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Division of Biomedical and Environmental Research

EVALUATIVE STUDIES IN NUCLEAR MEDICINE RESEARCH

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Interim Progress Report

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ABSTRACT

Data relating to the determination of the efficacy of radionuclide brain scanning have been analyzed. The data were gathered at a teaching hospital by use of a prospective questionnaire followed by a retrospective study of the result of the brain scan examination. Data analysis was accomplished using a method of pattern discovery which relates selected outcomes such as normal and abnormal brain scans to patient attributes (signs, symptoms, history, and previous test results). The objective of the analysis was the identification of patterns or clusters of patient attributes which have a high probability of acting as predictors of the outcome of the brain scan. The method is based on information theory and is capable of providing a quantitative measure of the amount by which a diagnostic test can be expected to reduce a physician's uncertainty regarding the disease state of a given patient. Results of the analysis to date show certain clusters of attributes which have the capability of predicting a normal scan with probabilities as high as .993. The three best (in the predictive sense) attribute clusters were capable of classifying 67% of the patient population as having normal scans with a probability better than .96. In these cases the brain scan contributed little or no information. Clusters of patient attributes were also identified for which the uncertainty in the outcome of the scan was significant. In these cases the information contributed by the scan in terms of reduction in physician uncertainty is likely to be significant.

Data has been obtained on 513 thyroid scan cases performed at a community hospital. These data consist of a prospective

questionnaire, patient history and the results of the thyroid scan. These data are currently being coded for analysis using the pattern detection approach described above.

1. Analysis of Brain Scan Data

Data related to the efficacy of brain scanning in 139 patients has been analyzed. The methods, results, and discussion are given in detail in the preprint presented as Appendix 1. The comments below serve to abstract the contents of Appendix 1. The potential utility of the results of this study in terms of the analysis of health care policy alternatives is outlined in the editorial presented as Appendix 2.

The method of obtaining the data has been described in detail in Reference 1. Basically, the method consisted of administering a prospective questionnaire to physicians ordering brain scans in a major teaching institution. The questionnaire was completed by medical students who, in addition to obtaining patient attributes such as signs, symptoms, history, and results of previous tests, also obtained the ordering physicians' apriori odds as to whether the scan would be normal or abnormal. The medical students then attended the film reading session to obtain the actual results of the scan for each patient.

The data gathering activity was structured insofar as possible to avoid biases in the data and as the exhibits in Reference 1 and Appendix 1 show, this was largely achieved. The data from the final patient sample of 139 cases was coded for computer analysis in the form shown in Exhibit 1. The data items shown in this exhibit were complete for all 139 patients and were augmented by the outcome states shown in Exhibit 2. The objective of the data analysis was to identify patterns or clusters of the patient's attributes shown in Exhibit 1 which could act with high probability of success as predictors of the outcome states shown in Exhibit 2. To date the analysis has concentrated on clusters of patient attributes which will act as predictors of a normal scan.

Exhibit 3 describes the first such cluster. This is a normal cluster which contains 63 of the 139 total cases representing 45% of all of the cases. In addition, it is worth nothing that there were no surprises in this cluster in the sense that there were no abnormal scans included with this group of normals. In addition, the next two clusters, #'s 2 and 3, also contained entirely normal cases and accounted between them for an additional 22% of the total patient population. Thus, the first three clusters spearated out a total of 67% of all of the cases and did so without including a single abnormal. For the first 67% of the cases, the analysis succeeded in perfectly partitioning the set with no errors (false negatives). Cluster #'s 4, 5, and 6 were also normal clusters but were not quite as precise in their prediction of normalcy as were the first three. However, again they selected normal cases with no errors.

By the time the analysis reached cluster #7, all but 18% or 25 cases had been accounted for and correctly classified as normals. Cluster #7, shown as Exhibit 4, is the first example of a cluster of abnormal cases. All four cases contained in this cluster were correctly classified as abnormal.

These results clearly indicate that patterns of patient attributes available to the physician prior to the ordering of a brain scan can be used to predict with a high degree of accuracy the results of the scan. This is particularly true in the case of the normal scans. Thus, it is highly likely that many of the scans ordered on patients in our sample conveyed relatively little information and consequently were not efficacious.

