Consensus

Group 6. Modalities and frequency of monitoring of patients with adrenal insufficiency. Patient education

Groupe 6. Modalités et rythme de surveillance au long cours chez le patient avec insuffisance surrénale. Éducation thérapeutique du patient

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Abstract

Patients with adrenal insufficiency require regular, specialised monitoring in order to optimise their replacement therapy, to detect signs of under- and over-dosage, and to examine for possible associated disorders (auto-immune disorders in the case of auto-immune primary adrenal insufficiency either isolated or as part of auto-immune polyendocrinopathy syndrome type 1; illnesses with underlying monogenic causes). The transition period between adolescence and adulthood represents an added risk of a breakdown in monitoring which requires particular attention from medical teams and coordination between adult and pediatric medical teams. It is essential to encourage patient autonomy in the management of their illness, notably their participation in treatment education programs, in particular programs that target avoidance of, or early treatment of acute adrenal insufficiency. The principal educational objectives for patients in such programs are: to be in possession of, and carry the necessary tools for their treatment in an emergency; to be able to identify situations of increased risk and the early signs of adrenal crisis; to know how to adjust their oral glucocorticoid treatment; to be capable of administering hydrocortisone by subcutaneous injection; to be able to predict and therefore adjust treatment to different situations (heat, physical exercise, travel) and to be able to correctly use the appropriate resources of the healthcare services. Other programs could also be developed to respond to needs and expectations of patients, notably concerning the adjustment of hydrocortisone dosage to avoid overdose in the context of chronic fatigue syndrome.

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Keywords: Consensus; Adrenal crisis; Addison’s disease; Corticotropin deficiency; Adult; Children; Monitoring; Auto-immune polyendocrinopathy; Complications; Quality of life; Patient education program; Prevention

Résumé

Les patients insuffisants surrénauxiens doivent bénéficier d’un suivi spécialisé régulier, afin d’optimiser le traitement substitutif, en recherchant des signes de sous-dosage et de surdosage, et pour rechercher d’éventuelles maladies associées (maladies auto-immunes en cas d’insuffisance surrénale primaire auto-immune isolée ou s’intégrant dans une polyendocrinopathie auto-immune de type 1 ; maladies associées dans certaines causes monogéniques). La période de transition de l’adolescence à l’âge adulte comporte un risque de rupture de suivi qui mérite une attention particulière du corps médical et une coordination des équipes médicales pédiatrique et adulte. Il paraît essentiel de favoriser l’autonomie des


SFE/SFEDP adrenal insufficiency consensus.
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patients dans la gestion de leur maladie, notamment en leur proposant de participer à des programmes d’éducation thérapeutique, en particulier des programmes visant à éviter ou traiter précocement l’insuffisance surrénale aiguë. Les principaux objectifs éducatifs sont les suivants : avoir sur soi les outils de sécurité ; savoir identifier les situations à risque et les symptômes d’insuffisance surrénale aiguë débutante ; savoir adapter le traitement oral par glucocorticoïde ; savoir administrer l’hydrocortisone par voie sous-cutanée ; savoir par anticipation adapter le traitement aux situations particulières (chauffe, exercice physique, voyages, …) ; utiliser de façon pertinente les ressources du système de soins. D’autres programmes pourraient être développés pour répondre aux besoins et attentes des patients, notamment concernant l’ajustement de la dose d’hydrocortisone, afin d’éviter le surdosage dans un contexte de fatigue chronique non spécifique.

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Mots clés : Consensus ; Insuffisance surrénale aiguë ; Maladie d’Addison ; Insuffisance corticotrope ; Adulte ; Enfant ; Polyendocrinopathie auto-immune ; Complications ; Qualité de vie ; Éducation thérapeutique ; Prévention

1. What are the methods used and the frequency of monitoring patients long-term in adrenal insufficiency?

R6.1: We recommend that adults with adrenal insufficiency have regular consultation by an endocrinologist at least once per year. Strong recommendations. Expert opinion.

R6.2: We recommend that children with adrenal insufficiency have regular consultation by a pediatric endocrinologist in a specialised center or reference center two to three times per year and more frequently in babies.

Strong recommendations. Expert opinion.

R6.3: In adults, we suggest clinical monitoring based on evidence of signs of over- or under-dosage, particularly for preventing the consequences of chronic overdose in bone, metabolic and cardiovascular parameters. For adjustment of glucocorticoid replacement, we do not recommend routine use of hormonal markers.

In children, we recommend clinical surveillance (growth, puberty) and examination for clinical signs of overdose or under-dosage. We do not recommend routine use of biochemical markers for adjustment of replacement therapy, except in congenital adrenal hyperplasia where we recommend regular assay of specific biochemical markers. In cases other than congenital adrenal hyperplasia, assay for ACTH is sometimes useful for evaluation of treatment compliance.

In adults and children, for adjustment of mineralocorticoid replacement, we suggest clinical surveillance (blood pressure, salt appetite, lower limb edema) and examination for biochemical signs of under-dosing (hyponatremia, hyperkalemia, elevated renin) or overdose (hypokalemia, undetectable renin levels or levels in the lower end of normal range).

Weak recommendation. Expert opinion.

Regular monitoring is necessary to evaluate the daily status of hormone replacement therapy, to identify the appearance of possible adrenal crisis and its cause, to examine for associated illness and ultimately to help the patient to better live with his illness [1].

1.1. Monitoring criteria

The objective of replacement therapy is to restore a state of health and a quality of life that is as close to normal as possible. At examination, the occurrence of acute episodes suggesting acute adrenal insufficiency need to be checked for and their cause, if possible, identified. Monitoring of patients is essentially by clinical signs to detect signs of glucocorticoid under dosage (fatigue, nausea, myalgia) or of mineralocorticoid under dosage (increased salt appetite, hypotension—especially postural) or signs of glucocorticoid overdose (weight gain, striae, skin fragility, amyotrophy, insomnia) or mineralocorticoid overdose (hypertension, edema).

