A CASE-BASED DIALOGUE SYSTEM FOR INVESTIGATING THERAPY INEFFICACY

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Keywords: Case-Based Reasoning, Therapy Support, Medicine, Endocrine, Psychiatry.

Abstract: ISOR is a Case-Based Reasoning system for long-term therapy support in the endocrine domain and in psychiatry. ISOR performs typical therapeutic tasks, such as computing initial therapies, initial dose recommendations, and dose updates. ISOR deals especially with situations where therapies become ineffective. Causes for inefficacy have to be found and better therapy recommendations should be computed. In addition to former already solved cases, ISOR uses further knowledge forms, especially medical histories of query patients themselves and prototypes. Furthermore, the knowledge base consists of therapies, conflicts, instructions etc. So, different forms and steps of retrieval are performed, while adaptation occurs as an interactive dialog with the user.

1 INTRODUCTION

In medical practice, therapies prescribed according to a certain diagnosis sometimes do not give desired results. Sometimes therapies are effective for some time but suddenly stop helping any more. There are many different reasons. A diagnosis might be erroneous, the state of a patient might have changed completely or the state might have changed just slightly but with important implications for an existing therapy. Furthermore, a patient might have caught an additional disease, some other complication might have occurred, or a patient might have changed his/her lifestyle (e.g. started a diet) etc.

For long-term therapy support in the endocrine domain and in psychiatry, we have developed a Case-Based Reasoning system, named ISOR, that not only performs typical therapeutic tasks but also especially deals with situations where therapies become ineffective. Therefore, it first attempts to find causes for inefficacy and subsequently computes new therapy recommendations that should perform better than those administered before.

ISOR is a medical Case-Based Reasoning system that deals with the following tasks:

- choose appropriate (initial) therapies,
- compute doses for chosen therapies,
- update dose recommendations according to laboratory test results,
- establish new doses of prescribed medicine according to changes in a patient's medical status or lifestyle,
- find out probable reasons why administered therapies are not as efficient as they should,
- test obtained reasons for inefficacy and make sure that they are the real cause, and
- suggest recommendations to avoid inefficacy of prescribed therapies.

ISOR deals with long-term diseases, e.g. psychiatric diseases, and with diseases even lasting for a lifetime, e.g. endocrine malfunctions.

For psychiatric diseases some Case-Based Reasoning systems have been developed, which deal with specific diseases or problems, e.g. with Alzheimer's disease (Marling and Whitehouse, 2001) or with eating disorders (Bichindaritz, 1994). Since we do not want to discuss various psychiatric problems but intend to illustrate ISOR by understandable examples, in this paper we focus mainly on some endocrine and psychiatric disorders, namely on hypothyroidism and depressive symptoms. Inefficacy of pharmacological therapy for depression is a widely known problem (e.g. (Barbee and Jamhour, 2002), (Cuffel et al, 2003), (Hirschfeld, Montgomery et al, 2002), (Keitner, Posternak, and Ryan, 2003), (Lam, Wan, Cohen, and Kennedy, 2002)). There are many approaches to

Schmidt R. and Vorobieva O. (2007).
A CASE-BASED DIALOGUE SYSTEM FOR INVESTIGATING THERAPY INEFFICACY.
In *Proceedings of the Second International Conference on Software and Data Technologies - PL/DPS/KE/WsMUSE*, pages 171-178

solve this problem. Guidelines and algorithms have been created (e.g. (Alacorn, Glover, Boyer, and Balon, 2000), (Expert Consensus Guideline Series, 2000) (Osser and Patterson, 1998)). ISOR gives reference to a psychopharmacology algorithm (Osser and Patterson, 1998) that is available on the website htp://mhc.com/Algorithms/Depression.

The paper is organized as follows. Firstly, we introduce typical therapeutic tasks, subsequently we present the architecture of ISOR and finally we illustrate how it works by examples.

2 TYPICAL THERAPEUTIC TASKS

As a consequence of our experiences with ICONS (Schmidt and Gierl, 2001) a system for antibiotic therapy advice, and with therapy support programs for hypothyroidism (Vorobieva, Gierl, and Schmidt, 2002), we believe that four tasks exist for medicinal therapies. The first one means computing an initial therapy, secondly an initial dose has to be determined, later on dose updates may be necessary, and finally interactions with further diseases, complications, and especially with already administered therapies have to be considered.

