# SIMULTANEOUS RECOMMENDATION OF BEST COST-BENEFIT CLINICAL DATA

**Simultaneous recommendation of best cost-benefit clinical data (symptoms, physical signs, and result of diagnostic tests and diagnostic procedures) to investigate in a patient at each diagnostic step is essential for a computer algorithm to be able to diagnose diseases afflicting actual patients. Two examples, one dramatic and the other non-dramatic, will illustrate this statement. (1) Dramatic example: a patient is rushed by ambulance to an emergency service; he is suffering an acute myocardial infarction complicated with congestive heart failure, cardiac arrhythmia, and shock. A program that recommends best cost-benefit clinical data sequentially, would first recommend an electrocardiogram; twenty minutes later, when the result is entered in the computer, the next recommendation would be a troponin analysis, then chest x-rays, and so on. Four hours later, the necessary tests to complete the diagnostic quest are finally available; unfortunately, the patient expired in the meantime. (2) Non-dramatic example: a patient comes to your office with fever, cough, and some abdominal discomfort. The computer recommends one test, perhaps a complete blood count; after two days the patient returns to your office for the result. This time the computer recommends an erythrocyte sedimentation rate, the patient has to have blood drawn again, return after another two days, and the physician still does not know what is going on. It is most likely that after the second or third visit the patient is consulting another physician who has no computer.**

This paper is part of our complete medical diagnostic program, described in detail in our book [2].

We summarize here only basic concepts of previous publications; for better understanding of this paper, the reader is encouraged to consult our previous publications.

Initial clinical data collection was achieved during the medical history and physical examination. We accepted whatever clinical data were revealed, without considering their rule-in or rule-out power. Subsequent clinical data collection is more selective, because we have a differential diagnosis list and a better-structured diagnostic process that enables to apply statistical and probabilistic concepts, and choose the best cost-benefit clinical datum next to investigate in the patient, based on cost, positive predictive value (PP value), and sensitivity (S).

A practical way to calculate S of a specific clinical datum for a given disease is to determine statistically the fraction of patients afflicted by this disease who manifest the clinical datum:

$$Sensitivity = \frac{Number\ of\ disease\ cases\ manifesting\ the\ clinical\ datum}{Total\ number\ of\ disease\ cases}$$

Our program calculates PP value with the following equation:

$$PP\ value\ i = \frac{Si}{S1 + \cdots + Si + \cdots + Sn} \quad (1)$$

Where PP value i = positive predictive value of the clinical datum for the disease i under consideration

Si = sensitivity of the clinical datum for the disease i under consideration

S1 ... Sn = sensitivities of the same clinical datum for corresponding diseases

In our context *cost* to obtain a clinical datum involves not only expense, but also risk and discomfort resulting from the required test or procedure. We assign to each clinical datum one of four overall cost categories: no cost (clinical data typically obtained through medical history and physical examination), small cost (*e.g.*, obtained through routine laboratory analysis, ECG, and other ancillary studies), intermediate cost (*e.g.*, colonoscopy, lymph node excision biopsy), and great cost (*e.g.*, liver biopsy, laparoscopy, laparotomy). *Benefit* of a clinical datum is measured by the magnitude of change it produces in the probability (P) of the respective diagnosis, in turn depending on the magnitude of PP value of clinical data present, which increase P, and the magnitude of S of clinical data absent, which decrease P. The mini-max procedure calculates these P for corresponding diagnoses. Detailed explanations can be found in our previous publication [2].

Mini-max procedure calculates probability (P) of potential diagnoses in the differential diagnosis list, based on PP value of clinical data (symptoms, physical signs, and results of tests and diagnostic procedures) present, favoring a diagnosis, and S of clinical data absent, disfavoring the diagnosis.

A recommended best cost-benefit clinical datum can be evaluated—before actually accomplishing the corresponding test or procedure—by *virtually* considering it either present or absent, while observing how much it improves the diagnostic outcome.

The best cost-benefit clinical datum function enables us to predict which new clinical datum will most increase or decrease the total probability (P) of a diagnosis, reducing the number of clinical data required to achieve a final diagnosis.

Few diagnostic computer programs recommend, based on probability calculation, a single best cost-benefit clinical datum next to investigate in the patient; we know of none that simultaneously recommends a **set** of such data.

Physicians typically order a set of several analyses, tests, or procedures *simultaneously*. If conclusion of diagnostic quest is attempted to be reached with only one next patient-physician encounter, it is theoretically necessary to investigate simultaneously all recommended best cost-benefit clinical data (provided the patient would survive all tests). If it is acceptable to reach conclusion of diagnostic quest with a reasonable number of patient-physician encounters, investigating best cost-benefit clinical data by successive gradually increasing cost categories, more consistent with actual medical practice, will considerably reduce the number of best cost-benefit clinical data and diagnoses to investigate.