Biochemical analyses carried out should include assays for plasma sodium and potassium (hyponatremia can reflect glucocorticoid or mineralocorticoid excess; hyponatremia and/or hyperkalemia can reflect glucocorticoid or mineralocorticoid under dosage). Filipsson et al. showed, in a large retrospective cohort study of 2424 adult patients with secondary adrenal insufficiency, that a dose higher than 20 mg/day equivalent of hydrocortisone was associated with an unfavorable plasma lipid profile with increased LDL cholesterol and triglycerides and additionally with an increase in waist circumference [2]. A
higher prevalence of abnormal glucose metabolism and dyslipidemia [3,4] as well as increased waist circumference was observed in adults with primary adrenal insufficiency treated with 25–30 mg/day hydrocortisone when compared to control subjects.

Plasma renin activity or direct assay of renin can be used for monitoring of mineralocorticoid replacement, the objective being to maintain renin in the high part of the normal range or slightly above normal (see chapter 4, paragraph 2-1-3). No routine assays of ACTH axis hormones are recommended (chapter 4, paragraph 1-4). In children with primary adrenal insufficiency other than congenital adrenal hyperplasia, assay of ACTH is sometimes useful to evaluate treatment compliance and to allow the dose of hydrocortisone to be adjusted, keeping in mind the risk of growth retardation in the case of overdosage.

1.2. Screening for complications

Examination for cardiovascular complications needs to be guided by clinical signs. There are currently no data on cardiovascular morbidity in patients with adrenal insufficiency. Studies on cardiovascular mortality are unclear: a Norwegian study did not identify an increased mortality in primary adrenal insufficiency [5] while a Swedish study reported a 2-fold increase in cardiovascular mortality [6]. Concerning cardiovascular risk associated with anterior pituitary deficiency, several reviews and meta-analyses have also shown contradictory observations and the existence of selection bias in examining the impact of ACTH deficiency linked to associated anterior pituitary deficiencies [7–9].

In terms of bone health, a reduction in bone mineral density has been reported, in some studies regardless of gender [10,11], while in other studies a reduction was seen only in women [12], specifically in menopausal women [13,14], and in others uniquely in men [15,16]. Conversely, some studies have not looked at bone loss [17–19] or only in patients on excessive dose of hydrocortisone [20]. The prevalence of fractures was only reported in two of these studies: the Norwegian study by Lovas et al. did not find more vertebral fractures than in the general population [11]; the Swedish study by Bjornsdotter et al. showed a risk of hip fracture 1.8-fold greater than in the general population [21]. A reduction in hydrocortisone dose from 30 to 20 mg/day was associated with an improvement in bone density: in the study by Schulz, Z-scores were significantly improved, from −0.93 ± 1.2 to −0.65 ± 1.5 in the spine and from −0.40 ± 1.0 to −0.28 ± 1.0 in the femur, 2 years after a reduction in equivalent dose of hydrocortisone from 30.8 ± 8.5 to 21.4 ± 7.2 mg/day in a group of 27 patients, whereas Z-scores did not change in a group that remained on the same hydrocortisone dose while Z-scores worsen in a group of patients where hydrocortisone dose was increased [22]. Furthermore, in a study by Peacey et al., bone density in the spine improved in 6 of 12 patients evaluated by Z-score, and in absolute value in 4 of 12 patients having received optimization of their hydrocortisone dose [23].

1.3. Evaluation of quality of life

In terms of quality of life, a large number of studies have shown an alteration in quality of life using generic questionnaires such as the self-administered Short-Form 36 (SF-36) or specific questionnaires such as AddiQoL. The factors determining a lower quality of life in patients which have been consistently identified in several studies are: female gender [24–27], although this difference is not present when using Z-scores adjusted for age and gender [28]; the association of other auto-immune conditions or co-morbidities [24,25,29–31]; a lower level of education [24,29] and not being in paid employment [29–31]. Patients report numerous problems, the most frequent being fatigue [27,31]. Some studies have also reported greater psychiatric morbidity (depression, anxiety) [26,28,32]. The impact of hydrocortisone dose on quality of life and physical symptoms, such as pain and fatigue, is controversial. Longitudinal studies have suggested an association between poorer quality of life and higher doses of hydrocortisone [26,28,33,34], with a negative correlation between dose of hydrocortisone and impairment due to physical state [34], without establishing a causal relationship (patients with a poorer quality of life were more likely to take higher doses of hydrocortisone to try to lessen their fatigue). There was a positive correlation between hydrocortisone dose and anxiety on one hand [34] and certain unadapted personality traits (impulsivity, irritability, opposition, defiance, narcissism) on the other hand [26]. Double blind crossover studies of increased hydrocortisone doses on quality of life have shown divergent results, with a negative effect [35], neutral effect [36,37] or positive effect [38,39] all being reported. It should be noted that several confounding factors could explain these heterogeneous results: factors other than the dose of hydrocortisone were modified (number of daily doses, timing of doses) [38,39]; the ‘high’ dose of hydrocortisone was not higher than 30 mg/day [36–38]; the normal dose of hydrocortisone taken by patients was higher than the ‘low’ dose described in Wernemoes Buning et al. (median dose 25 mg/day, interquartile doses 20–30 mg versus 15–20 mg for the low dose and 30–40 mg for the high dose) [39]; the duration of the studies were relatively short, between two weeks and three months, which probably did not allow evaluation of physical changes, nor changes in quality of life. The tool generally used for quality of life measures was the self-administered SF-36 questionnaire, which takes into account the perceived quality of life over the preceding 4 weeks [35,37,39].

1.4. Management of associated pathologies

A cohort study on a Swedish population of patients with adrenal insufficiency showed that these patients took more medications than control subjects, notably anti-hypertensives, cholesterol-lowering drugs, drugs for treating bone disorders as well as hypnotics and sedatives [40].
Table 1
Clinical manifestations and recommendations for surveillance of patients with adrenal insufficiency suffering from auto-immune polyendocrinopathy type 1 (PEA1 or APECED syndrome) (additional to specific surveillance of adrenal insufficiency detailed elsewhere) from [55,63–65].