In the following we illustrate the four tasks by our programs that deal with therapy support for hypothyroid patients. The antibiotics therapy adviser ICONS deals only with two of these tasks: computing initial therapies and initial doses.

2.1 Computing an Initial Therapy

Probably, the most important task for therapies is the computation of initial therapies. The main task of ICONS is to compute promising antibiotic therapies even before the pathogen that caused the infection is determined in the laboratory. However, for hypothyroidism ISOR does not compute initial therapies but only initial doses, because for hypothyroidism only one therapy is available: it is thyroid hormone, usually in form of levothyroxine.

2.2 Computing an Initial Dose

In ICONS the determination of initial doses is a rather simple task. For every antibiotic a specific calculation function is available and has to be applied.

For hypothyroidism the determination of initial doses (figure 1) is more complicated. Firstly, a couple of prototypes exist. These are recommendations that have been defined by expert commissions. Though we are not sure whether they are officially accepted, we call them guidelines. The assignment of a patient to a fitting guideline is obvious because of the way the guidelines have been defined. With the help of these guidelines a range for good doses can be calculated.

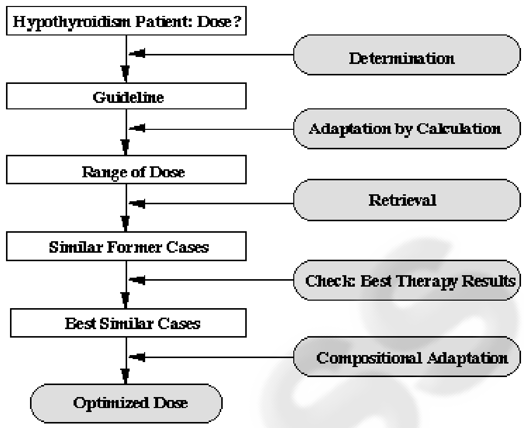

Figure 1: Determination of an initial levothyroxine dose.

To compute a dose with best expected impact, we retrieve similar cases whose initial doses are within the calculated ranges. Since cases are described by few attributes and since our case base is rather small, we use Tversky's sequential measure of dissimilarity (Tversky, 1977). On the basis of those retrieved cases that had best therapy results an average initial therapy is calculated. Best therapy results can be determined by values of a blood test after two weeks of treatment with the initial dose. The opposite idea to consider cases with bad therapy results does not work here, because bad results can also be caused by various other reasons.

To compute optimal dose recommendations, we apply two forms of adaptation. First, a calculation of ranges according to guidelines and patients attribute values. Secondly, we use compositional adaptation. That means, we take only similar cases with best therapy results into account and calculate the average dose for these cases, which has to be adapted to the query patient by another calculation.

2.3 Updating the Dose in a Patient's Lifetime

For monitoring a hypothyroidism patient, three basic laboratory blood tests (TSH, FT3, FT4) have to be undertaken. Usually the results of these tests correspond to each other. Otherwise, it indicates a more complicated thyroid condition and additional tests are necessary. If the results of the basic tests show that the patients thyroid hormone level is normal, it means that the current levothyroxine dose is OK. If the tests indicate that the thyroid hormone level is too low, the current dose has to be increased by 25 or 50 μg, if it is high, the dose has to be decreased by 25 or 50 μg ((DeGroot, 1994), (Hampel, 2000)). So, for monitoring, adaptation means calculating according to some rules, which are based on guidelines. Since an overdose of levothyroxine may cause serious complications for a patient, a doctor cannot simply consider test results and symptoms that indicate a dose increase but additionally he/she has to investigate reasons why the current dose is not appropriate any more. In ISOR this situation is described as a problem of therapy inefficiency. In most cases the solution is obvious, e.g. puberty, pregnancy etc. These situations are covered by adaptation rules. Sometimes cases are observed in which the hypothyroidism syndromes are unexplained. For these cases ISOR uses the problem solving program.

2.4 Additional Diseases or Complications

It often occurs that patients do not only have hypothyroidism, but they suffer from further chronic diseases or complications. Thus, a levothyroxine therapy has to be checked for contraindications, adverse effects and interactions with additionally existing therapies. Since no alternative is available to replace levothyroxine, if necessary additionally existing therapies have to be modified, substituted, or compensated ((DeGroot, 1994), Hampel, 2000)).

