A Cost-Effective Agent for Clinical Trial Assignment

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Abstract— **The purpose of a clinical trial is to evaluate a new treatment procedure. When medical researchers conduct a trial, they recruit participants with appropriate medical histories. To select participants, the researchers analyze medical records of the available patients, which has traditionally been a manual procedure. We describe an intelligent agent that helps to select patients for clinical trials. If the available data are insufficient for choosing patients, the agent suggests additional medical tests and finds an ordering of the tests that reduces their total cost.**

Keywords— **Medical expert systems, automated diagnosis, clinical trials.**

I. Introduction

A *clinical trial* is an experiment with a new treatment procedure. When medical researchers test a new treatment, they recruit patients with appropriate health problems and medical histories. The selection of patients has traditionally been a manual procedure, and recent studies have shown that clinicians can miss up to 60% of the eligible patients [9, 10, 14, 26, 35, 38].

If the available records do not provide enough data, clinicians perform medical tests as part of the selection process. The costs of most tests have declined over the last decade, but the number of tests has significantly increased [33, 36], which is partially due to inappropriate ordering of tests [1, 25]. Clinicians can reduce the cost by first requiring inexpensive tests and then using their results to avoid some expensive tests; however, finding the right ordering may be a complex problem.

The purpose of the described work is to automate the selection of patients for clinical trials and minimize the cost of related tests. We have developed an agent that identifies appropriate trials for each patient, and built a knowledge base for breast-cancer trials.

II. Previous Work

Researchers began to work on medical expert systems in the early seventies. Shortliffe *et al.* developed the MYCIN system, which diagnosed bacterial diseases [5, 30, 31]. Its knowledge base consisted of *if-then* rules, which allowed for the analysis of symptoms and evaluation of the certainty of the diagnosis. Experiments showed that MYCIN correctly diagnosed common diseases, which led to the development of other medical systems [5, 19], such as NEOMYCIN, PUFF, CENTAUR, and VM. Shortliffe *et al.* created a system for selecting chemotherapy treatments, called ONCOCIN [32], which also evolved from MYCIN.

Lucas *et al.* constructed a rule-based system for diagnosing liver and biliary-tract diseases [16], but it often gave an incorrect diagnosis [12, 23]. Korver and Lucas converted the initial system into a Bayesian network, which improved its performance [13, 15].

Musen *et al.* built a rule-based system, called EON, that selected AIDS patents for clinical trials [20]. Ohno-Machado *et al.* developed the AIDS^2 system, which also assigned AIDS patients to clinical trials [21]. They integrated logical rules with Bayesian networks, which helped to make decisions in the absence of some data.

Bouaud *et al.* created a cancer expert system, called ONCODOC, that suggested alternative clinical trials for each patient and allowed a physician to choose among them [3, 4]. Séroussi *et al.* used ONCODOC to select participants for clinical trials at two hospitals, which helped to increase the number of selected patients by a factor of three [27, 28, 29].

Hammond and Sergot created the OaSiS architecture [11], which combined the techniques from earlier systems, including EON and ONCOCIN. Smith *et al.* built a system that assisted a clinician in selecting medical tests and reducing their number and cost [17, 18, 33].

Fallowfield *et al.* studied how physicians selected cancer patients for clinical trials, and compared manual and automatic selection [8]. They showed that expert systems could improve the selection accuracy; however, their study also revealed that physicians were reluctant to use these systems. Carlson *et al.* conducted similar studies with AIDS trials, and also concluded that expert systems could lead to a more accurate selection [6].

Theocharous developed a Bayesian system that selected clinical trials for cancer patients [24, 34]. It learned conditional probabilities of medical-test outcomes and evaluated the probability of a patient's eligibility for each trial. On the negative side, the available medical records were often insufficient for learning accurate probabilities. Furthermore, when adding a new clinical trial, the user had to change the structure of the underlying Bayesian network.

To address these problems, Bhanja *et al.* built a rule-based system for the same task [2]. We have continued that work, extended the system, and added a mechanism for reducing costs involved in patient selection.

III. Example

We have developed an intelligent agent that helps to select clinical trials for eligible patients. It prompts a clinician to enter the results of medical tests, and identifies appropriate trials. If the available records do not provide enough data, the agent suggests additional tests.