<table>
<thead>
<tr>
<th>Affected organ(s)</th>
<th>Frequency of occurrence (%)</th>
<th>Age at occurrence</th>
<th>Initial tests, then repeated each 2–3 years, or sooner in case of clinical justification</th>
<th>Annual monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucocutaneous manifestations</strong></td>
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<tr>
<td>Mucocutaneous candidiasis</td>
<td>83–100</td>
<td>Childhood</td>
<td>Stomatological examination ± other specialist consultations, dermatology, ophthalmology if necessary</td>
<td>Stomatological examination ± other specialist consultations, dermatology, ophthalmology if necessary</td>
</tr>
<tr>
<td>Hypoplasia of dental enamel</td>
<td>77</td>
<td>Childhood</td>
<td>FSH, LH, E2</td>
<td>FSH, LH, E2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>29–37</td>
<td>Childhood</td>
<td>TSH, AB anti-TPO</td>
<td>TSH</td>
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<tr>
<td>Keratoconjunctivitis</td>
<td>12–35</td>
<td>Childhood</td>
<td>Fasting blood glucose, AB anti-IA2, anti-insulin, anti-GAD</td>
<td></td>
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<tr>
<td>Vitiligo</td>
<td>12–13</td>
<td>Childhood</td>
<td>IGF1, FSH, LH, ACTH</td>
<td>IGF1, FSH, LH, ACTH</td>
</tr>
<tr>
<td><strong>Endocrine manifestations</strong></td>
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<td>Hypoparathyroidism</td>
<td>79–93</td>
<td>Childhood</td>
<td>Review, Endocrinology screen, phaso-calcium levels</td>
<td>Review, Endocrinology screen, phaso-calcium levels</td>
</tr>
<tr>
<td>Ovary (ovaritis)</td>
<td>60</td>
<td>2nd to 3rd decade</td>
<td>FSH, LH, E2</td>
<td>FSH, LH, E2</td>
</tr>
<tr>
<td>Testis</td>
<td>&lt; 25</td>
<td>3rd to 5th decade</td>
<td>FSH, LH, Testosterone</td>
<td>FSH, LH, Testosterone</td>
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<tr>
<td>Thyroiditis</td>
<td>3–10</td>
<td>3rd decade</td>
<td>TSH, AB anti-TPO</td>
<td>TSH</td>
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<tr>
<td>Type I diabetes</td>
<td>2–12</td>
<td>2nd to 3rd decade</td>
<td>Fasting blood glucose, AB anti-IA2, anti-insulin, anti-GAD</td>
<td></td>
</tr>
<tr>
<td>Lymphocytic hypophysitis</td>
<td>5–7</td>
<td>Childhood</td>
<td>IGF1, FSH, LH, ACTH</td>
<td>IGF1, FSH, LH, ACTH</td>
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<td>Gastroenterology manifestations</td>
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<td>Malabsorption</td>
<td>15–18</td>
<td>Childhood</td>
<td>Examinations, Clinical examination, serum albumin and ferritin</td>
<td>Examinations, clinical examination, serum albumin and ferritin</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>12–20</td>
<td>Childhood</td>
<td>AB anti-GAD65</td>
<td>Hepatic function markers</td>
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<td>Gastritis</td>
<td>13–15</td>
<td>2nd to 3rd decade</td>
<td>NFS, vitamin B12, anti-intrinsic factor and anti-gastric parietal cell antibodies</td>
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<tr>
<td><strong>Other non-endocrine manifestations</strong></td>
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<tr>
<td>Interstitial nephritis</td>
<td>&lt; 10</td>
<td>2nd to 3rd decade</td>
<td>Urea, creatinine, blood pressure, plasma ions</td>
<td>Urea, creatinine, blood pressure, plasma ions</td>
</tr>
<tr>
<td>HTA with hypokalemia</td>
<td>15</td>
<td>Childhood or young adult</td>
<td>Urea, creatinine, blood pressure, plasma ions</td>
<td>Urea, creatinine, blood pressure, plasma ions</td>
</tr>
<tr>
<td>Obliterative bronchiolitis</td>
<td>10 à 20</td>
<td></td>
<td>Clinical examination ± pulmonary function tests and CT scan if clinically indicated</td>
<td>Clinical examination ± pulmonary function tests and CT scan if clinically indicated</td>
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<tr>
<td>Splenic atrophy</td>
<td></td>
<td></td>
<td>Hemogram, examination for Howell Jolly bodies</td>
<td>Hemogram</td>
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<tr>
<td>Auto-immune hemolytic anemia, large granular lymphocytic leukemia</td>
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<td></td>
<td>Clinical examination</td>
<td>Clinical examination</td>
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<td>Severe infections</td>
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<td>Myocarditis</td>
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<td>Pulmonary hypertension</td>
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<td>Progressive muscular atrophy</td>
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<td>Vasculitis</td>
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<td>Connective tissue disease</td>
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<tr>
<td>Febrile skin rashes</td>
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<td>Anxiety, depression</td>
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1.5. Screening for associated auto-immune disorders
The prevalence of other auto-immune disorders is increased in patients who suffer from auto-immune primary adrenal insufficiency [41,42]:

- Hashimoto’s thyroiditis was found in half of the women and a quarter of the men studied in a Norwegian cohort [27] and in more than 60% of patients in an Italian cohort [43];
- Basedow’s disease was found in 14% of patients [43];
R6.4: We recommend that patients with auto-immune primary adrenal insufficiency are examined systematically for associated auto-immune disorders, at least annually and more frequently in cases where there are early clinical signs of such disorders. The range of initial biochemical tests (excluding auto-immune polyendocrinopathy type I) includes: TSH, anti-thyroperoxidase antibodies; fasting blood glucose, anti-GAD antibodies, anti-IA2 (islet antigen 2) antibodies; blood cell count, vitamin B12, anti-gastric parietal cell antibodies, anti-intrinsic factor antibodies and anti-transglutaminase antibodies. The list of tests to be carried out in follow up includes: TSH, fasted blood glucose, blood cell counts and vitamin B12. Women of child-bearing age should be warned of the risk of premature ovarian insufficiency. First-degree relatives should be warned of the signs of primary adrenal insufficiency and dysthyroidism. We recommend regular screening for potential associated pathologies in the case of auto-immune polyendocrinopathy type 1 (Table 1) or in some genetic-linked adrenal insufficiencies. Strong recommendation. Expert opinion.