ISOR performs three tests. The first one checks if another existing therapy is contraindicated to hypothyroidism. This holds only for very few therapies, namely for specific diets like soybean infant formula, which is the most popular food for babies who do not get enough mother's milk but it prevents the effect of levothyroxine. Such diets have to be modified. Since no exact knowledge is available to explain how to accomplish this, our program just issues a warning saying that a modification is necessary.

The second test considers adverse effects. There are two ways to deal with them. A further existing therapy has either to be substituted or it has to be compensated by another drug. Such knowledge is available, and we have implemented corresponding rules for substitutional and compensational adaptation.

The third test checks for interactions between both therapies. We have implemented some adaptation rules, which mainly attempt to avoid the interactions. For example, if a patient has heartburn problems that are treated with an antacid, a rule for this situation states that levothyroxine should be administered at least four hours after or before an antacid. However, if no adaptation rule can solve such an interaction problem, the same substitution rules as for adverse effects are applied.

3 SYSTEM ARCHITECTURE

ISOR is designed to solve typical problems, especially inefficacy of prescribed therapies that can arise in different medical domains. Therefore most algorithms and functions are domain independent. Another goal is to cope with situations where important patient data is missing and/or where theoretical domain knowledge is controversial.

ISOR does not generate solutions itself. Its task is to help users by providing all available information and to support them to find optimal solutions. Users shall be doctors, maybe together with a patient.

Technically, ISOR is implemented in Delphi 7, the format for the case and knowledge bases is Paradox 7, and retrieval is performed by SQL.

In addition to the typical Case-Based Reasoning knowledge, namely former already solved cases, ISOR uses further knowledge components, namely medical histories of query patients themselves and prototypical cases (prototypes). Furthermore, ISOR's knowledge base consists of therapies, conflicts, instructions etc. The architecture is shown in figure 2.

In this section we explain the components and in the next chapter we present examples to show how the main knowledge components work together.

3.1 Medical Case Histories

Ma and Knight (Ma and Knight, 2003) have introduced a concept of case history in Case-Based Reasoning. Such an approach is very useful when we deal with chronic patients, because often the same complications occur again, former successful solutions can be helpful again, while former unsuccessful solutions should be avoided.

The case history is written in the patient's individual base as a sequence of records. A patient's base contains his/her whole medical history, all medical information that is available: diseases, complications, therapies, circumstances of his/her life etc. Each record describes an episode in a patient's medical history. Episodes often characterise a specific problem. Since the case base is problem oriented, it contains just episodes and the same patient can be mentioned in the case base a few times, even concerning different problems.

Information from the patient's individual base can be useful for a current situation, because for patients with chronic diseases very similar problems often occur again. If a similar situation is found in the patient's history, it is up to the user to decide whether to start retrieval in the general case base or not.

In endocrinology, case histories are designed according to a standard scheme, one record per visit. Every record contains the results of laboratory tests and of an interrogatory about symptoms, complaints and physiological conditions of a patient.

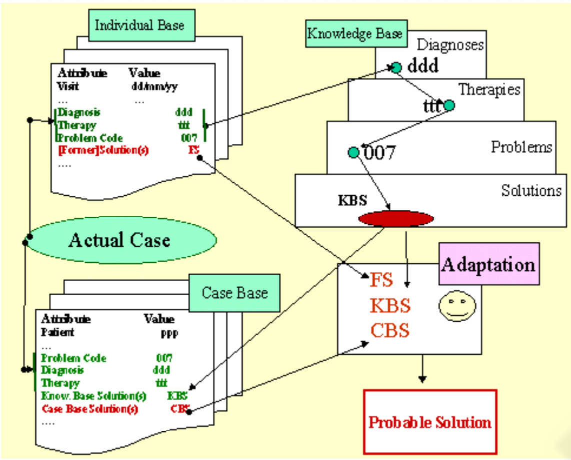

Figure 2: ISOR's architecture.

Therefore the retrieval of former similar situations from the individual base of an endocrine patient is easy to organise.

For psychiatric patients, case histories are often unsystematic and they can be structured in various forms. A general formalisation of psychiatric cases and their histories is not achieved yet. The design of case histories is problem dependent.