2. Thyroid Scan Program

Approximately one year ago we began a program to examine the use and efficacy of the thyroid scan in a manner similar to the brain scan analysis reported above. However, in the case of the thyroid scan it was our hope to capitalize on our access to the community hospitals in Michigan in order to observe the use of a nuclear medicine diagnostic procedure in a non-teaching setting. In order to obtain a sufficient patient volume we selected two hospitals, St. John's and Beaumont, in the north Detroit area and enlisted the cooperation of their respective chiefs of nuclear medicine in our study. Fortunately, both were willing to participate and we have instituted programs at both institutions.

To date we have obtained and are in the process of analyzing data on 513 thyroid scan patients seen in the past year. These data consist of the items shown in Exhibits 5, 6, and 7 for each patient. Exhibit 5 is a facsimile of a questionnaire used by a skilled interviewer, usually the nuclear medicine technologist, to obtain basic patient data and attributes. We assume in our data analysis that the same data was known to the referring physician at the time the test was ordered. Exhibit 6 is again a facsimile of a patient history taken by the nuclear medicine specialist prior to the examination. Following the examination the physician's report shown in Exhibit 7 is filed along with the history and patient attribute data.

We have obtained to date 513 complete cases as described above. The data in each of these cases is coded on the form shown in Exhibit 8 for transcriptions to punched card form. As soon as we have completed the transcription work we will begin processing this data using the pattern recognition algorithm. Using this procedure we intend to address the following problems to define significant signs and symptoms.

a) This includes:

Groups of signs and symptoms which when present, indicate that a thyroid scan would be most informative.

Groups of signs and symptoms which when present, indicate that a thyroid scan would not be informative, i.e., the result of the test can be predicted with good accuracy. This especially pertains to situations in which a negative (normal) result can be predicted.

b) To measure the actual amount of information in the test and the amount of information perceived to be in the test by the referring physician. We expect the latter to be larger than the former. By measuring the differences, we should be able to place upper and lower limits on the causes of the differences (presumed to be perceived risks or cost).

Reference 1, ERDA Report COO-2427-5, Biologic Considerations in Anatomic Imaging with Radionuclides, June, 1975, E. James Potchen, Principal Investigator.

EXHIBIT 1

ATTRIBUTES USED IN DATA ANALYSIS

1. Sex---------------------------------- Male   Female

2. Age---------------------------------- ____________

3. Is the decision to do a brain scan based (in part) on the results of another diagnostic procedure?
   Yes   No

   Specifically:

   Lumbar Puncture
   EEG
   Skull X-ray
   Arteriogram
   Echo

4. Headache------------------------------ Yes   No

5. Seizure------------------------------- Yes   No

6. Neoplasm------------------------------ Yes   No   Suspect

7. History of Trauma--------------------- Yes   No

8. Cortical Deficit---------------------- Yes   No

9. Motor Deficit------------------------- Yes   No

10. Sensory Abnormality------------------ Yes   No

11. Visual Field Defect------------------ Yes   No

12. Alteration of Brain Stem------------- Yes   No

13. In your opinion, what is the probability that this brain scan will be normal?
    ____
    0% 20% 40% 60% 80% 100%

14 & 15. Will you alter your management of this patient if the result of this brain scan is:
   (1) Normal   Yes   No
   (2) Abnormal   Yes   No

   Efficacy ____________%
   Defense ____________%
   Innovation;
   Curiosity ____________%
   Other ____________%   Total = 100%

   Chemotherapy
   Radiation Therapy
   Pharmacotherapy
   Anticipated Surgery
   Other

16. Results of the brain scan   Normal   Abnormal

EXHIBIT 2

OUTCOMES USED IN DATA ANALYSIS

1. In your opinion, what is the probability that this brain scan will be normal?

   0% 20% 40% 60% 80% 100%

2,3. Will you alter your management of this patient if the result of this brain scan is:

(i)	Normal	Yes	No
(ii)	Abnormal	Yes	No

4. Efficacy ____________%
   Defense ____________%
   Innovation-Curiosity ____________%
   Other

5. Therapy currently being undertaken for patient's primary problem (Specify type, dosage, etc.)

   Chemotherapy
   Radiation therapy
   Pharmacotherapy
   Other

6. In your opinion, did the results of the scan contribute significantly to your management of the patient?

7. Results of scan:

   Normal
   Abnormal

EXHIBIT 3

CLUSTER NO. 1

Primary Features (All of the following)

Cortical Deficit	No
History of Neoplasm	No
Scan Indicated by Previous Test	No

Secondary Features (One or more of the following)