- type 1 diabetes is present in 10–15% of Scandinavian patients, less frequently in other populations [43–45];
- thyroiditis and type 1 diabetes tend to appear before adrenal insufficiency (for Hashimoto’s thyroiditis, in 50% of cases, for Basedow’s disease and type 1 diabetes in 70% of cases), but can equally be diagnosed simultaneously or appear later;
- premature ovarian insufficiency is found in 7–8% of Norwegian and Polish patients [27,44]. The prevalence is higher when there are other associated auto-immune disorders (16% in patients with an auto-immune thyroid pathology and/or type 1 diabetes found in an Italian cohort) [46].

The mean age when ovarian insufficiency was diagnosed was 32 (18–40 years), compared to 36 (17–62 years) for age at diagnosis of adrenal insufficiency [44,46].

- auto-immune gastritis with or without Biermer’s disease can be associated in around 10% of patients [27,44]. Celiac disease appears to be less frequent (3.5% of patients in a Polish cohort) [44]. Auto-immune gastritis and celiac disease have a tendency to appear after adrenal insufficiency;
- vitiligo was found in around 10% of patients in an Italian cohort [43] and appeared in most cases before adrenal insufficiency. Alopecia is considerably rarer (3% of patients in the same cohort) and again more frequently preceded adrenal insufficiency.

Few studies have analyzed the predictive value of specific antibodies against affected organs in the case of primary auto-immune adrenal insufficiency, with the exception of a recent Italian retrospective study of 492 patients [43]:

- for thyroid disorders, when anti-thyroid antibodies are detected, the risk of clinical or subclinical hypothyroidism was 8% per year (mean surveillance of 3.5 years);
- for pancreas disorders, where anti-glutamic acid decarboxylase (anti-GAD65) or anti-islet cell (ICA) antibodies are present, the risk of occurrence of diabetes was 2% per year (mean surveillance 6 years);
- for digestive disorders, in the case of positivity for antiparietal cell antibodies and/or intrinsic factor antibodies, the risk of developing an auto-immune gastritis with or without Biermer’s anemia was 2% per year (mean surveillance 5 years) and if positive for anti-transglutaminase antibodies, the risk of developing celiac disease was 30% per year (mean surveillance 3 years) in type II auto-immune polyendocrinopathy syndrome.

 Keeping in mind the high prevalence of thyroid disorders, notably hypothyroidism, in patients with auto-immune adrenal insufficiency, an initial examination including TSH assay and test for anti-thyroperoxidase (TPO) antibodies is recommended:

- If TSH is found to be moderately elevated and the test for anti-TPO antibodies is negative, no treatment with levothyroxine should be given, and TSH should be measured again one month after the start of replacement therapy for adrenal insufficiency. In fact, TSH can be moderately increased, between 4–10 mU/L because of the loss of inhibition of the TSH axis in adrenal insufficiency [47,48];
- If TSH is elevated and anti-TPO antibodies are present, beginning replacement therapy with levothyroxine is suggested, however this should be after the commencement of replacement therapy for adrenal insufficiency. In fact, the introduction of levothyroxine prior to hydrocortisone risks inducing adrenal crisis due its action of accelerating the metabolism of residual cortisol [49].

In the course of monitoring, there should be annual screening for TSH (± anti-TPO antibodies). If anti-TPO antibodies are detected, there is no need to test for these in the future.

The principal reason for screening for type 1 diabetes is to avoid spontaneous evolution towards a state of diabetic ketoacidosis. The psychological stress caused by the knowledge that the subject is positive for pancreas antibodies, several years before the onset of the disease, may discourage this strategy. Studies that have evaluated the psychological impact of screening in children (BABYDIAB, TEDDY, Fr1da) identified a reduction in parental anxiety over time, to have symptoms of anxiety and depression that were comparable to the general population [50–52]. Screening for type 1 diabetes in the first check-up is done by assay of fasting blood glucose, testing for anti-GAD antibodies, anti-IA2 antibodies and anti-insulin antibodies. If antibodies are present, examinations should be completed by an
oral glucose tolerance test and assay of HbA1c, following which the patient and their family should be informed of the signs of hyperglycemia and of ketoacidosis. In the absence of antibodies at the initial screening, review should be by annual test of fasting blood glucose (± anti-GAD and anti-IA2 antibodies depending on the context).

Screening for auto-immune diseases of the digestive system is warranted due to their insidious and non-specific character, often responsible for a delay in diagnosis. These should be screened for by blood cell counts, vitamin B12 assay, tests for anti-parietal cell antibodies, anti-intrinsic factor antibodies and anti-transglutaminase and/or gliadin antibodies in the case of elevated risk. The biochemical tests in follow-up should be: blood cell count and vitamin B12 assay. In the case of positive antibody results, these do not require re-testing in follow-up.

In the case of premature ovarian insufficiency, there are no good quality antibody tests for use in screening. The evaluation of ovarian reserve therefore relies on classic measures (cycles, estradiol assay, FSH, AMH, pelvic ultrasound at the end of the cycle for antral follicle counts and measurement of endometrial thickness). Preserving patient fertility can then be discussed as a function of these results.

Auto-immune diseases are found in other family members in 10% of patients in the Norwegian cohort [2]. The existence of auto-immune Addison’s disease in the family should therefore be indicated on medical records of other family members, in order that they are examined for signs suggestive of auto-immune disorders.