In both domains, we first search in the query patient's history for similar problems and for similar diagnoses.

3.2 Knowledge Base, Case Base, and Prototypes

The knowledge base contains information about problems and their solutions that are possible according to the domain theory. It has a tree structure and it consists of lists of diagnoses, corresponding therapies, conflicts, instructions, and medical problems (including solutions) that can arise from specific therapies. The knowledge base also contains links to guidelines, algorithms and references to correspondent publications ((Alacorn, Glover, Boyer, and Balon, 2000), (Expert Consensus Guideline Series, 2000), (Osser, and Patterson, 1998)).

The case base is problem oriented. Thus a case in the case base is just a part of a patient's history, namely an episode that describes a specific problem that usually has a solution too. So, the case base represents decisions of doctors (diagnosis, therapies) for specific problems, and their generalisations and their theoretical foundations (see the examples). A solution is called "case solution", abbreviated "CS". Every case solution has (usually two) generalisations, which are formulated by doctors. The first one is expressed in terms of the knowledge base and it is used as a keyword for searching in the knowledge base. Such a generalisation is called "knowledge base solution", abbreviated "KBS". The second generalisation of a solution is expressed in common words and it is mainly used for dialogues. It is called "prompt solution", abbreviated "PS".

Former cases (attribute value pairs) in the case base are indexed by keywords. Each case contains keywords that have been explicitly placed by an expert. For retrieval three main keys are used: a code of the problem, a diagnosis, and a therapy. Further keys such as age, sex etc. can be used optionally.

Prototypes (generalized cases) play a particular role. Prototypes help to select a proper solution from the list of probable or available solutions. A prototype may help to point out a reason of inefficacy of a therapy or it may support the doctor's choice of a drug.

3.3 Retrieval, Adaptation, and Dialogue

For retrieval keywords are used. Since our system is problem oriented, the first one is a code that implies a specific problem. The second keyword is the diagnosis and the other ones are retrieved from the knowledge base.

Adaptation takes place as a dialogue between the doctor, the patient, and the system. The system presents different solutions, versions of them, and asks questions to manifest them. The doctor answers and selects suggestions, while the patient himself or herself suggests possible solutions that can be considered by the doctor and by the system.

We differentiate between two steps of adaptation. The first one occurs as a dialogue between ISOR and a user. Usually, doctors are the users. However, sometimes even a patient may take part in this dialogue. The goal of these dialogues is to select probable solutions from all information sources mentioned in sections 3.1 and 3.2. Pieces of information are retrieved by the use of keywords. Specific menus support the retrieval process. The first step of adaptation can be regarded as partly user based: ISOR presents lists of probable solutions and menus of keywords, the user selects the most adequate ones. The second adaptation means proving obtained solutions. This proving is rule based and it includes further dialogues, laboratory test results, and consultations with medical experts. While the procedures supporting the first adaptation step are domain independent, the adaptation rules of the second step are mainly domain dependent.

4 EXAMPLES

By three examples we illustrate how ISOR works. The first and the second one are from the endocrine domain, the third one deals with a psychiatric problem.

4.1 Hypothyroidism

4.1.1 Inefficacy of Levothyroxine Therapy

Every morning a mother gives her 10 year-old boy not only the prescribed Levothyroxine dose but also vitamin pills. These pills have not been prescribed but they are healthy and have lately been advertised on TV. Part of this medication is Sodium Hydrocarbonate (cooking soda) that causes problems with Levothyroxine.

Individual base. The same problem, inefficacy of Levothyroxine therapy, is retrieved from the patient's history. The solution of the former problem was that the boy did not take the drug regularly. This time it must be a different cause, because the mother controls the intake.

Knowledge base. It has a tree structure that is organised according to keys. One main key is *therapy* and the keyword is *Levothyroxine*. Another keyword is *instructions*. These instructions are represented in form of rules that concern the intake of Levothyroxine. For Levothyroxine a rather long list of instructions exists. Since the idea is that the boy may break an instruction, this list is sorted according to the observed frequency of offences against them in the case base.

Concerning these instructions a couple of questions are asked, e.g. whether the boy takes Sodium Hydrocarbonate together with Levothyroxine. Since the mother is not aware of the fact that Sodium Hydrocarbonate is contained in the vitamin pills, she gives a negative answer and no possible solution can be established by the knowledge base. However, *soda* is generated as one keyword for retrieval in the case base.