A computer can emulate such human behavior by iterating the best cost-benefit clinical data function, first assuming each newly recommended best cost-benefit clinical datum as virtually present and then as virtually absent, while observing the effect that each iteration has on the P of each diagnosis. Such iterations can be represented by a trichotomy tree (see example of Fig. 1 on next page). Each tree represents a single diagnosis in the differential diagnosis list. Virtual branches represent best cost-benefit clinical data present or absent; nodes represent the probability (P) and cost of the diagnosis. As an example, let's concentrate only on the black branches (arrows) of Fig. 1: each node originates three new branches and four cost level iterations are involved; accordingly, the total number of branches is $3^1 + 3^2 + 3^3 + 3^4 = 120$. Each top branch originating at a node assumes that the best cost-benefit clinical datum is present; accordingly, it increases P of the diagnosis and is depicted by an ascending arrow. Each middle branch assumes that *this* best cost-benefit clinical datum is absent; accordingly, it is disregarded, does not change P, and is depicted by a horizontal arrow. Each bottom branch assumes that the best cost-benefit clinical datum is absent; accordingly, it decreases P and is represented by a descending arrow. The same middle branch also assumes that this best cost-benefit clinical datum is

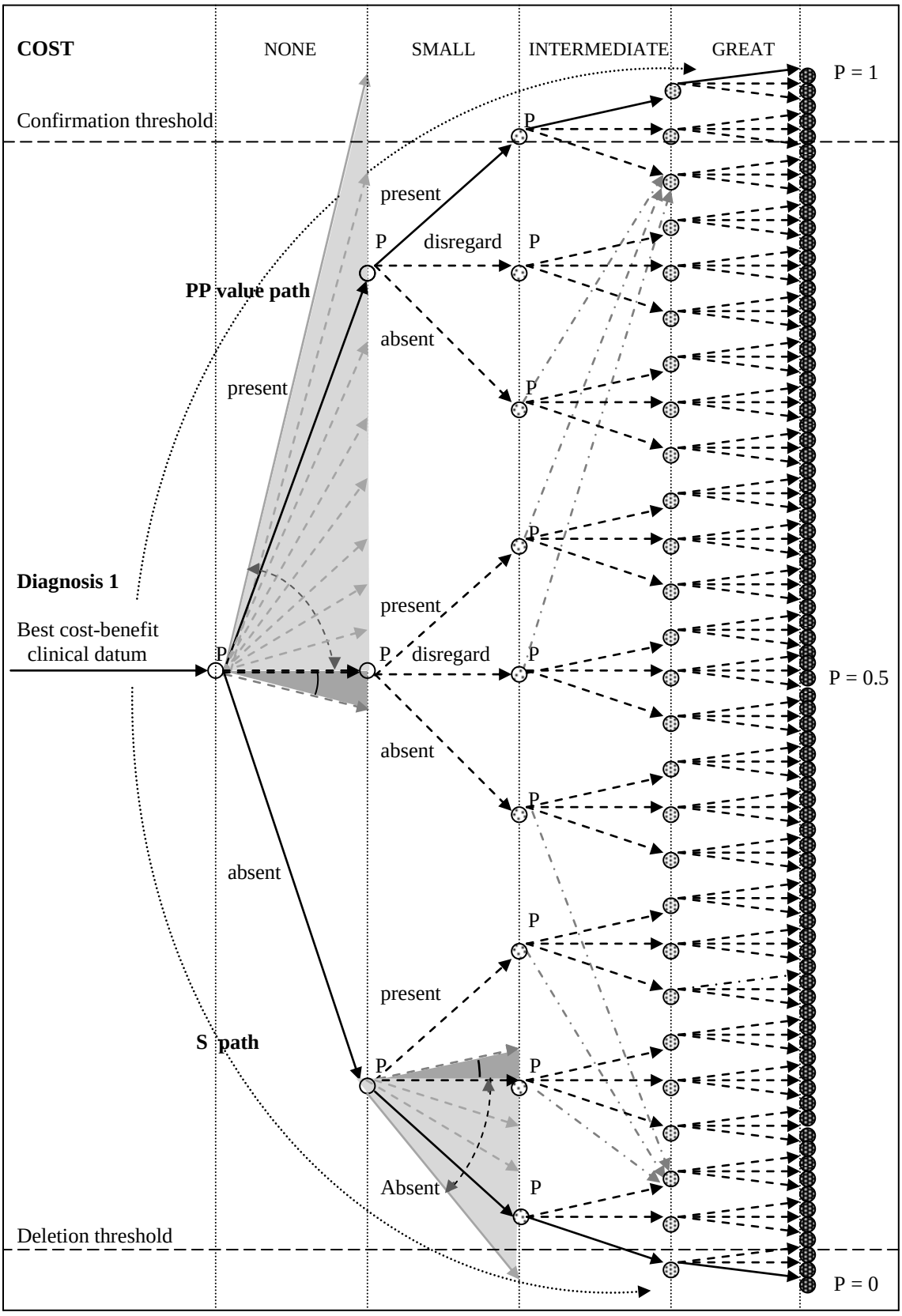


**FIGURE 1. Trichotomy tree.** Each branch (arrow) represents a best cost-benefit clinical datum. Each node (circle) represents the cumulative P and cost of the diagnosis. See text for further explanation.
○ NO COST; ⊙ SMALL COST; ⊚ INTERMEDIATE COST; ● GREAT COST

present, disregarded, and does not change P. Additionally, this middle branch represents situations in which no best cost-benefit clinical datum was found; accordingly, it offers no best cost-benefit clinical data to investigate. This reduces the best cost-benefit clinical data to investigate to only two branches per node, the top (present) and the bottom (absent) branches; the middle branch is preserved however, because it takes us to a next node. In the entire tree, the total number of best cost-benefit clinical data to investigate now is reduced to 80. This result, multiplied by the number of diagnoses in the differential diagnosis list yields the number of best cost-benefit clinical data to investigate, provided no best cost-benefit clinical data are shared with other trees (diagnoses).

A clinical datum frequently is shared by diverse diagnoses. However, a best cost-benefit clinical datum selected for its great PP value, and present, is either very characteristic or pathognomonic for a diagnosis. Such a clinical datum is typically shared with only a few trees or none; when a best cost-benefit clinical datum is selected for its great S, and absent, it might be shared by diverse diagnoses.