More rarely, in around 14% of cases, notably in children and adolescents, auto-immune adrenal insufficiency is part of an auto-immune polyendocrinopathy type 1 (PEA1 or Auto-immune Poly Endocrinopathy Candidiasis Ectodermal Dystrophy (APECED) syndrome) (see Chapter 3). The multiple potential clinical problems and their serious nature warrant particular surveillance. In fact, some visceral manifestations (fulminant hepatitis, obliterative bronchiolitis, interstitial nephritis) or neoplastic disease (large granular lymphocytic leukemia, oral-esophageal carcinoma or gastric carcinoma) are potentially fatal [53,54]. The frequency and usual age of occurrence as well as the modalities of surveillance are summarized in Table 1.

In this polyendocrinopathy, hypoparathyroidism and chronic mucocutaneous candidiasis often precede adrenal insufficiency (together they make up the classic Whitaker triad), but can also sometimes occur after adrenal insufficiency [55]. Their frequency in PEA1 (Table 1) warrants the following annual checks:

- examination of calcium and phosphorous levels (at minimum, calcemia). Anti-NALP5 antibodies initially appeared to be specific for hypoparathyroidism in PEA1 [56] but later studies have not confirmed these findings [57]. Anti-calcium sensing receptor antibodies lack sensitivity in this pathology [57]. It is therefore not recommended to systematically test for these as part of screening;
- a cutaneous examination including skin appendages and buccal cavity by an experienced clinician, such as a dermatologist, stomatologist and/or gastroenterologist in the case of identified clinical cause of infection. In fact, other than the discomfort caused by recurrent candidiasis, the risk of mucocutaneous candidiasis progressing to carcinoma, if neglected, should not be ignored [53,54]. Examination of the skin also allows screening for other mucocutaneous signs such as vitiligo, alopecia, ungula dystrophy and dental enamel hypoplasia.

Ophthalmological examination should also be carried out if there is suspicion of keratoconjunctivitis.

In PEA1, other auto-immune disorders are less common (Table 1). Amongst the antibodies described as being specific for certain disorders, very few are actually assayed, at least in France, due to the rarity of the pathology [58]. Screening for these disorders therefore rests largely on clinical examination combined with simple biochemical tests, or physical examinations. On the other hand, some antibodies are found in auto-immune diseases other than PEA1 and are thus routinely measured. However, data from the literature supports their predictive value:

- endocrine disorders: patient questioning and hormone assays are in the forefront when examining the possibility of hypogonadism. Thyroid disorders which are usually rare, are more commonly found in adrenal insufficiency, usually presenting as hypothyroidism. In the case of anti-thyroid antibody positivity, the risk of hypothyroidism is 3% per year (mean surveillance of 7 years in the Italian study) [43]. Type 1 diabetes often presents later: anti-IA2 antibodies and anti-insulin being the best predictors of type 1 diabetes in this pathology [58]. Biochemical tests for pituitary markers can be performed to screen for hypophysitis;
- non-endocrine diseases: in the case of anti-parietal cell antibodies and/or anti-intrinsic factor antibodies, the risk of patients with adrenal insufficiency developing auto-immune gastritis is 2.6% per year (mean surveillance of 6yr)[43]. Malabsorption is frequently seen in PEA1, anti-GAD65 antibodies in this case correlate with malabsorption and not with type 1 diabetes. Celiac disease is unusual in PEA1 and therefore systematic screening for it is not necessary. Malabsorption is most likely linked to auto-immune damage to enterochromaffin cells or to the exocrine pancreas [58–61]. Auto-immune hepatitis of varying degrees of severity has been shown, however, fulminant forms have also been described. Anti-LKM1 antibodies are detected in 50–75% of cases of hepatitis in PEA1, but their predictive value has not been proven. The serious nature of this illness warrants an annual liver examination as a minimum. Patients should also be screened for splenic atrophy, since this increases the risk of infection and can possibly be prevented by anti-pneumococcal vaccination [54];
- rare manifestations: screening for rare disorders is justified by their serious nature: tubulointerstitial nephritis, HTA with hypokalemia from apparent mineralocorticoid excess, obliterator bronchiolitis [62]. Other rarer disorders are listed in
Table 1, and are not explored except where clinical symptoms suggest their presence;
• lastly, the psychological impact (depression, anxiety, alcoholism) and the social consequences of this complex pathology need to be taken into account [53];
• other than the recommended annual monitoring, it is important to warn patients of the risk of occurrence of serious clinical problems and symptoms that require rapid clinical attention [54].

R 6.5: We recommend a genetic counselling consultation in patients with adrenal insufficiency where an underlying genetic cause is suspected. Strong recommendation. Expert opinion

1.6. Screening for genetic forms of adrenal insufficiency

Some cases of adrenal insufficiency are hereditary and linked to a monogenic cause. These are the principal cause of primary adrenal insufficiency in pediatric patients (see Chapter 3). A genetic counselling consultation should be proposed to patients with these anomalies, to identify family members who may carry the genetic anomaly and/or are already suffering from the disorder, to inform them of the risks of having children with the anomaly and/or the inform them regarding the disorder itself.

2. Patient education

Patient education (PE) is an essential element of the non-pharmacological management of patients and does not consist simply of providing informations. It aims for the patient to acquire and maintain competency that will protect them from potentially life-threatening risks linked to their disease and to help them to be both more independent and to better live with their illness.

PE is recommended by the two published international consensus studies in the management of adrenal insufficiency [1,54]. The benefit of PE in adrenal insufficiency is assumed, based on the positive effect seen in other chronic diseases [66,67]. However, the results of studies with a good level of evidence were not as good as was expected of this therapeutic approach. Only two published studies on PE in patients with adrenal insufficiency have been published (Table 2) [68,69] (Fig. 1).