So, the following solutions are retrieved from the knowledge base, the third one does not fit for the boy.

Knowledge base solution 1: Sodium Hydrocarbon
Knowledge base solution 2: Soy
Knowledge base solution 3: Estrogene

Case base. Using the keyword *soda* eight cases with the following seven solutions are retrieved (case solution 4 occurs twice).

Case solution 1: Aspirin Upsa
Case solution 2: Cooking Soda
Case solution 3: Soluble juice
Case solution 4: Alka Seltzer
Case solution 5: “Invite”
Case solution 6: Vitamin “Teddy”
Case solution 7: Lime Pills”

Thus we get a list of drugs and beverages that contain sodium Hydrocarbonate, all of them belong to the generalised solution “soluble”.

Solution. The boy admits to take Levothyroxine together with an instantiation of the generalised solution “soluble”, namely soluble vitamin.

Recommendation. The boy is told to take vitamin four hours later than Levothyroxine. Additionally, further interactions between vitamin and Levothyroxine must be checked, because it might be necessary to adjust the Levothyroxine dose.

4.1.2 Improving the Efficacy by Dose Updates

Figure 3 shows an example of a case study. We compared the decisions of an experienced doctor with the recommendations of ISOR. The decisions are based on basic laboratory tests and on lists of observed symptoms. Intervals between two visits are approximately six months. In this example there are three deviations between the doctor's and ISOR's decisions, usually there are less. At the second visit (v2), according to laboratory results the Levothyroxine should be increased. ISOR recommended a too high increase. The applied adaptation rule was not precise enough. So, we modified it. At visit 10 (v10) the doctor decided to try to decrease the dose. The doctor's reasons were not included in our knowledge base and since his attempt was not successful, we did not alter any adaptation rule. At visit 21 (v21) the doctor increased the dose because of some minor symptoms of hypothyroidism, which were not included in ISOR's list of hypothyroidism symptoms. Since the doctor's decision was probably right (visit 22), we added these symptoms to the list of hypothyroidism symptoms of ISOR.

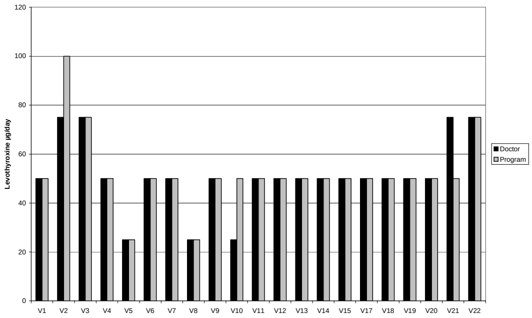

Figure 3: Dose updates recommended by our program compared with doctor's decision. V1 means the first visit, V2 the second visit and so on.

4.2 Inefficacy of Psychiatric Drugs

Originally, ISOR was developed for the endocrine domain, especially for hypothyroidism, but later on it has been generalised. Now it can solve the same types of problems in different medical domains. Now we present an example from psychiatry.

A man, 55 years of age, has been treated for depression for 15 years. Symptoms of depression appeared after he was cruelly beaten near his house. Since he did not see any connection between his depression and the violence, he did not tell it to his doctor. At first, the antidepressant Tofranil for intake in the morning and the sedative Tisercin for better sleep at bedtime were prescribed. Later on, during another depression stage the antidepressant Fluoxetine helped. Now, his problem is that neither Fluoxetine, nor any other proposed antidepressant helps any more.

Retrieval. Keywords are used to retrieve information from all data sources. Since optional keywords about a patient's feeling (e.g. *feeling worse*) are used for retrieval of the patient's medical history, even biographical events of a patient can be retrieved.

Individual base. Since the problem of inefficacy of an antidepressant never arose in the patient's past, no solution can be found. However, indirect information was retrieved. The keyword *feeling better* provided a trip to Switzerland, while the result of the keyword *feeling worse* provided a trip to Israel, where the latest very severe depression began.