In Fig 1, black arrows, solid or dashed, representing best cost-benefit clinical data, depict only a particular example; exterior solid arrows, in this example, represent greatest PP value clinical data present or greatest S clinical data absent. In actual cases the arrows can have any direction, represented by the straight grey dashed arrows, in the area of the light grey triangles, resulting in diverse P (nodes).

The dashed arc shows the entire gamut of possible arrows. The smaller dark grey area, spanned by a solid arc encompasses best cost-benefit clinical data resulting from broken monotony [1]: data that having a greater PP value however reduce P instead of increasing it; or data having a greater S however increase P, instead of reducing it. These reductions or increases of P, produced by broken monotony against the general rule, are of small magnitude and can be ignored without compromising accuracy. Pale grey dash-dot arrows show that processing a specific clinical datum results in the same P irrelevant from which P value they depart, because mini-max procedure that calculates resulting P, considers PP values and S for this datum and diagnosis, without involving initial P.

In a single tree, in each cost category, the best cost-benefit clinical datum present, represented by the top branch, typically has a great PP value and strongly supports a diagnosis. The best cost-benefit clinical datum absent, represented by the bottom branch, typically has a great S and strongly opposes a diagnosis. Occasionally, an identical best cost-benefit clinical datum, when it has a great PP value *and* a great S, may be recommended simultaneously in the top and bottom branch. This apparent opposition is not conflicting because it refers to *virtual present and absent alternatives* that do not coexist in a real patient case.

Processing the entire **set** of best cost-benefit clinical data perhaps could at once confirm as final those diagnoses with a P close to 1 and rule out those with a P close to 0. However, exhaustively traversing all branches of this exponentially growing tree is limited by the increasing number of clinical data to investigate and the cost involved. At best, a partial traversing will enable us to move only a few steps forward. Fortunately, heuristic shortcuts might dispel this concern. Clinical data present of great PP value that strongly favor a diagnosis are unlikely to be opposed by clinical data absent of great S that strongly disfavor the same diagnosis. Accordingly, when a diagnosis with an initial great P is processed, we would expect the algorithm to recommend a best cost-benefit clinical datum of greater PP value that would further enhance that P, rather than recommend a best cost-benefit clinical datum of great S. Conversely, when a diagnosis with an initial small P is processed, we would expect the algorithm to recommend a best cost-benefit clinical datum of greater S that would further reduce that P, rather than recommend a best cost-benefit clinical datum of great PP value. This expectation would favor virtual traversing from present to present branches toward greater P values of the diagnosis or from absent to absent branches toward smaller P values of the diagnosis. Thus in the tree, the process

would tend to traverse solid exterior branches only, while avoiding zigzag traversal along dashed alternating present and absent interior branches.

If we elect not to *exclusively* traverse extreme exterior branches, a few virtual best cost-benefit clinical data alternatively absent and present can be accepted. This maintains traversal *near* the exterior branches, leading to nodes with P near to diagnosis confirmation or elimination values.

Ideally, the algorithm explores—for each diagnosis in the differential diagnosis list—all possible virtual traversals until greatest or smallest P are attained, or until all available clinical data are exhausted. To accomplish this goal, prompts and authorization requests to continue in the next greater cost category must be bypassed. Cost momentarily is disregarded so as to obtain an ample overview of all best cost-benefit clinical data available. A decision regarding which best cost-benefit clinical data to select and up to what cost can be made afterwards according to disease severity.

Experimenting with our new prototype program showed that recommended best cost-benefit clinical data could be very numerous, sometimes several hundred, increasing prohibitively the cost and burden to investigate all of them. This mandated the devising of heuristic strategies to reduce this number without compromising the efficiency and accuracy of the diagnostic quest.

Regarding which heuristic strategies to devise for selecting a **set** of recommended best cost-benefit clinical data, the following considerations seem valid. An important advantage of our program is that it lists all best cost-benefit clinical data able to modify P of each diagnosis, and each clinical datum recommended shows in advance the value of resulting P when this clinical datum is found either present or absent. A tradeoff exists between the burden or cost of requesting an excessive number of recommended best cost-benefit clinical data and the risk of missing valid diagnoses by requesting an insufficient number. The following strategies and parameters are devised to reduce the number of best cost-benefit clinical data recommended while minimizing the risk of missing valid diagnoses.

Our program involves four types of heuristic strategies to safely reduce the number or burden to process best cost-benefit clinical data to investigate: (1) Each investigated and processed clinical datum that yields more benefit (greater diagnosis P change) supersedes and removes all other recommended clinical data in the same cost category that produce less benefit (smaller diagnosis P change). (2) Grouping clinical data according to test or procedure necessary to investigate them. (3) Parameters. (4) Abridged best cost-benefit output files. These strategies are not mutually exclusive; they are applied simultaneously.

### 1. *Best cost-benefit clinical data superseding and removing less beneficial clinical data*

While our new program first displays all best cost-benefit clinical data, as soon as such a clinical datum is confirmed present or absent, all other clinical data that produce a smaller change of P in the same cost category and for the same diagnosis are removed from the recommended clinical data list, which reduces remarkably the number of clinical data to investigate in the patient.