There is currently no common standard PE program for patients with adrenal insufficiency. The objective of this consensus document is to propose frames of reference to then facilitate development of a PE programs to benefit patients with adrenal insufficiency. For such a program, the following points will be defined:
• the themes to be included;
• the target population;

R 6.6: We recommend the development of patient education programs, particularly programs that aim to avoid or lead to early treatment of acute adrenal insufficiency, for the patients and their family or carers. We recommend the implementation of programs following the HAS (National Health Authority) procedure including the stages of education in diagnosis, the application of the program and its evaluation. We recommend the inclusion of the following principal educational objectives:
• to always carry the necessary emergency equipment;
• to be able to identify the situations at increased risk and the early symptoms of acute adrenal insufficiency;
• to know how to adjust oral glucocorticoids in acute situations or in anticipation of altered requirements, particularly in situations of: heat, physical exercise, travel, physical or psychological stress;
• to know how to administer hydrocortisone by subcutaneous injection;
• to appropriately use the resources of the health-care system;
• to be able to explain their pathology and its treatment to a member of their family or carer.

Strong recommendation. Expert opinion

• the educational message;
• the different steps in a PE program;
• conditions for implementation of a PE program.

2.1. Included themes
2.1.1. Adrenal crisis

Both of the existing consensus documents recommend PE to assist in avoiding or obtaining early treatment of acute adrenal insufficiency [1,54]. Acute adrenal insufficiency is a complication that has life-threatening implications for the patient. Physicians treating patients with acute adrenal insufficiency may have little knowledge of the complication since the signs and symptoms are non-specific and inconsistent. Acute adrenal insufficiency can resemble gastroenteritis on presentation, with abdominal pain, nausea, vomiting and diarrhea or can resemble a febrile infection, more or less severe depending on the impact of hemodynamic changes. It is possible that it may in some cases mimic septic shock. Some patients report headache, dizziness, bone and joint pain or diffuse myalgia as the main symptoms. Hypoglycemia is not commonly found in adults [70], contrary to what is seen in young children. Classic biochemical anomalies (hyponatremia, hyperkalemia and functional renal
insufficiency) are not consistently found (Fig. 2). Hence, a retrospective analysis of records from 67 patients with 21-hydroxylase deficiency who had 106 acute episodes labeled acute adrenal insufficiency, only detected hyponatremia in 30% of cases, hyperkalemia in less than 25% of cases and functional renal insufficiency in around 10% of cases (Fig. 3) [71]. Since gastroenteritis and infections are frequent causes of consultations in emergency while acute adrenal insufficiency is rare, intensive care physicians are likely to consider common pathologies and miss the diagnosis of acute adrenal insufficiency (Fig. 4). Additionally, in these medical situations, advice regarding anti-inflammatory corticosteroids can be incorrectly applied to patients with adrenal insufficiency (reducing treatment in the case of infection, not re-administering treatment after vomiting more than an hour after oral administration, failing to increase the treatment dose in the case of general anesthesia. See http://www.cortisone-info-fr). A German study showed that when responding to a questionnaire almost 15% of physicians, in an internal medicine service at a University hospital, ticked the box ‘reduction of glucocorticoid replacement by 50%’ in case of acute intercurrent illness in a patient with adrenal insufficiency [72]. Patients also report having been refused treatment with hydrocortisone on the grounds of the risk of complications of anti-inflammatory corticosteroids (see http://www.addisons.org.uk/info/experiences). A Canadian study of pediatric patients, showed that in the period 1998–2007, the protocol for management of patients with adrenal insufficiency was not applied in 26% of patients (17/66) in emergency admissions and in 20% (7/36) of patients in planned admissions, despite the existence and wide distribution of the written

### Table 2

<table>
<thead>
<tr>
<th>Published PE programs for patients with adrenal insufficiency.</th>
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<tbody>
<tr>
<td>Number of patients</td>
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<td>Causes</td>
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<td>Session(s)</td>
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Fig. 1. Errors in adapting hydrocortisone treatment in two given scenarios: (fever in the morning on the upper timeline and fever in the middle of the night on the lower timeline) for patients whose replacement therapy normally consists of one tablet in the morning and one at midday.

Fig. 2. Emergency cards identifying the patient as having adrenal insufficiency.
2.1.2. Other themes

The respective effects of glucocorticoid, mineralocorticoid and androgen treatments should be explained and the differences outlined.

Some patients feel the need to increase their daily glucocorticoid dose in response to alterations in their quality of life, particularly in response to chronic fatigue [2,28,33,34,82]. In fact, around 10% (23/334) patients were taking more than 30 mg/day equivalent dose of hydrocortisone in a recent German study [34] even though chronic overdose of hydrocortisone has adverse clinical effects in the long term, something which should be explained during a PE program.

The transition period from adolescence to adulthood carries a risk for patients with adrenal insufficiency, as they may escape medical monitoring with the consequent risk of lack of treatment compliance or interruption of treatment, and thus an increased risk of adrenal crisis. This subject also needs to be addressed in PE workshops (Fig. 5).

The psychosocial impact of the disease, its impact on efficiency at work, on quality of life, on sexual function and fertility and the long-term evolution of the disease, are equally themes that should be discussed (Fig. 6).

3. Target population

All patients with adrenal insufficiency are susceptible to suffering an episode of acute adrenal insufficiency, even though some of the factors that increase the risk of adrenal crisis have been identified (see Chapter 5). Priority patients for PE are those at higher risk of developing acute adrenal insufficiency and their parents/carers: the family of babies and young children (greater incidence of infection and hypoglycemia); patients who have already suffered acute adrenal insufficiency; those with primary adrenal insufficiency; patients with an associated pathology (polyendocrinopathy type 1, diabetes insipidus); pregnant women; patients experiencing unusual and altered working hours, large climatic variations and/or who are susceptible to infection.

protocol [73]. In this same study, over the same period 1998–2007, only 47% of patients received an increased dose of glucocorticoid before admission, underlining the need for optimizing PE programs in the parents.