Motor Deficit	No
Visual Field Defect	No
Headache	Yes
Seizure	Yes
Age unver 44	
History of Trauma	Yes

Estimated Probabilities

$$P(\text{Normal scan}) = .993 \begin{matrix} +.000 \\ -.016 \end{matrix}$$

$$P(\text{Abnormal scan}) = .007 \begin{matrix} +.014 \\ -.000 \end{matrix}$$

A typical case from Cluster No. 1 presented with all of the primary attributes and:

Headache
Seizure
History of Trauma
Visual Field Defect

EXHIBIT 4

CLUSTER NO. 7

Primary Features (All of the following)

Male, over 44	Yes
Sensory Abnormality	No
Visual Field Defect	No
Seizure	No

Secondary Features (One or more of the following)

Motor Deficit	Yes
Cortical Deficit	Yes
Previous History of Neoplasm	Yes
Decision Based on Previous Test	Yes
Alteration of Brain Stem Function	Yes

Estimated Probabilities

$$P(\text{Normal Scan}) = .11 \begin{smallmatrix} +.17 \\ -.02 \end{smallmatrix}$$

$$P)\text{Abnormal Scan}) = .89 \begin{smallmatrix} +.02 \\ -.18 \end{smallmatrix}$$

A typical case from Cluster No. 7 presented with all of the primary features and:

Indication via a Previous Test
History of Neoplasm
Alteration of Brain Stem Function
Motor Deficit
Diagnosed as a Tumor (Primary)

EXHIBIT 5

THYROID FUNCTION TEST QUESTIONNAIRE

Hospital Number: 7 0311170 (2) DATE March 29, 1976

..FERRING PHYSICIAN ________ ( ) Male (X) Female AGE 38

REASON FOR TEST ________

PREVIOUS TESTS: ( ) T7 ( ) Thyroid Scan ( ) Other

SYMPTOMS:

(X) Fatigue, weakness
(X) Overweight
(X) Cold Sensitivity
(X) Fluid retention
( ) Dry skin
( ) Muscle cramps
( ) Nervousness
(X) Weight change +25 lbs
( ) Excess perspiration
( ) Irritability
( ) Splitting nails
( ) Irregular menses
( ) Tremor, hyperactivity
( ) Underweight
( ) Heat Sensitivity
( ) Hair loss
( ) Exophthalmos
( ) Rapid heart beat

THYROID:

( ) Enlargement ( ) Nodules ( ) Surgery DATE ________ ( ) I-131 Therapy DATE ________

( ) Difficulty swallowing ( ) Choking sensation ( ) Feels "lump in throat"

HISTORY OF PAST THYROID PROBLEMS None

FAMILY HISTORY OF THYROID DISEASE None

No feed since 9:30 Dosed 2:30 5 hr fast

RECENT RADIOACTIVE DOSES ________ BKG ________ cpm

*Pregnancy No Hx of liver disease None

DRUGS AFFECTING I-131 UPTAKE		DRUGS AFFECTING T7 TEST	
*Thyroid	None	Thyroid	None
*Anti-thyroid	None	Anti-thyroid	None
*Iodides	None	Estrogens	None
*X-ray media	None	Steroids	None
Vitamins	None	Salicylates	None
Cough medicine	None	Butazolidin	None
hma medicinos	None	Dilantin	None

Othor drugs Water pills, Dristan

MAJOR ILLNESSES Gall bladder out

*May be reason to cancel radioiodine dose. CONSULT PHYSICIAN.

725-13

EXHIBIT 6

Typical Patient History Data

Patient Name: Age: 38 Date: 3/29/76

Hospital No: 7 0311170 (2) Nuclide: 131 I

Procedure: Thyroid Scan/Uptake Amount: 10 uCi

History:

Patient has been feeling:

-- Tired
-- Tendency to Sleep
-- Weight Gain 25 lb/4-5 months
--Constipation
--Irregular periods
--closer, longer
--cold sensitivity

No family history of Thyroid (problems)

Water Pills Diazide

Exam

--Thyroid is not palpable
--Hands slightly cold
--Blood pressure not checked
--Heart (rate) 75/min

Remarks:

T7, TSH

6HR Uptake_____%

24HR Uptake 15 %

T_3_____% T_4_____%

T_7 Date________________

EXHIBIT 7

Facsimile of Radioisotope Scan Report

Hospital Number 7 0311170 (2) Date 3/29/76

Patient's Name ______________ Referring Phys. ______________

THYROID SCAN

Indications:

This is a 38-year old female who has complaint of symptoms of hypothyroidism. The thyroid gland is not palpable and the patient generally appears euthyroid.