In Figure 1(a), we give a simplified example of eligibil-

(a) Eligibility criteria

1. The patient is female.
2. She is at most forty-five years old.
3. Her cancer stage is II or III.
4. Her cancer is not invasive.
5. At most three lymph nodes have tumor cells.
6. Either
   - the patient has no cardiac arrhythmias, or
   - all tumors are smaller than 2.5 centimeters.

(b) Tests and questions

General information
What is the patient's sex?
What is the patient's age?

Mammogram, Cost is $150
What is the cancer stage?
Does the patient have invasive cancer?

Biopsy, Cost is $300
What is the cancer stage?
How many lymph nodes have tumor cells?
What is the greatest tumor size?

Electrocardiogram, Cost is $200
Does the patient have cardiac arrhythmias?

Fig. 1. Example of eligibility criteria, tests, and questions.

(a) Acceptance	**(b) Rejection**
$sex = \text{FEMALE}$ and	$sex = \text{MALE}$ or
$age \leq 45$ and	$age > 45$ or
$stage \in \{\text{II, III}\}$ and	$cancer \in \{\text{I, IV}\}$ or
$invasive = \text{NO}$ and	$invasive = \text{YES}$ or
$lymph\text{-}nodes \leq 3$ and	$lymph\text{-}nodes > 3$ or
($arrhythmias = \text{NO}$ or	($arrhythmias = \text{YES}$ and
$tumor\text{-}size \leq 2.5$)	$tumor\text{-}size > 2.5$)

Fig. 2. Logical expressions for the criteria in Figure 1(a).

$$\left(\begin{array}{l} sex = \text{FEMALE} \text{ and} \\ age \leq 45 \text{ and} \\ stage \in \{\text{II, III}\} \text{ and} \\ invasive = \text{NO} \text{ and} \\ lymph\text{-}nodes \leq 3 \text{ and} \\ arrhythmias = \text{NO} \end{array}\right) \text{ or } \left(\begin{array}{l} sex = \text{FEMALE} \text{ and} \\ age \leq 45 \text{ and} \\ stage \in \{\text{II, III}\} \text{ and} \\ invasive = \text{NO} \text{ and} \\ lymph\text{-}nodes \leq 3 \text{ and} \\ tumor\text{-}size \leq 2.5 \end{array}\right)$$

Fig. 3. Disjunctive normal form of the acceptance expression.

ity criteria for a clinical trial. This trial is for young and middle-aged women with a noninvasive cancer at stage II or III. When testing a patient's eligibility, a clinician has to order three medical tests (Figure 1b).

The agent first prompts a clinician to enter the patient's sex and age. If the patient satisfies the corresponding conditions, the agent asks for the mammogram results and verifies Conditions 3 and 4; then, it requests the biopsy and electrocardiogram data. If the patient's records already include some test results, the clinician can answer the corresponding questions while entering the personal data, before the agent selects test procedures. For example, if the records indicate that the cancer stage is IV, the clinician can enter the stage along with sex and age, and then the agent immediately determines that the patient is ineligible for this trial.

IV. Knowledge Base

The agent's knowledge base includes questions, medical tests, and logical expressions that represent eligibility criteria for each trial. We give a simplified example of tests and questions in Figure 1(b), and logical expressions in Figure 2.

The agent supports three types of questions; the first type takes a yes/no response, the second is multiple choice, and the third requires a numeric answer. For example, the cancer stage is a multiple-choice question, and the tumor size is a numeric question. The description of a medical test includes the test name, dollar cost, and list of questions that can be answered based on the test results (Figure 1).

We encode the eligibility for a clinical trial by a logical expression that does not have negations, called the *acceptance expression.* It includes variables that represent medical data, as well as equalities, inequalities, "set-element" relations, conjunctions, and disjunctions (Figure 2a). In addition, the agent uses the logical complement of the eligibility criteria, called the *rejection expression,* which also does not have negations (Figure 2b). It describes the conditions that make a patient ineligible for the trial.

The agent collects data until it can determine which of the two expressions is TRUE. For instance, if a patient's sex is MALE, then the rejection expression in Figure 2(b) is TRUE, and the agent immediately determines that this trial is inappropriate. If the sex is FEMALE, the agent asks more questions.

If the knowledge base includes multiple clinical trials, the agent checks a patient's eligibility for each of them. It first asks for the tests related to multiple trials, and then requests additional tests for specific trials. After getting each new answer, the agent re-evaluates the patient's eligibility for each trial.