### 2. *Grouping clinical data according to test or procedure necessary to investigate them*

The total amount of best cost-benefit clinical data recommended simultaneously may be large, but many of these diverse clinical data can be investigated by a single procedure (*e.g.*, a colonoscopy investigates at a single session intestinal polyps, diverticula, ulcers, masses, etc.; a single blood draw provides a sample used to investigate multiple clinical data, such as complete blood count, erythrocyte sedimentation rate, chemistry, and others). Typically, an apparently great number of clinical data

recommended can be investigated with only a few diverse procedures (*e.g.*, laboratory tests, ECG, and chest X-rays). We realized the importance of the diagnostic program to display the recommended best cost-benefit clinical data grouped by procedures necessary to investigate and order them. In a modern, well organized medical environment these orders could be automatically transmitted electronically to the corresponding facility: clinical laboratory, radiology, procedure specialist, suggesting at the same time the clinical data most important to confirm present or absent. What actually matters is the number of diverse types of tests involved; frequently, a great number of data can be investigated simultaneously with only a single blood draw, urine sample, imaging, or procedure. However, the cost of diverse tests or procedures may be additive. Our program displays recommended best cost-benefit clinical data sorted by cost and type of test or procedure in output files *Data Cost Procedure Quantity*, *Abridged Data Cost Procedure Quantity*, *Global Overview*, and *Abridged Global Overview*, which facilitates requesting them simultaneously (these files will be explained later).

Each new clinical datum added to the database, must also be added to the input file—*Data Procedures*—listed with the corresponding test or procedure that obtains it; otherwise, this clinical datum will be missing from the above mentioned output files.

### 3. *Parameter strategies*

An input file called *Parameters* enables the user to select empirical values for diverse parameters, which limit the number of best cost-benefit clinical data to investigate.

*Trim No Cost parameters*

*Trim Present No Cost* parameter removes only from *no cost* best cost-benefit clinical data *present* those recommended clinical data present unable to *increase* P of diagnosis more than the parameter empirical value, leaving those clinical data able to produce a *change of P equal or greater than the value* at which the parameter was set. Benefit is measured by the magnitude of P change. We exempted from being affected and removed by this strategy only the clinical datum present that results in the greatest increase of P (upper exterior arrow of trichotomy tree), because we consider it of great diagnostic importance. The greater the *Trim Present* value is set, the less recommended best cost-benefit clinical data are displayed, but the more inaccurate the diagnostic quest may become. However, the clinical data removed are the ones at the bottom of the *no cost best cost-benefit clinical data present* list which produce little change in P of the diagnosis and will most likely be superseded by best cost-benefit clinical data producing a greater P change. Small values of this parameter, and consequent small changes of diagnostic P do not affect diagnostic accuracy; we tentatively set this parameter at 100 per mil (our current program expresses P values in per mil entire number (as opposed to a decimal: 100 per mil = 0.10). However, the need and magnitude of such empirical approach will be better evaluated when a database with all known diseases and clinical data will become available.

*Trim Absent No Cost* parameter removes only from *no cost* best cost-benefit clinical data *absent* those recommended clinical data absent unable to *decrease* P of diagnosis more than the parameter empirical value, leaving those clinical data able to produce a *change of P equal or greater than the value* at which the parameter was set. We exempted from being affected and removed by this strategy only the clinical datum absent that results in the greatest decrease of P (lower exterior arrow of trichotomy tree), because we consider it of great diagnostic importance. The greater the *Trim Absent* value is set, the less recommended best cost-benefit clinical data are displayed, but the more inaccurate the diagnostic quest may become. However, the clinical data removed are the ones at the bottom of the *no cost best cost-benefit clinical data absent* list which produce little change in P of the diagnosis

and will most likely be superseded by best cost-benefit clinical data producing a greater P change. Small values of this parameter and consequent small changes of diagnostic P do not affect diagnostic accuracy; we tentatively set this parameter at 100 (0.10). However, the need and magnitude of such empirical approach will be better evaluated when a database with all known diseases and clinical data will become available.

The *no cost* best cost-benefit clinical data display compensates for an incomplete medical history and physical examination, prompting the examiner to do a better job. Investigating more initial *no cost* clinical data present during the first consultation selects more diagnoses, brings P of diagnoses closer to their final values, which in turn reduces the number of best cost-benefit clinical data to be displayed in greater cost categories, and reduces the possibility of missing concurrent diagnoses, were the newly processed clinical data to introduce new potential diagnoses.

*Trim Greater Cost parameters*

When *no cost* clinical data do not conclude the diagnostic quest, best cost-benefit clinical data are selected from *small* and *intermediate cost categories*. The reason why we created a separate trim greater cost clinical data parameter is because in this case, tests or procedures are involved and presence or absence of selected clinical data cannot be immediately verified. Separate no cost and greater cost parameters enable the user to set at different values each of them, if convenient.

*Trim Present Greater Cost* parameter deserves exactly the same comments as *Trim Present No Cost* (see above), with the only difference that it applies to *small, intermediate, and great cost* best cost-benefit clinical data *present* instead of no cost clinical data.

*Trim Absent Greater Cost* parameter deserves exactly the same comments as *Trim Absent No Cost* (see above), with the only difference that it applies to *small, intermediate, and great cost* best cost-benefit clinical data *absent* instead of no cost clinical data.

When the best cost-benefit clinical datum in *small cost* category yields little P change of the corresponding diagnosis, whereas the one in *intermediate cost* category yields a much greater P change, skip the former cost category and directly select the datum from the latter. Leave great cost clinical data to subsequent diagnostic rounds. Conversely, when a smaller cost category datum reaches confirmation or deletion threshold for the diagnosis, obviously greater cost category data will be disregarded.