Procedure:

The patient was injected with 10 mCi ^{99m}-Tc Pertechnetate ILV. and a thyroid scan was obtained with scintillation camera. Ten uCi of I-131 was given orally and 24 hours later an uptake reading was obtained.

Results:

RADIOACTIVE IODINE UPTAKE TEST

	NORMAL VALUES	PATIENT
24	Hours 15 - 32%	15%

The radioactiveiodine uptake is within normal limits being 15% at 24 hours. The thyroid scan shows minimal lack of uniformity in distribution of radioactivity throughout the thyroid gland. The size of the gland appears to be about 1 1/2 normal size. There are no discrete hot or cold defects.

Impression:

Probably normal thyroid scan; euthyroidism. The euthyroidism is confirmed by normal T7 and TSH tests.

EXHIBIT 8

CODING SHEET FOR RETROSPECTIVE THYROID SCAN STUDY

1. Sex 0 = Female 1 = Male 1. ___

(2. 3.) ___ ___

2. Age

3. Reason for test

Pat, make up list of code #'s for 0-9 for the major reasons. 4. ___
Remember to keep tract of the list.

PREVIOUS TESTS

5. ___

4. T7 M = missing 0 = no 1 = yes

6. ___

5. Thyroid scan M = missing 0 = no 1 = yes

7. ___

6. Other M = missing 0 = no 1 = yes

SYMPTOMS

8. ___

7. Fatigue, Weakness

9. ___

8. Overweight

10. ___

9. Cold sensitivity

11. ___

10. Fluid retention M = missing 0 = no 1 = yes

12. ___

11. Dry skin

13. ___

12. Muscle cramps

14. ___

13. Nervousness

15. ___

14. Weight change

16. ___

15. Amount of change 0 = no change 1 = -21-25 2 = - 16-20 3 = -11-15
4 = -6-10 5 = -1-5 6 = +1-+5 7 = +6-+15
8 = +16=+20 9 = greater than +25

17. ___

16. Excess perspiration

18. ___

17. Irritability

19. ___

18. Splitting nails

20. ___

19. Irregular menses

21. ___

20. Tremor, hyperactivity M = missing 0 = no 1 = yes

22. ___

21. Underweight

23. ___

22. Heat Sensitivity

24. ___

23. Hair loss

25. ___

24. Exopthalmos

SECOND CODING SHEET

25. Rapid heart beat 26. ___

26. Other - make list 27. ___

THYROID

27. Enlargement 28. ___

28. Nodules 29. ___

29. Difficulty swallowing M = missing 0 = no 1 = yes 30. ___

30. Choking sensation 31. ___

31. Feels "lums in throat" 32. ___

32. Surgery M = missing 0 = no 1 = yes 33. ___

33. Date of surgery M = missing 0 = no 1 = within a year
2 = greater than a year 34. ___

34. I-131 Therapy M = missing 0 = no 1 - yes 35. ___

34½. Date of therapy 0 = no 1 = yes 36. ___

35. History of past thyroid problems 37. ___

36. Family history of thyroid disease 0 = no 1 = yes 38. ___

37. Recent radioactive doses 39. ___

38. Pregnancy 0 = no 1 = yes 40. ___

39. HX of liver disease 41. ___

DRUGS AFFECTING I-131 UPTAKE

40. Thyroid 42. ___

41. Anti-thyroid 43. ___

42. Iodides 0 = no 1 = yes 44. ___

43. X-ray media 45. ___

44. Vitamins 46. ___

45. Contains iodide or affects thyroid? 47. ___

46. Cough medicine 48. ___

47. Contains iodide or affects thyroid? 49. ___

48. Asthma medicines 50. ___

49. Contains iodide or affects thyroid? 51. ___

THIRD CODING SHEET

50. Other drugs   0 = no   1 = yes   52. ___

51. Contains iodide or affects thyroid?   53. ___

DRUGS AFFECTING T7 TEST

52. Thyroid   54. ___

53. Anti-thyroid   55. ___

54. Estrogens   0 = no   1 = yes   56. ___

55. Steroids   57. ___

56. Salicylates (aspirin)   58. ___

57. Butazolidin   (A large gamma is the sign that all questions were negative)   59. ___

58. Dilantin   60. ___

59. Major illnesses   M = missing   0 = none   1 = Heart   2 = Kidney   3 = Other endocrine   4 = Other   61. ___

60. Nucleotide   M = missing 0 = none   1 = I-131   2 = I-123   3 = Tech-99m   4 = I-125   5 = I-127   6 = Fluoro   7 = Tech+I-131   8 = Tech+I-123   9 = Other   62. ___