V. Order of Tests

If a patient's records do not include enough data, the agent asks for additional tests; for example, if the records do not provide data for the eligibility criteria in Figure 1, the agent asks for the mammogram, biopsy, and electrocardiogram. The total cost of tests may depend on their order; for instance, if we begin with the mammogram, and it shows that the cancer stage is IV, then we can immediately reject the trial in Figure 1 and avoid the more expensive tests.

We have explored heuristics for ordering the tests, based on the test costs and the structure of acceptance and rejection expressions. The heuristics use a disjunctive normal form of these expressions; that is, each expression must be a disjunction of conjunctions. For example, the rejection expression in Figure 2(b) is in disjunctive normal form, whereas the acceptance expression in Figure 2(a) is not. If the system uses ordering heuristics, it converts this acceptance expression into the disjunctive normal form shown in Figure 3.

The agent chooses the order of tests that reduces their expected cost. After getting the results of the first test, it re-evaluates the need for the other tests and revises their ordering. The choice of the first test is based on three criteria. The agent scores all required tests according to these criteria, computes a linear combination of the three scores for every test, and chooses the test with the highest score.

1. Cost of the test. The agent prefers cheaper tests. For instance, it may start with the mammogram, which is cheaper than the other two tests in Figure 1.

2. Number of clinical trials that require the test. When the agent checks a patient's eligibility for several trials, it prefers tests that provide data for the largest number of trials. For example, if the electrocardiogram gives data for two different trials, the agent may prefer it to the mammogram despite its higher cost.

3. Number of clauses that include the test results. The agent prefers the tests that provide data for the largest number of clauses in the acceptance and rejection expressions. For example, the mammogram data affect both clauses of the acceptance expression in Figure 3 and two clauses of the rejection expression in Figure 1(b). On the other hand, the electrocardiogram affects only one clause of the acceptance expression and one clause of the rejection expression; thus, the agent should order it after the mammogram.

VI. User Interface

The agent includes a web-based interface that allows clinicians to enter patients' data through remote computers; the interface consists of five screens (Figure 4).

The start screen is for adding and retrieving patients (Figure 5). After a user enters a patient's name, the agent displays a list of the available trials (Figure 6). The user can choose a subset of these trials, and then the agent checks eligibility only for the selected trials. The next screen is for basic personal and medical data, such as sex, age, and cancer stage (Figure 7).

After the agent gets the basic data, it prompts the user for medical information related to specific trials (Figure 8). When the user enters medical data, the agent continuously re-evaluates the patient's eligibility and shows the decision for each trial. If the patient is ineligible for some trials, the user can find out the reasons by clicking the *"Why"* button. The interface also includes a screen for the review and modification of the previous answers, similar to the screen in Figure 8.

VII. Experiments

We have built a knowledge base for the breast-cancer clinical trials at the H. Lee Moffitt Cancer Center, applied the agent to retrospective data from 187 past patients and 57 current patients, and compared the results with manual selection by clinicians at the cancer center.

We summarize the results for the past patients in Table I, and the results for the current patients in Table II. The "same matches" column includes the number of patients who have been selected by both human clinicians and the automated agent. The "new matches" column gives the number of patients who have been matched by the agent but potentially missed by human clinicians. Finally, the last column shows the number of patients whose available records are incomplete. Clinicians have found trials for these patients, but the agent cannot identify these matches because of missing data. The agent has found a number of matches potentially missed by human clinicians; thus, it can help to recruit more patients for clinical trials.

TABLE I
Results of matching 187 past patients.

Clinical Trial	Same Matches	New Matches	Missing Data
10822	10	5	0
10840	0	19	3
11072	48	26	19
11378	4	19	3
11992	5	6	0
12100	8	20	13
12101	20	30	0

TABLE II
Results of matching 57 current patients.

Clinical Trial	Same Matches	New Matches	Missing Data
11132	4	1	1
11971	3	0	0
12100	0	2	0
12101	4	21	0
12601	0	1	0
11931	1	8	0
12775	1	4	0

In Table III, we give the mean test costs with and without the ordering heuristics for the 187 past patients. The results show that the implemented heuristics reduce the costs by more than a factor of two.