*Difference Cost Parameters*

*Present Difference Cost*. It is expected that the greatest P resulting from processing *great cost* best cost-benefit clinical data *present* will achieve an additional increase over greatest P resulting from processing best cost-benefit clinical data present in all lower cost categories (no, small, and intermediate cost). All great cost clinical data unable to achieve an additional increase greater than the value set for *Present Difference Cost* parameter are removed from their list. This precludes the selection of great cost clinical data present when they produce no or only insignificant extra increase of P. If the selected smaller cost clinical datum happens to be absent, the removed great cost data will be redisplayed at next program iteration. When a smaller cost clinical datum results in the same P as a great cost clinical datum, setting the parameter *Present Difference Cost* at an even very small value, such as 001, suffices to remove the clinical datum in the great cost list.

*Absent Difference Cost*. It is expected that the smallest P resulting from processing *great cost* best cost-benefit clinical data *absent* will achieve an additional decrease below smallest P resulting from processing best cost-benefit clinical data absent in all lower cost categories (no, small, and intermediate cost). All great cost clinical data unable to achieve an additional decrease greater than the value set for *Absent Difference Cost* parameter are removed from their list. This precludes the selection of great cost clinical data absent when they produce no or only insignificant extra decrease of P. If the smaller cost clinical data happens to be present, the removed great cost data will be redisplayed at next program iteration. When a smaller cost clinical datum results in the same P as a great cost clinical datum, setting the parameter *Absent Difference Cost* at an even very small value, such as 001, suffices to remove the clinical datum in the great cost list.

When any diagnosis in the differential diagnosis list has not been confirmed or ruled out, especially when patient's condition is urgent or critical, select at once *great cost* best cost-benefit clinical data, unless cost is prohibitive in the context of medical-social circumstances.

*Confirmation Threshold and Deletion Threshold parameters*

*Confirmation threshold* for diagnoses enables the user to select an empirical P value for this parameter. Diagnoses that reach P equal to or greater than this parameter are confirmed as final diagnoses. Our current tentative default level is P = 900 (0.90).

*Deletion threshold* for diagnoses enables the user to select an empirical P value for this parameter. Diagnoses that reach P equal to or smaller than this parameter are ruled out. Our current tentative default level is P = 100 (0.10).

Confirmation and deletion thresholds reduce the number of best cost-benefit clinical data to investigate when judiciously setting their values. The lower the former and the higher the latter, the less clinical data are necessary to reach their levels and the less diagnoses remain to be processed, but also the greater the risk to improperly confirm or rule out diagnoses.

However, an advantage of our current diagnostic program is that diagnoses ruled out are not definitively deleted; when entering in the computer any new clinical datum, present or absent, our program iterates from the beginning, reprocessing all clinical data. If some new clinical data increase the P of the ruled out diagnoses above the deletion threshold, the corresponding best cost-benefit clinical data will be redisplayed at next program iteration.

*Cutoff parameters*

*Cutoff Present* enables the user to select a P cutoff level that removes from the best cost-benefit clinical data present list all recommended data (considered not worth to be investigated) that yield a diagnosis P below this level. This cutoff point should be set at a level that reasonably separates the clinical data below, very unlikely to result in a P able to confirm the diagnosis, from the clinical data above that have the potential, at next iterations, to increase diagnosis P to a confirmatory value. Our current tentative default level is P = 200 (0.20). Cutoff Present level represents the lower limit that together with the confirmation threshold, representing the upper limit, define a zone or range that encompasses the best cost-benefit clinical data present recommended to be processed (see Fig. 2 below). Cutoff Present strategy implies the risk of ruling out potentially correct diagnoses with their P temporarily below this level. This is not critical because the removed diagnoses are not definitively deleted; they remain hidden and will be reprocessed at every new program iteration, and corresponding

best cost-benefit clinical data will be redisplayed if some new supporting clinical data increase diagnoses P above the Cutoff Present level.

*Cutoff Absent* enables the user to select a P cutoff level that removes from the best cost-benefit clinical data absent list all recommended data (considered not worth to be investigated) that yield a diagnosis P above this level. This cut off point should be set at a level that reasonably separates the clinical data above, very unlikely to result in a P able to delete the diagnosis, from the clinical data below that have the potential, at next iterations, to decrease diagnosis P to a rule out value. Our current tentative default level is P = 500 (0.50). Cutoff Absent level represents the upper limit that together with the deletion threshold, representing the lower limit, define a zone or range that encompasses the best cost-benefit clinical data absent recommended to be processed (see Fig. 2 below). Both zones limited by cutoff present and cutoff absent tend to overlap partially. Cutoff Absent strategy implies the risk of ruling out potentially correct diagnoses with their P temporarily above this level. This is not critical because the removed diagnoses are not definitively deleted; they remain hidden and will be reprocessed at every new program iteration, and corresponding best cost-benefit clinical data will be redisplayed if some new clinical data decrease the diagnoses P below the Cutoff Absent level.

If *Cutoff Present* value is smaller than *Cutoff Absent* value (as in Fig. 2), the mentioned cutoff present and absent zones overlap and the best cost-benefit clinical data present and absent yielding a diagnosis P in the overlapping zone are recommended. If *Cutoff Present* value is greater than *Cutoff Absent* value, the mentioned cutoff present and absent zones do not overlap and the best cost-benefit clinical data present and absent yielding a diagnosis P in the non-overlapping area between zones are not recommended. If the user wants to cancel cutoff parameters and respective zones, to enable display of all recommended best cost benefit clinical data, parameters must be set at following values: *Cutoff Present* = 000 and *Confirmation threshold* = 999, to include all best cost-benefit clinical data present; *Cutoff Absent* = 999 and *Deletion threshold* = 000, to include all best cost-benefit clinical data absent.

### 4. *Abridged best cost-benefit output files*

This strategy to reduce the number of best cost-benefit clinical data involves abridged output files, which have in common displaying only the best cost-benefit clinical datum with greatest PP value and S in each cost category (clinical data represented by the exterior arrows of the trichotomy tree, Fig. 1).