61. Dosage   M = missing   1 - less than 25 uCi   2 = 25-50 uCi   3 = 51-75 uCi   4 = 76-100 uCi   5 = 101-125 uCi   6 = 126-150 uCi   7 = 151-175 uCi   8 = 176-200 uCi   9 = greater than 200 uCi   63. ___

62. Results   0 = Normal   1 = Low uptake   2 = High uptake   64. ___

63. Range   0 = Normal   1 = 0-7%   2 = 8-14%   3 = 33-40%   4 = 41-48%   5 = 49-56%   6 = 57-64%   7 = 65-72%   8 = 73-80%   9 = over 80%   65. ___

IMPRESSION (Extract this information from the RADIOISOTOPE SCAN REPORT)

64. Goiter   0 = no   1 = diffuse   2 = nodular   3 = both   66. ___

65. Hyperthyroid   0 = no   1 = yes   (includes anything labeldd "toxic")   67. ___

66. Hyppthyroid   0 = no   1 = yes   68. ___

67. Carcinoma, Adenoma (all Neoplasms)   0 = no   1 = yes   69. ___

68. Thyroiditis   (all inflamations, Hashimoto's)   0 = no   1 = yes   70. ___

69. Normal   0 = normal   1 = abnormal   2 = don't know   71. ___

. Recommendations   0 = None   1 = T7   2 = Repeat scan in future   72. ___

APPENDIX 1

PRELIMINARY DRAFT

"Efficacy and Information in Radionuclide Brain Scanning"

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Bruce Johnston
Richard Auld
Carl A. Johnson
Gregory S. Pudhorodsky

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The value of a radionuclide brain scan in clinical medicine relates to its capacity to detect intracerebral pathology in a safe, efficient and effective manner. Owing to these properties the radionuclide brain scan has been widely applied as a "screening test" in patients suspected of having intracranial disease. This usage undoubtedly contributes significantly to the estimated 2.8 million radionuclide brain scans performed in the United States per year at an estimated cost of $200 million. However, as the cost of health care in the United States becomes an increasingly important issue, the indications for the clinical use of diagnostic procedures such as the radionuclide brain scan must be re-examined with the objective of increasing the efficacy of the procedure.

The ability to detect an intracerebral lesion which is confirmed subsequently be an alternative diagnostic modality, e.g., angiography or pathologic study, e.g., surgery or autopsy, has been used as the criteria to establish the clinical efficacy of radionuclide brain scanning. Although this definition of efficacy is simple and the components objectively measurable, it is unfortunately limited in that there is no mechanism for inclusion of a measure of the benefit to the patient.

In fact, since the capacity to merely detect intracerebral lesions is not necessarily correlated with a beneficial effect on patients, it seems reasonable to seek alternative criteria for evaluating the efficacy of radionuclide brain scanning.

Recent studies have shown that despite the tenfold increase in the use of radionuclide brain scans there is no demonstrable improvement in the morbidity or mortality from cerebral disease[1]. Others have reasonably argued that the brain scan has its highest utility in confirming normality in the worried well. Obviously a confirmation of normality could have a beneficial effect on patients, e.g., improved quality of life. However, one could more reasonably argue that the appropriate objective of a diagnostic procedure relates to its capacity to provide information which could influence the management of patients. With the availability of new techniques which provide many alternative strategies to evaluate patients with suspected intracranial pathology, it becomes increasingly important for us to identify criteria for efficacy which relate to the effect the procedure has on the management of patients rather than merely the detection of pathology or the confirmation of normality.

The outcome of a diagnostic procedure in terms of its relative value vs. an alternative procedure should ideally be related to the effect it has on the management of patient who perceives disease. Unfortunately, although considerable research is underway in an effort to better define the patient's perceptions of his quality of life as affected by disease, the subjective impression of a sense of well being has been difficult to measure. Until such a time as we have more reliable measures of the effect of a diagnostic procedure on patient management, alternative criteria for efficacy will have to be used to design the most appropriate diagnostic strategy in management of patients.