VIII. Scalability

The time complexity of evaluating the acceptance and rejection expressions is linear in their size. Experiments on a Sun Ultra 10 have shown that the evaluation takes about 0.02 seconds per question, and the time is linear in the number of questions. Typical eligibility conditions for a clinical trial include ten to thirty questions; thus, the evaluation time is 0.2 to 0.6 seconds per trial.

TABLE III
Cost savings by test reordering.

Clinical Trial	Average Dollar Cost: Without Test Reordering	With Test Reordering
10822	$20	$8
10840	$0	$0
11072	$556	$194
11378	$34	$0
11992	$87	$34
12100	$0	$0
12101	$24	$22

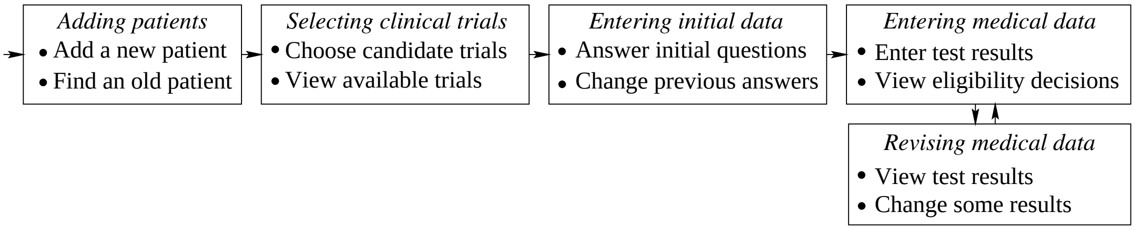

Fig. 4. Entering a patient's data. The web-based interface for data entry consists of five screens. We show these screens by rectangles and the transitions between them by arrows.

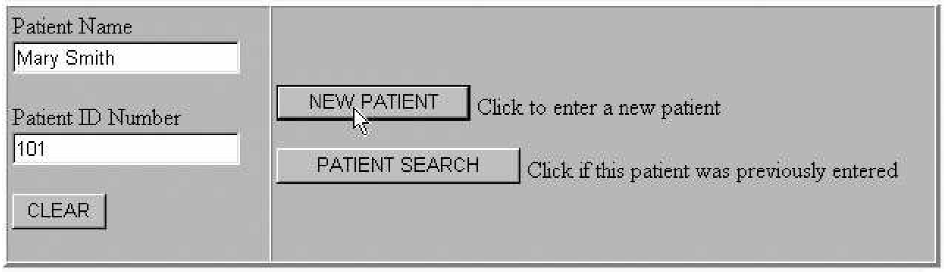

Fig. 5. Adding new patients and retrieving existing patients.

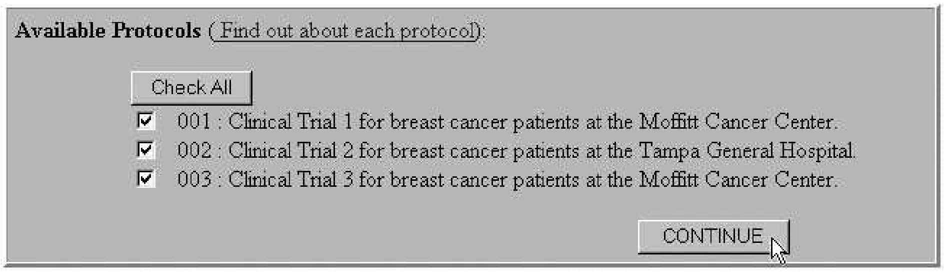

Fig. 6. Selecting clinical trials.

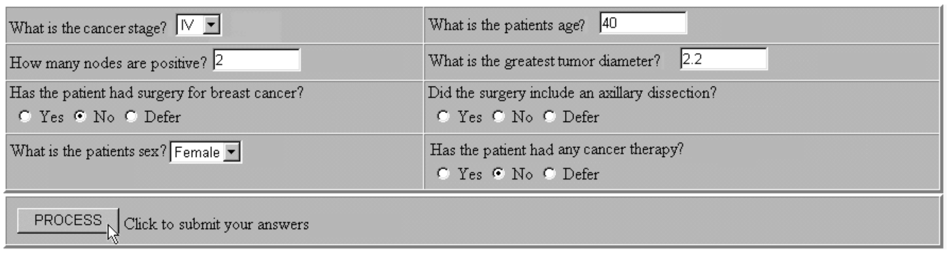

Fig. 7. Entering basic information for a patient.