Feeling better: A trip to Switzerland
Feeling worse: A trip to Israel

The knowledge base contains information about depression, anxiety and other psychiatric diseases, possible complications and references to their theoretical grounds ((Davidson, 1991), (Flor-Henry, P., 1983), (Gelder, Lopez-Ibor, and Andeasen, 2000), (Leonhard, 1979), (Tucker and Liotti, 1989)). References to similar problems are retrieved, the most remarkable one is a link to the algorithm for psychopharmacology of depression (http://mhc.com/Algorithms/Depression, (Osser and Patterson, 1998). Though the idea of the algorithm is to solve the problem of non-response to an antidepressant, it does not really fit here, because it does not cover the situation that a therapy helped for some time and then stopped having an effect.

Case base. Eleven cases with similar depression problems are retrieved. Three of them are characterised by the general idea *depression is secondary to anxiety resulting from a psychical trauma*.

Case solution 1: Severe stress during the World War 2
Case solution 2: Bad experience in a Jail
Case solution 3: Sexual assault in childhood

The other cases have solutions that are generalised to *changes in therapy*.

Adaptation. ISOR displays retrieved information pieces. In this case, two strategies are offered. The first one suggests trying some other therapy. This strategy is supported by the majority of the retrieved cases and partly by theoretical recommendations. The second strategy means to check the diagnosis. This strategy is supported by three retrieved cases and by the patient's medical history. The choice between both strategies is up to the user. In this example the doctor chooses to attempt the second strategy at first. The doctor is especially led by the patient's medical history, because Switzerland is usually associated with a safe life (especially in comparison to life in Russia), while living in Israel is considered as unsafe. Furthermore, this strategy is supported by the general situation that some sedative drugs (e.g. Tisercin at the beginning) had helped for some time.

ISOR offers a list of questions for the favoured strategy and as a result the doctor concludes that in this case depression is in fact only second to anxiety. The man is permanently afraid of possible violence and anxiety is based on strong fear that occurred long ago.

Explaining remarks. Diagnosing anxiety needs good medical skills, because patients try to suppress traumatic events from their memory (Stein, 2003). In this example depression even served as a mechanism of suppression. The accepted case-based solution spared the patient unnecessary experiments with other psychopharmacological drugs.

So, the first problem is solved, a new diagnosis is ascertained.

The next problem is prescription of a therapy. According to the domain theory and to our knowledge base anxiety implies Neuroleptics (Gelder, Lopez-Ibor, and Andeasen, 2000.), (Kalinowsky, and Hippius, 1969). Many of them are available but a good choice is not trivial.

Individual base. From the patient's history those sedatives (Neuroleptics) are retrieved that he took in his lifetime and that had positive effects on his psychical condition: Tisercin and Paxil, which is a drug that has both sedative and antidepressive effects.

Prototype. Among those prototypes that have been defined by doctors (based on their long experience with cases) the prototypical solution Paxil is retrieved.

Adaptation. Before described, every drug must be checked for conflicts with the patient's additional diseases and already existing therapy. Though the query patient has already taken Paxil in the past, our system checks all possible conflicts. If necessary, adaptation has to be performed. In this case no conflicts are discovered and Paxil is prescribed.

5 CONCLUSION

We have presented a CBR system that helps doctors to solve medical problems, particularly to investigate causes of inefficacy of therapies. It includes different knowledge containers, namely a case base, a knowledge base, prototypes, and individual bases of patients that reflect their medical histories. Information retrieved from these containers is arranged in form of dialogues.

The case base plays a central role in the dialogue forming process. It serves as a kind of filter when the knowledge base suggests too many possible solutions for the problem (as in the first example). In this situation the most typical cases are retrieved from the case base. When a solution from the knowledge base is not convincing or when it is hardly adaptable, the case base may provide better alternatives (as in the third example).

Generalisations, keywords and references to other knowledge components belong to the case base. The adaptation program uses them to create dialogues. In the part that concerns the case base and the dialogues ISOR can be considered as domain independent.

The design of the case base and our implementation allow solving problems from different medical domains. Specific, domain dependant features are attributed mostly to the individual base, because every domain requires a special design of case histories. The knowledge base in ISOR is domain-oriented, but all algorithms and functions are completely domain independent.

ACKNOWLEDGEMENTS

We thank Dr. Monika Mix, Children's Hospital of the University Clinic of Rostock, and Prof. Nikolai Nikolaenko, Sechenov Institute of Evolutionary Physiology and Biochemistry in St.Petersburg, for their data and for their help and time during our consultations.

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