The inefficiency of educational approaches that are limited to distributing information has been well documented in other chronic illnesses, for example asthma [74]. A significant proportion of patients do not have an emergency card (identifying them as having adrenal insufficiency) or other means of alerting healthcare workers, respond incorrectly to questionnaires on emergency scenarios, and do not correctly adjust their treatment in stressful situations [75–79]. Lastly, the lack of efficacy of training by the only crisis experience has also been shown in asthma [80] and is confirmed in acute adrenal insufficiency, since the risk of an episode of acute adrenal insufficiency was shown, in a German prospective study, to be about 3-fold higher in patients who have had a previous episode [81].
3.1. The educational messages

Consistency in educational messages to be delivered is necessary, particularly for adaptation of treatment. There are two strategies: the first, and most commonly used, is to modify the dose of hydrocortisone depending on the severity of the intercurrent condition (presence of fever, severity of fever, severe or mild illness, minor or major surgery) based on plasma cortisol levels observed in various conditions (anesthesia, different surgical procedures, diverses infections) [1,54,83]. A second strategy could be proposed with the aim of reducing and simplifying the instructions given. The arguments in favor of the second strategy are:

- plasma cortisol levels are very variable between individuals depending on intercurrent conditions. It is, thus, impossible to define a regimen that suits each individual and in each situation. In the acute state, priority needs to be given to prevention of acute adrenal insufficiency, and not to the risk of overdose. It is therefore preferable to recommend supplementation that will cover even the most severe conditions;

- in basal state, after inhibiting the ACTH axis using dexamethasone, there is a high degree of variability between individuals after administration of oral or parenteral hydrocortisone [84,85]. The impact of oral or parenteral hydrocortisone supplementation on cortisol levels in acute conditions is not known, but could equally be highly variable between individuals;

- the numerous different regimens suggested probably do not help in their application. In the absence of studies, the instructions offered rely on patient feedback and on the routine or habitual practices of clinicians.

The instruction ‘to double or triple the dose of hydrocortisone’ is ambiguous. The majority of patients understand that they need to increase the dose of hydrocortisone at the times that they normally take their medication, but because of this they do not increase their dose until several hours after the intercurrent condition arises, and thus are not appropriately dosed at the end of the day and during the night (Fig. 1). More accurate patient instructions that are adapted for the normal daily dose taken by the patient may avoid these pitfalls.

Digestive problems are the principal factor triggering acute adrenal insufficiency [77,78]. They affect the absorption of hydrocortisone and necessitate administration of parenteral hydrocortisone. Early injection of hydrocortisone can avoid the development of dehydration and hemodynamic problems. It is therefore recommended that the patient or their family administer hydrocortisone by injection as soon as possible rather than waiting for the arrival of a care provider at their home or at an emergency department, considering the delay that this may cause. Furthermore, some patients report a lack of understanding...
R6-7: We suggest that the dose of hydrocortisone be adjusted in situations likely to cause acute adrenal insufficiency (see Chapter 5), with in adults, the dose of fludrocortisone being increased by 50 µg per 24 hr in the case of extreme heat.

- for adult patients who usually take one 10 mg hydrocortisone tablet in the morning and one at midday, in situations likely to cause acute adrenal insufficiency, we suggest the following advice: ‘Immediately take 2 tablets of hydrocortisone, regardless of the time of day, then 2 tablets in the morning, 2 tablets at midday and 2 tablets in the evening for 2–3 days until symptoms have gone’;
- for pediatric patients, we suggest to double or triple the dose of hydrocortisone, divided into three administrations per day, with one dose around midday and one at night. This regimen should be started immediately in the case of a situation of increased risk and continued until 24 hr after symptoms have disappeared. We suggest that situations of prolonged fasting are avoided due to the risk of hypoglycemia. Weak recommendation. Expert opinion

R6-8: We suggest that an injection of hydrocortisone be delivered

- after the second episode of vomiting or diarrhea in less than half a day;
- in the case of altered consciousness where oral administration is not possible;
- during childbirth, general anesthesia or in resuscitation/intensive care. Weak recommendation. Expert opinion

R6-9: We suggest the following advice for particular circumstances: for intense and prolonged sporting activity in adults and adolescents: ‘Take supplementary 5 mg hydrocortisone every 3 hr, commencing 1 hr before the start of physical activity’.

In case of air travel greater than 6 hr in adults: ‘Take supplementary 10 mg hydrocortisone every 6 hr until breakfast time in the country where you arrive’.

In the case of extreme heat and/or excessive sweating: ‘Drink more water than usual and add more salt to food; otherwise in adults, increase fludrocortisone by 50 µg’.

Weak recommendation. Expert opinion

of the necessity to rapidly administer an injection of hydrocortisone, in some healthcare teams or a refusal to follow the protocol. A study on the patient care in episodes of adrenal crisis found a delay in commencing an emergency treatment in 46% of patients with Addison’s disease [86]. A German study showed that less than 30 min after subcutaneous injection of 100 mg hydrocortisone, patients had a plasma cortisol level greater than 36 µg/dL (1000 nmol/L), and that patient acceptance of this mode of injection was good. The time after subcutaneous injection to achieve this level is only slightly greater than that for intramuscular injection (mean 22 min after subcutaneous injection versus 11 min after intramuscular injection). If the subcutaneous injection is delivered early, before a state of shock arises, it is likely that absorption is little different to that for an intramuscular injection delivered by professional healthcare staff [85].

In cases of intense, but short duration physical activity (less than 30 min), it is not necessary to increase the dose of hydrocortisone [87,88]. There are no published studies on severe prolonged physical activity such as long distance running, triathlon, triathlon, squash, competition cycling or speed skating (see classification of sport, Mitchell [89]). Administration of 2.5–5 mg of hydrocortisone each 3 hr, starting 1 hr before the commencement of physical activity [90] or taking 5–10 mg supplementary hydrocortisone [70,90,91] have been suggested, but neither of these strategies has been evaluated.

