due to vitamin B12 deficiency rather than high Phe concentrations, while a combination of anesthesia and vitamin B12 deficiency may lead to further deterioration of the patient [57–59]. No one knows the weight yet of brisk reflexes at the longer term as a parameter for neurological outcome. Do patients with longer or more exaggerated brisk reflexes develop any motor (“pyramidal”) impairment in the end? Therefore, at present, we just have to follow this clinical sign thoroughly.

## 4. Behavior and quality of life

There is limited knowledge about possible psychiatric problems in PKU, and there is a particular lack of such data in relation to the neurobiology of PKU. Some findings, however, have been sufficiently replicated to render them important enough to take into consideration when assembling a standardized outcome battery. These include the presence of internalizing behavior problems, specifically a proneness to depression, anxiety and phobic tendencies [46]. For aggression or antisocial behavior little evidence exists showing lower-than-normal levels. Attention Deficit Hyperactivity Disorder-type behaviors have been observed in PKU, but evidence has particularly been provided for attention problems rather than hyperactivity [47].

Health related quality of life (HRQoL) is a subjective measure of an individual's satisfaction or happiness regarding domains of life that affect health or are affected by health. The effects of having PKU on the HRQoL of patients can be assessed in cohort studies with validated questionnaires. A number of these studies have been published. First in 1992 Weglage et al. evaluated 34 early treated adolescents with a normal IQ, with a personality inventory and a biographic inventory [48]. Patients demonstrated less autonomy, a more negative self description, less extraversion and impulsiveness, a feeling of not being quite healthy, and more grave and a higher level of dependency from their families. The HRQoL of 37 patients with PKU between 3 and 18 years of age was evaluated in 2002 by Landolt et al. [49]. Their parents completed a generic questionnaire, the TNO-AZL Questionnaire for Children's Health-Related Quality of Life, and the Child Behavior

Checklist. The only deviation in the PKU group was a reduction of positive emotions, and psychological adjustment in patients with PKU was better than in a healthy reference group. The authors concluded that a normal HRQoL is possible for patients with PKU. The same was found in a study of the course of life, sociodemographic outcomes and health-related quality of life in 32 early treated patients with PKU age 18 to 30 years [50]. Patients completed the Course of Life questionnaire (a validated questionnaire evaluating accomplishment of developmental tasks and achievement of developmental milestones), the generic RAND-36 Health Survey, and the generic cognitive scale of the TNO-AZL Adult Quality of Life questionnaire. The results of the Course of Life and Health-Related Quality of Life questionnaires were comparable to controls, except that a higher percentage received special education in primary school. Their educational attainment, however, was comparable to that of their peers. A study of 67 early treated patients, who completed the Profile of Quality of Life in the Chronically Ill, a questionnaire on quality of life and social status, also reported the outcome to be in the same range as in the controls [51]. Schooling and professional career corresponded approximately to the control collective. However, evaluation of the social state of PKU patients revealed a tendency toward lower or delayed autonomy, and a low rate of forming normal adult relationships in which to have children.

In a very recent study seventy two early treated patients demonstrated a normal HRQoL at the time of transfer from pediatric to adult care, and a marital status compared to the general population, but fewer patients with PKU had children [52].

Together, these studies do not demonstrate an absolute negative effect of having PKU on the HRQoL of the patients, but there are trends toward delayed autonomy and possibly a lower rate of forming adult relationships and having children. In our experience, if we report the normal HRQoL results to our patients, they frequently feel that it does not do justice to the efforts they make to lead a “normal” life.

In 2010, Gentile et al. proposed the possibility that early- and well-treated patients experience hidden (subtle) disabilities, that are not detected with the generic questionnaires but which do affect their daily lives [53]. As reported in the above section, there are many reports of deficits in executive functioning in patients with PKU. Possibly, these executive functioning deficits may lead to psychosocial deficits that are not always visible (including social difficulties and psychosocial problems, such as forming interpersonal relationships, achieving autonomy, attaining educational goals, and having healthy emotional development). Furthermore, it was recently demonstrated with a randomized controlled trial that high phenylalanine values have a strong negative effect on the mood of patients, perceived by the patients themselves as well as by relatives and friends [37]. This may be expected to affect social functioning of the patients.