***Global Overview*** recommends the best cost-benefit clinical data *after parameter settings*. These clinical data are displayed hierarchically by increasing cost categories, quantity in each category and total quantity recommended, sub grouped by procedure to obtain them, diagnoses to which each refer, and whether assumed present or absent. Each diagnosis shows corresponding P before and after virtually processing each recommended clinical datum. *Global Overview* provides the most convenient information for a rational selection of a set of best cost-benefit clinical data.

***Abridged Global Overview*** (Fig. 3 below) is an abridged version of *Global Overview* with similar grouping, but displaying only the best cost-benefit clinical datum with greatest PP value and S in each cost category (clinical data represented by the exterior arrows of the trichotomy tree, Fig. 1), able to produce P change of corresponding diagnosis, *after parameter settings*. Because there are four cost categories (no, small, intermediate, and great cost), and for each of them, 2 exterior arrows (clinical datum present with greatest PP value and clinical datum absent with greatest S), at most only 8 clinical data are recommended per diagnosis, but if some are not able to change P then these data will be even less. *Abridged Global Overview* achieves an important heuristic reduction in the number of recommended best cost-benefit clinical data, with program remaining highly efficient and accurate.

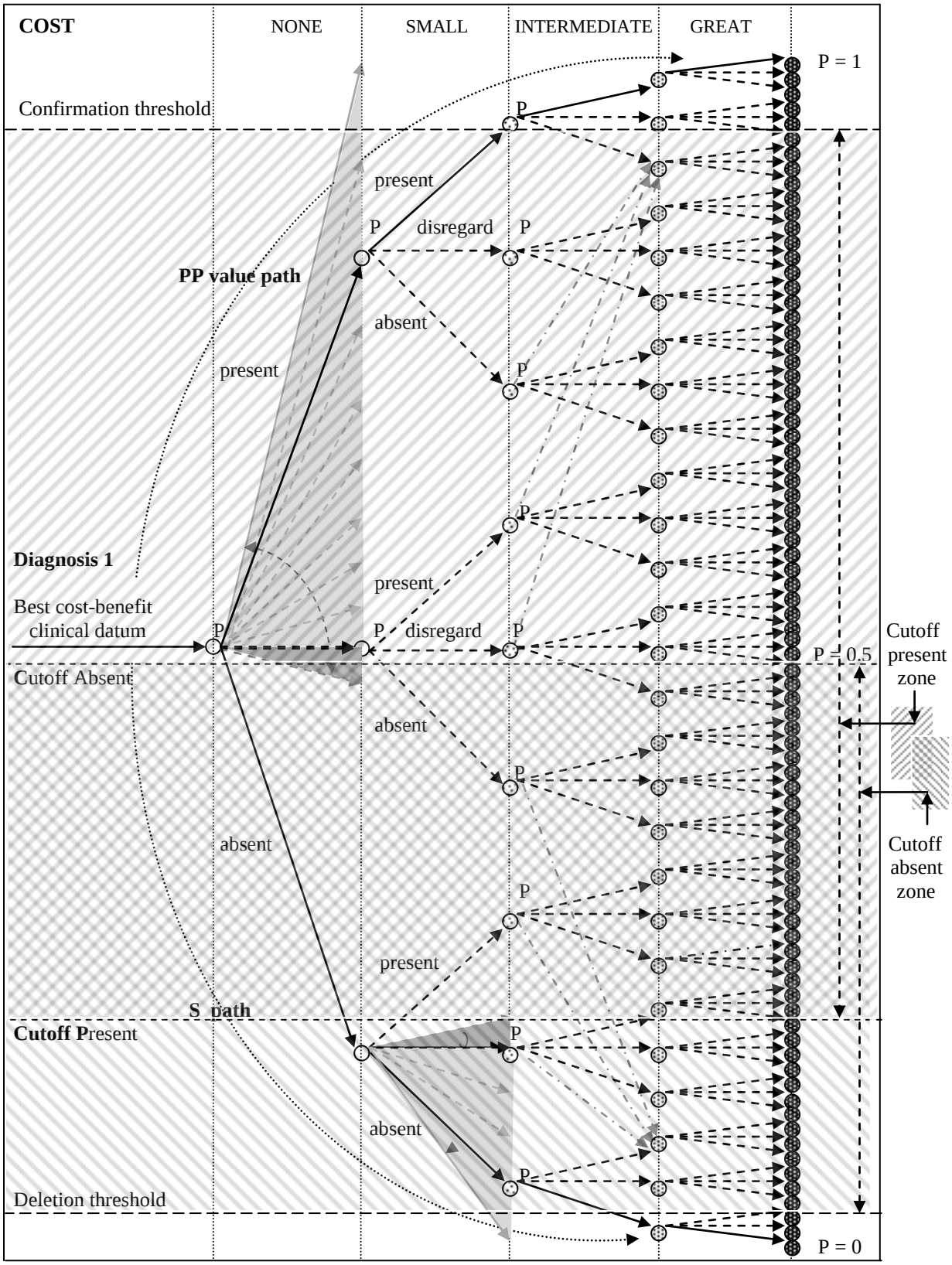


**FIGURE 2**. Showing trichotomy tree with superimposed cutoff present and cutoff absent zones (see text)

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***No cost best cost-benefit clinical data:***