3.2. Steps in the PE program

3.2.1. Educational diagnosis

Patient education should start with an individual interview with the multidisciplinary team, based on validated information documents (validated by the regional health authority [ARS in France]). This will assist the patient to understand their situation, with their illness and to obtain information on their needs and wishes, what they understand and believe in terms of health, and also what they see as their problems. As in any patient education, it is indispensable that the care giver have an approach that favors optimal education (empathetic attitude, open questions, active listening, reformulating questions, positive reinforcement). There is a need to encourage patients to recount their daily life: administration of hydrocortisone in one dose in the morning rather than in two or three doses during the day; delay in taking the first dose; adults taking a dose late at night mimicking the childhood regimen of two doses at the two ends of the day; delay in filling prescription for their medication leading to the need to ‘economise’ their tablets by taking a lower daily dose or only every second day; experiences of treatment interruption that was well (or less well) supported or tolerated. Two polar attitudes in the management of treatment by patients are encountered: first ‘corticophobic’ patients and second those who take doses that are too high. The ‘corticophobic’
Table 3
Examples of program sessions aimed at early treatment or avoidance of acute adrenal insufficiency.

<table>
<thead>
<tr>
<th>Stages</th>
<th>Principal objectives</th>
<th>Learning tools</th>
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<tbody>
<tr>
<td>Better understanding your disease</td>
<td>List the signs of acute adrenal insufficiency</td>
<td>Visualised discussion (Métaplan®)</td>
</tr>
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<td></td>
<td>Recognise the early signs of acute adrenal insufficiency</td>
<td>Photolangaga®</td>
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<td></td>
<td>Explain the differences between hydrocortisone and anti-inflammatory corticosteroids</td>
<td>Description of an episode of acute adrenal insufficiency by one or more patients</td>
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<td>Know the signs and consequences of chronic hydrocortisone overdose</td>
<td>Outline of treatments</td>
</tr>
<tr>
<td>Managing your treatment</td>
<td>Know how to identify situations that require adaptation of their treatment</td>
<td>Card game–information/overdose</td>
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<td></td>
<td>Know how to adjust their oral medication</td>
<td>Card game: risky situations</td>
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<td></td>
<td>Know when and how to administer hydrocortisone by injection</td>
<td>Quiz</td>
</tr>
<tr>
<td></td>
<td>Know how to make up their ‘emergency kit’</td>
<td>Timeline</td>
</tr>
<tr>
<td>Living with their disease</td>
<td>Facing up to difficult situations</td>
<td>Training in preparing and carrying out an injection (practical handout/video)</td>
</tr>
<tr>
<td></td>
<td>Adapting daily life</td>
<td>Toolbox or case with equipment for injection</td>
</tr>
<tr>
<td></td>
<td>Identifying useful resources</td>
<td>Decision wheel</td>
</tr>
</tbody>
</table>

Patient is reluctant to increase his doses because he believes that this will have the same consequences as Cushing’s syndrome or anti-inflammatory corticosteroids, or he confounds hydrocortisone and anti-inflammatory corticosteroid compounds, and their family and carers (including health professionals) reinforce this error. Other patients are prone to taking excessive doses due to frustration with symptoms such as chronic pain or fatigue. These two attitudes can co-exist in the same patient, such as chronic over-dosing but failure to adjust their treatment correctly in the face of an acute illness. The lack of self-confidence, belief in the infallibility of the doctor’s word and denial of their illness—all are obstacles to rapid adaptation of treatment by patients themselves. Particular situations should be researched and considered: exposure to extremes of temperature; rhythm of daily life; work, sleep, intensive sporting activity, fasting and travel. Some patients may have given up sporting activity or travel because of the fear of acute adrenal insufficiency occurring. The possibility of restoring control over their disease will be a strong motivation for learning.

Patient education allows the establishment of personalized goals for the patient. The principal educational objectives are the following:

- to carry at all times the tools necessary to cope with an emergency (card identifying the patient as having adrenal insufficiency (Fig. 2), ± personal alarm, hydrocortisone tablets, and in the case of mineralocorticoid deficiency, fludrocortisone tablets, injectable hydrocortisone and equipment for injection, instructions for treatment in case of emergency in French and potentially in foreign language) (Fig. 3);
- to be able to identify risky situations and the first symptoms of acute adrenal insufficiency;
- to know how to adjust oral glucocorticoid treatment;
- to know the signs and the consequences of chronic hydrocortisone overdose;
- to know how to administer hydrocortisone by subcutaneous injection (Figs. 5 and 6);
- to know how to adapt treatment for particular situations: heat, intense physical exercise, travel;
- to possess a card identifying the patient as having adrenal insufficiency and the emergency card;
- to know how to use the relevant resources of the healthcare system and associated resources (Association Surrénales (Adrenal Association), France. http://www.surrenales.com).

3.2.2. Sessions

The sessions to be held should be defined by the education team depending on the local resources and constraints (individual sessions and/or group or collective sessions, ambulatory, in hospital, dedicated room, dedicated health care teachers...) as well as the educational means and methods to be used. The summary at the end of the patient’s program then needs to be sent to others who are involved in managing the patient. The PE is
then reinforced during later consultations or hospital admissions (Table 3).

3.2.3. Program evaluation

At the end of the PE session, the knowledge and competencies acquired by the patients to manage their disease independently and the short, medium and long-term consequences should be evaluated. Tools for evaluating knowledge and skills should be used for this, with the final objective being to establish an educational checklist and to determine which pathways should be developed in the future.

3.2.4. The conditions for putting PE programs into practice

PE programs need to be established within the framework that is authorized by current legislation (Legifrance. Decree 2010-904, August 2, 2010, relating to conditions for authorization of patient therapeutic education programs: http://www.legifrance.gouv.fr/affichTexte.do?jsessionid=F90D5E8ACEF64507C4A83D3FA700CD8D.tpdpio04v3?cidTexte=JORFTEXT000022664533&categorieLien=id).

A national program is currently being developed.

Disclosure of interest

The authors declare that they have no competing interest.

References