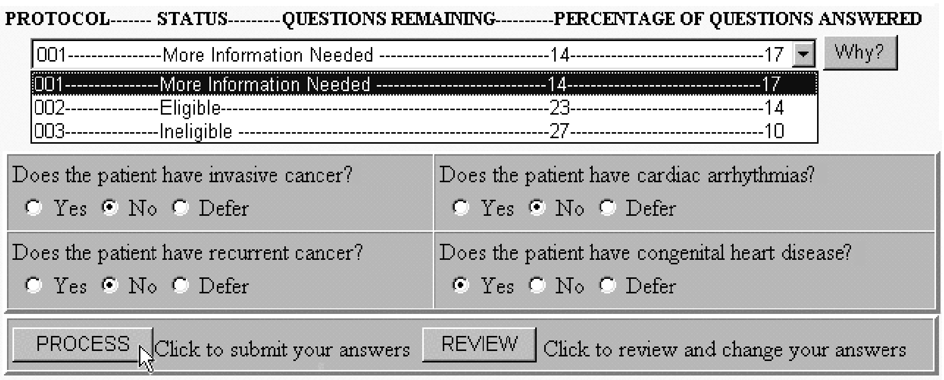

Fig. 8. Entering medical data.

(a) Eligibility criteria

1. The patient is female.
2. She is at most forty-five years old.
3. Either
   - her cancer is not invasive, or
   - her cancer is not recurrent.
4. Either
   - at most three lymph nodes have tumor cells, or
   - all tumors are smaller than 2.5 centimeters.
5. Either
   - the patient has no cardiac arrhythmias, or
   - the patient has no congenital heart disease.

(b) Acceptance expression

$sex = \text{FEMALE}$ and
$age \leq 45$ and
($invasive = \text{NO}$ or $recurrent = \text{NO}$) and
($lymph\text{-}nodes \leq 3$ or $tumor\text{-}size \leq 2.5$) and
($arrhythmias = \text{NO}$ or $congenital = \text{NO}$)

(c) Reduced expression

$sex = \text{FEMALE}$ and
$age \leq 45$ and
$invasive\text{-}and\text{-}recurrent = \text{NO}$ and
($lymph\text{-}nodes \leq 3$ or $tumor\text{-}size \leq 2.5$) and
$arrhythmias\text{-}and\text{-}congenital = \text{NO}$

Fig. 9. Reducing the number of disjunctions. The conversion of the eligibility criteria (a) into a logical expression (b) leads to an explosion in the size of the corresponding disjunctive normal form. We can prevent the explosion by replacing some disjunctions with single questions (c).

The linear scalability is an important advantage over Bayesian systems, which do not scale to a large number of clinical trials [7, 21, 23]. The authors of these systems have reported that the sizes of the underlying networks are superlinear in the number of trials [22, 37], and the training time is superlinear in the network size [24, 34].

If the agent uses the cost-reduction heuristics, it converts the acceptance and rejection expressions into disjunctive normal form, which can potentially lead to an explosion in their size. For example, if eligibility conditions are as shown in Figure 9(a), the agent initially generates the expression in Figure 9(b). If the agent converts it to disjunctive normal form, the resulting expression consists of eight clauses.

Although the conversion may result in impractically large expressions, experiments have shown that this problem does not arise in practice because the number of nested disjunctions is usually small. Furthermore, we can eliminate some disjunctions by combining their elements into longer questions. For instance, we can represent Condition 3 in Figure 9(a) by a single question: "Does the patient have both invasive and recurrent cancer?" If we apply this modification to Conditions 3 and 5, then we obtain the expression in Figure 9(c), and its conversion to disjunctive normal form results in an expression with two clauses.

IX. Concluding Remarks

We have developed an agent that automatically assigns patients to clinical trials. We have described the representation of selection criteria, heuristics for ordering of tests, and a web-based interface for entering patients' data, which will enable physicians across the country to access a central repository of clinical trials.

Experiments have confirmed that the agent has the potential to find more participants for clinical trials. They have also shown that the ordering of medical tests affects their overall cost, and the implemented heuristics can reduce the cost of finding trial participants. The heuristics do not account for the probabilities of possible test results, and we plan to add probabilistic reasoning as part of the future work.

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