## 5. Neurophysiological and neuroimaging alterations and outcome

Owing to their impressive temporal and spatial resolution, respectively, neurophysiological and neuroimaging techniques are excellent tools for the non-invasive *in vivo* study of the central nervous system functions and structure in PKU subjects. Several papers published in the 80s and 90s focused on the signal transmission inside the central nervous system and were based on the recording of latency and amplitude of early components of multimodal Evoked Potentials (EP). The most consistent result was the increase of the latency of the main component (P100) of Visual Evoked Potentials (VEP), which was reported in 9 out of 12 studies [54–65], and affected mainly patients older than 10. Clinical consequences and prognostic value of this alteration, if any, remain to be elucidated. Only a few longitudinally designed studies have been performed so far. A maturational lag of some brainstem auditory evoked potentials (BAEP) and VEP components with mainly postnatal development was detected during the first year of life in early treated PKU infants and was not associated with any concomitant developmental disorder [66]. In older patients EP latencies were not affected by

transient (Leuzzi V, unpublished data) or persistent [67,68] Phe variations, Tyrosine, Tryptophan [15], and L-DOPA [61,69] supplementation. On the contrary, early and continuous administration of Long-Chain PUFA improved VEP P100 latency at the age of 12 months [70,71].

Event-Related Potentials (ERP) allow for the measurement of brain activity from 1 m to the next and intercept many aspects of attention and perception, which appear to operate on a temporal scale. A few cross-sectional studies have been performed in the last decade in PKU patients using different paradigms and tasks [72–75]. Relevant results were: a) the derangement of ERP generation in late-treated patients; b) the impairment of early sensory processing in early-treated and on off diet patients; c) problems with response inhibition; d) the impairment of a number of components involved in selective attention, which were influenced by high Phe value; e) scarce accuracy in the task execution, that improves with age in PKUs (but not in the controls). Future perspectives in this field should involve the assessment of the outcome of neurophysiological alterations and the exploration of the linkage between neuropsychological and neurophysiological alterations.

Brain white matter (WM) alterations on T2-weighted and Flair MRI sequences were initially described in a few patients suffering from neurological deterioration after diet discontinuation. Afterwards, similar alterations were also detected in over 90% of early treated PKU patients without symptoms of neurological deterioration (for a review, see [15]). Most of them were young adult off diet patients. The fact that WM alterations can be reversed by a strict diet over a few months [76] strongly points to the causative role of (CNS) Phe. However, other factors are probably involved as suggested by a) the occurrence of WM variation (improvement or worsening) in patients who did not change their Phe values, and b) the wide variability of WM involvement under similar value of blood and CNS Phe [77,78]. Most of the studies find a weak or no direct link with mental development and functioning, even if some relations between the degree of WM alteration and neuropsychological disorders were found [79]. However, also in this case the variability in clinical outcome (i.e. impairment in patients without WM alteration) suggests the contributing role of additive unknown factors. Moreover, the hypothesis that WM abnormality results in an impairment of neural transmission was not confirmed by neurophysiological studies [58]. Only a few data are available on the outcome of WM MRI alterations as detected by serial examinations. Preliminary results suggest that WM alterations are correlated with lifetime and concurrent Phe level, age (with a marked inter-individual variability), and sex (females showing a greater vulnerability than males).

In conclusion, results to date from MRI examinations and neurophysiological studies do not seem to significantly improve the predictive power of clinical and biochemical examinations in relation to neuropsychological and psychosocial outcomes. Therefore, these should, for now, be used for research purposes or to explore specific clinical conditions. Future topics for these powerful techniques should include the identification of a set of preclinical neuro-anatomic or/and neuro-physiologic alterations, which are predictive of the clinical and behavioral outcomes.