**8**

**G0001 MEDICAL HISTORY**

**C0262 (acholic stools)**
D0020 (VIRAL HEPATITIS)
total P: 227
present total P: 677

**G0002 PHYSICAL EXAMINATION**

**C0562 (Horner's syndrome)**
D0001 (AORTIC DISSECTION)
total P: 213
present total P: 663

**C0379 (new/worsened regurgitant murmur)**
D0024 (ACUTE INFECTIVE ENDOCARDITIS)
total P: 220
present total P: 714

**C0327 (dark urine)**
D0020 (VIRAL HEPATITIS)
total P: 227
absent total P: 19

**C0238 (funduscopic abnormalities for pheochromocytoma)**
D0012 (PHEOCHROMOCYTOMA)
total P: 364
present total P: 365

**C0019 (hypertension)**
D0012 (PHEOCHROMOCYTOMA)
total P: 364
absent total P: 64
D0001 (AORTIC DISSECTION)
total P: 213
absent total P: 82

**C0078 (tachycardia)**
D0024 (ACUTE INFECTIVE ENDOCARDITIS)
total P: 220
absent total P: 15

**C0096 (rumbling diastolic murmur)**
D0004 (MITRAL STENOSIS/RHEUMATIC HEART DISEASE)
total P: 640
present total P: 841

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***Small cost best cost-benefit clinical data:***

**7**

**G0004 LABORATORY TESTS**

**C0384 (blood cultures for acute endocardits)**
D0024 (ACUTE INFECTIVE ENDOCARDITIS)
total P: 220
present total P: 612
D0024 (ACUTE INFECTIVE ENDOCARDITIS)
total P: 220
absent total P: 9

**C0331 (serologic testing for hepatitis)**
D0020 (VIRAL HEPATITIS)
total P: 227
present total P: 1000

**C0313 (abnormal liver function tests)**
D0020 (VIRAL HEPATITIS)
total P: 227
absent total P: 0

**C0244 (elevated twenty four-hour urine catecholamines and metanephrines)**
D0012 (PHEOCHROMOCYTOMA)
total P: 364
present total P: 1000
D0012 (PHEOCHROMOCYTOMA)
total P: 364
absent total P: 54

**C0229 (suppressed TSH)**
D0011 (HYPERTHYROIDISM)
total P: 692
present total P: 1000

**G0006 ULTRASOUND**

**C0044 (abnormal aorta ultrasound)**
D0001 (AORTIC DISSECTION)
total P: 213
present total P: 1000
D0001 (AORTIC DISSECTION)
total P: 213
absent total P: 12

**G0007 ECHOCARDIOGRAM**

**C0102 (mitral stenosis on echocardiogram)**
D0004 (MITRAL STENOSIS/RHEUMATIC HEART DISEASE)
total P: 640
present total P: 1000

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***Intermediate cost best cost-benefit clinical data:***

**4**

**G0008 IMAGING: CT AND/OR MRI**

**C0245 (adrenal mass on imaging)**
D0012 (PHEOCHROMOCYTOMA)
total P: 364
present total P: 897
D0012 (PHEOCHROMOCYTOMA)
total P: 364
absent total P: 64

**C0045 (abnormal aorta MRI)**
D0001 (AORTIC DISSECTION)
total P: 213
absent total P: 12

**C0046 (computed tomography for aortic dissection)**
D0001 (AORTIC DISSECTION)
total P: 213
present total P: 1000

**G0009 SCANNING**

**C0233 (thyroid radionuclide scan)**
D0011 (HYPERTHYROIDISM)
total P: 692
present total P: 1000

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***great cost best cost-benefit clinical data:***

**2**

**G0013 ANGIOGRAPHY**

**C0047 (aortography)**
D0001 (AORTIC DISSECTION)
total P: 213
present total P: 1000

**C0103 (mitral stenosis on catheterization)**
D0004 (MITRAL STENOSIS/RHEUMATIC HEART DISEASE)
total P: 640
present total P: 1000

***Total:*** **21**

**FIGURE 3.** *Abridged Global Overview*

***Data Cost Quantity*** recommends the best cost-benefit clinical data able to change P of diagnoses *after parameter settings*, grouped by cost categories and indicating partial quantity of these data in each, and total quantity. The limitations of *Data Cost Quantity* is that it does not indicate the procedure to obtain these data, diagnosis to which each refer, recommendation for presence or absence, nor resultant P after processing; if this information is sought, the user must resort to other files. However, if there is no need for this missing information, the advantage of this file is that the recommended best cost-benefit clinical data are not so dispersed as in other files, but in more compact groups. When they are numerous, it is easier and faster to copy them in blocks and paste them side by side from *Data Cost Quantity* into *Present Data* or *Absent Data* files, avoiding the need to "Find" them one by one.

***Abridged Data Cost Quantity*** is an abridge version of *Data Cost Quantity*, displaying only the best cost-benefit clinical data with greatest PP value and S in each cost category, able to produce P change *after parameter settings*, indicating quantity of data in each cost category and total quantity. Same as *Data Cost Quantity* it facilitates coping and pasting of clinical data into *Present Data* or *Absent Data* files.

***Data Cost Procedure Quantity*** recommends best cost-benefit clinical data able to change P of diagnoses *after parameter settings*, grouped by cost categories, displaying quantity in each category, sub grouped by procedure to obtain them. This file is similar to *Data Cost Quantity*, but adds procedure to obtain each clinical datum. There is no mention of diagnoses, presence or absence of clinical data, nor P. Same as *Data Cost Quantity* it facilitates coping and pasting of clinical data into *Present Data* or *Absent Data* files.