MRS and PET studies have increased our understanding of brain neuropathology. Especially the studies of Pietz et al. have learned us that large neutral amino acids may decrease brain Phe concentrations and improve EEG outcome, either due to a decrease of the brain Phe concentrations or an increase of one or more of the other large neutral amino acids [80]. The studies by Weglage et al. and the discussion afterwards have learned us that still many issues of brain Phe measurement are unsolved [81,82]. First, it has to be proven that consecutive MRS measurements result in comparable brain Phe concentrations using the same MRS in the same institute. This has been done recently [83]. Next, some centers with proven experience within this field need to compare their data, probably by measuring their patients in the various institutes. These studies will help us to further understand the role of brain Phe concentrations. In contrast to MRS, PET studies do not involve concentrations but processes, such as energy

metabolism (which informs on activity of various cerebral regions) [84], protein metabolism [85,86], and transport across the blood–brain barrier [87].

## 6. Neurological outcome

Given all these possibilities of measures we tend to forget the pure clinical data of brain function, clinical neurological evaluation. In contrast with the poor neurological outcome in untreated PKU patients especially with spasticity and epilepsy, only some papers address real neurological issues in early and continuously treated PKU patients. Problems observed in early treated PKU patients are brisk reflexes and tremor that may develop in PKU patients especially after adolescence [88–91]. These are not known to have clear clinical relevance, but data relating this kind of outcome to metabolic control are scarce. Such data might also help to establish the metabolic targets of treatment. Therefore, future studies can further take into account the possible existence of relation between brisk reflexes and treatment parameters either at present or in history.

## 7. Statements

The authors developed the following statements that may help determining the instruments that can be used in long-term monitoring of PKU-patients:

1. IQ tests are not the optimal instrument to monitor cognitive outcome of early and continuously treated patients.
2. In monitoring neuropsychological outcome of PKU patients at various ages, the executive functions ‘working memory’ and ‘inhibition of prepotent responding’ should feature, preferably in combination with each other, or in combination with other aspects of cognition, such as sustained attention, high perceptual demands and motor control.
3. There is a great demand for measurement of social information processing and emotional control in early and continuously treated PKU patients, and measurement of these should be part of long-term monitoring of PKU patients.
4. The BRIEF may be a valuable instrument for monitoring daily life EF and emotional control of PKU patients, but it is unlikely, at present or in the future, that it can replace (computerized) laboratory tasks in this process.
5. Studies on HRQoL with generic validated questionnaires may be inadequate to detect hidden deficits so that development of a PKU specific questionnaire is needed to evaluate the HRQoL of PKU patients.
6. MRS and PET studies may help us to understand the cerebral pathophysiology in PKU, but do not appear to be of added value in longitudinal monitoring of patients.

The following statements are more hypothetical, and are particularly aimed at eliciting more research activities so that they might ultimately become important for longitudinal monitoring of PKU-patients as well:

1. Conventional brain MRI examination as well as neurophysiological studies should be restricted to PKU patients presenting unusual clinical symptoms such as neurological and/or mental deterioration, tremor, epilepsy, etc.
2. Stimulating topics for the future research in these fields are: a) the exploration of the neurophysiological and/or neuroimaging correlates of neuropsychological alterations in PKU patients; b) the identification of a set of preclinical neuro-anatomical and/or neuro-physiological alterations reflecting the individual vulnerability to Phe.
3. Mood is affected by high Phe values. A validated measure for mood and well-being needs to be developed and may well prove a strong measure of therapeutic effects in patients with PKU.

4. Further studies should especially be aimed at validation of MRS results as obtained in various centers by various apparatus.
5. It might be interesting to use brisk reflexes as outcome measure to develop the safe metabolic target especially in adolescent and adult patients.
6. Regular monitoring, whether this concerns neuropsychological, behavioral or neurological measurements, should be evaluated not only by clinicians and researchers, but also by the patients and their families themselves in order to increase the number of potential benefits for them (cf. [92]).

## 8. Conclusion

This paper summarizes the present knowledge of today's most important measures of outcome in PKU patients. Notwithstanding the progress in knowledge, there is an evident need for integration at various levels. Whereas in the past research was performed in different institutes that were often unaware of each others' activities, efforts should be made to integrate knowledge in future multicenter research programs. PKU-patients are likely to benefit most from a more integrated approach both in and across clinical and research settings. Such a translational approach will increase our understanding of PKU-pathophysiology and benefit the development of new treatment strategies.

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