***Abridged Data Cost Procedure Quantity*** is an abridge version of *Data Cost Procedure Quantity*, displaying only the best cost-benefit clinical data with greatest PP value and S in each cost category, able to produce P change *after parameter settings*, indicating quantity of data in each cost category, total quantity, and procedure to obtain them. Same as *Data Cost Quantity* it facilitates coping and pasting of clinical data into *Present Data* or *Absent Data* files.

Our program displays the total quantity of recommended best cost-benefit clinical data and partial quantity for each cost category, in *Global Overview*, *Abridged Global Overview*, *Data Cost Quantity*, *Abridged Data Cost Quantity*, *Data Cost Procedure Quantity*, and *Abridged Data Cost Procedure Quantity* output files. This saves the need to count them one by one, facilitating comparison of diverse strategies and how changes in the diverse *parameters* affect such quantity.

***Parameter Affected Differential*** is a differential diagnosis list with all diagnoses sorted by descending P, but displaying best cost benefit clinical data only for diagnoses with P above deletion threshold, *after parameter settings*.

***Abridged Parameter Affected Differential*** is an abridged version of *Parameter Affected Differential*, displaying only the best cost-benefit clinical data with greatest PP value and S in each cost category, able to produce P change *after parameters setting*.

**Strategies depending on abridged best cost-benefit output files**

These abridged files are: *Abridged Data Cost Quantity*, *Abridged Data Cost Procedure Quantity*, *Abridged Parameter Affected Differential*, and *Abridged Global Overview*.

As said before, the two output files we like best are *Global Overview* and *Abridged Global Overview*, because they provide the most complete information to rationally select best cost-benefit clinical data and order the corresponding tests or procedures, and most efficiently reach conclusion of diagnostic quest. Sometimes, *Data Cost Procedure Quantity* and *Abridged Data Cost Procedure Quantity* may become handy for easier and faster transfer of these data to the input files *Present Data* or *Absent Data* files or to request the corresponding tests or procedures.

When ascending in cost categories, the recommended best cost-benefit clinical data become scarcer, more exclusive for specific diagnosis, more supportive or eliminatory of diagnoses. The diagnostic process becomes clearer and the difference between the number of recommended best cost-benefit clinical data in abridged and corresponding non-abridged files diminishes considerably and even becomes equal.

At first thought, abridged strategies bring up the concern that diagnosis might be incorrectly processed because the recommended greatest PP value was absent or the greatest S best cost-benefit clinical datum was present, and a datum with smaller PP value or S was not recommended. However, this would occur only at the current diagnostic round; iterating the same strategy will reach the convenient clinical datum at further rounds. This strategy to recommend the exterior arrows by successive layers of gradually smaller PP value or S could be called "onion strategy". Although it reduces the number of best cost-benefit clinical data to investigate, it could require some extra diagnostic rounds, with corresponding extra patient-physician encounters, if the diagnosis is not confirmed or ruled out at a previous encounter.

**Best cost-benefit clinical data next to investigate** are displayed in several output files—*Comprehensive Differential Diagnosis List*, *Global Overview*, *Abridged Global Overview*, *Data Cost Quantity*, *Abridged Data Cost Quantity*, *Data Cost Procedure Quantity*, *Abridged Data Cost Procedure Quantity*, *Parameter Affected Differential*, and *Abridged Parameter Affected Differential*—some affected by parameters and others not. Best cost-benefit clinical data are sorted by increasing cost categories. In each such category, best cost-benefit clinical data assumed present and able to increase the current total P of the diagnosis are shown in decreasing order of resulting P, until no clinical data exists able to increase the current P. Best cost-benefit clinical data assumed absent and able to decrease the current total P of the diagnosis are shown in increasing P value order, until no clinical data exists able to decrease the current P.

"None" means that the program could not find any best cost-benefit clinical datum in the corresponding cost category, able to increase or decrease total P of corresponding diagnosis.

Each iteration of our program starts from the beginning, reprocessing all clinical data previously processed and new ones entered in the computer; this is very convenient because it gives a chance to diagnoses, previously ruled out due to their small P, to reenter the competition, if the new clinical data confer them a greater P. Recalculated P for all diagnoses selected by all clinical data present, and all best cost-benefit clinical data able to change these P, are displayed in *Comprehensive Differential Diagnosis List*.

## COMMENTS

Simultaneous recommendation of a set of best cost-benefit clinical data next to investigate at each step of the diagnostic quest is essential for a program to be capable to diagnose diseases in actual patients. This function is based on positive predictive value (PP value) of clinical data present and sensitivity (S) of clinical data absent, in turn applied by our mini-max procedure to determine the probability (P) of each diagnosis in the differential diagnosis list. Such a function will reach efficiently and at lowest overall cost one or more final diagnoses corresponding to the diseases afflicting a patient, representing an invaluable advantage for patients, physicians, other health providers, health insurance companies, malpractice lawyers, and the entire medical establishment.

## CONCLUSIONS

Our algorithm and program, although somewhat complex, is straightforward, especially when compared to other attempts in this field. It emulates a clinician's diagnostic reasoning. It is logical and mathematically simple. Bayes formula is used with modifications, because it is unable to process properly interdependent clinical data (as are most symptoms) and concurrent diseases. To facilitate implementation and updating of the algorithm, we tend to avoid complicated tools of artificial intelligence, such as causal, hierarchical, and probabilistic trees and networks. The algorithm freely uses heuristic procedures, so as to preclude excessive proliferation of clinical data and diagnoses. It promises to be user friendly because it is expressed in natural language, is rational, and readily understandable. Determination of accurate sensitivity of clinical data and integration of clinical entities into complex clinical presentation models will be labor-intensive. A complete database with all known diseases, clinical data, clinical presentations, and other information can be created; this major task will require a dedicated team of medical specialists.

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