Recent studies on diagnostic decision making and efficacy of diagnostic procedures have yielded many approaches to this problem. One such approach relates to the possibility of anticipating the outcome of the diagnostic procedure prior to its application. If one could reliably assert that the procedure will provide a normal examination in patients with specific signs and symptoms, then the need for the procedure in those cases would decrease.

This study was undertaken to test a new analytic tool, entropy minimax multivariate analysis, as a means to develop criteria to measure the efficacy of radionuclide brain scanning. Since the analysis has been applied in this instance to the possibilities of determining normality prior to the diagnostic procedure, it appears that it is equally applicable as a means to appreciate whether or not other diagnostic methods such as computerized tomographic brain scan will yield beneficial results to a specific group of patients.

Methods

For purposes of this study we have defined diagnostic efficacy as follows: In order to be efficacious, a diagnostic procedure must yield a result that can be shown to have a significant probability of affecting the management of patient's disease. This definition does not relate to the frequency of normal vs. abnormal results and does not necessarily relate to pathologic correlation. Initial studies were designed to assess whether or not it would be possible to reliably predict normality in patients that physicians felt warranted having the diagnostic procedure.

The source of material for this study was ^{99m}Tc pertechnetate brain scans performed in a university hospital. A breakdown of the patient population is seen in Figure 1. Patients and the referring physician were interviewed using a standardized encounter form which provided data on the variables presented in Figure 2. These variables were selected from the possible indications for the radionuclide brain scan based on our prior experience with the physicians referring the patients in this study. Each of the variables was clarified in detail on the encounter form, Figure 3.

Entropy minimax is a form of multivariate analysis which can be applied to attribute-outcome analysis. This technique detects patterns or clusters of attributes which, when observed together, affect the probability of a particular outcome state. The information provided by each attribute is measured relative to the entire constellation of attributes used in the decision process. Information in this context is defined as the reduction of uncertainty, or alternatively as a change in the entropy of the physician's state of knowledge. Thus, the technique allows one to ascertain the probable information provided by knowing any attribute, or set of attributes, in relation to a possible outcome.

The application of entropy minimax as a tool to study diagnostic decision making has previously been published.[2] Essentially, the method allows for the detection of non-random patterns in an n-dimensional patient attribute matrix. In this instance, the set of analysis variables is composed of the signs and symptoms seen in patients referred for brain scans in one institution. The program discovers the patterns (aggregate clusters of signs and symptoms) and then identifies the probability of a specific outcome in relation to each cluster or pattern of attributes. The clusters of diagnostic attributes which affect the outcome of the diagnostic procedure can thus be identified.

Outcomes in this study were limited to normal or abnormal brain scan results. Admittedly, being able to apriori identify whether a brain scan will be normal or abnormal is not necessarily sufficient to determine its appropriate application to a specific patient. Abnormal scans have many patterns, some of which can yield more diagnostic information than simple normal or abnormal characteristics. However, if one could reliably ascertain that the scan would be normal from the patient's signs and symptoms, then one could anticipate that the procedure would have relatively little efficacy in influencing decision in the management of the patient. The analysis variables could be tested aginst an alternative diagnostic procedure to seek those procedures in which the outcome cannot be reliably predicted by the signs and symptoms, i.e., procedures which have a higher probability of providing information about the patient's disease. The maximum information to be yielded by a procedure would be in clusters where the probability of a normal outcome or an abnormal outcome is ½, i.e., a random state. In this instance the diagnostic procedure has the greatest probability of altering the physician's state of knowledge regarding the patient. Thus, in comparing two diagnostic procedures which may be considered as indicated by a symptom complex (cluster of analysis variables), one would anticipate more information from that procedure whose outcome could less reliably be predicted from the signs and symptoms themselves. As the probability of a normal result approaches one or zero, then the procedure has less relative efficacy than an alternative diagnostic procedure where the results cannot be predicted with such certainty.

Results

The results of the entropy minimax program are displayed by listing primary attributes (i.e., required of every patient falling into this group) and secondary attributes (one or more of which is included in every patient in this group).

When the data collected from the encounter forms was analyzed using the entropy minimax multivariate analysis, 13 clusters of analysis variable (groups of patients with similar signs and symptoms) yielding non-random relationships of the analysis variables and the outcome state were identified. Five clusters will be presented here as examples of the technique. These clusters were selected because they were typical of the most common clusters seen in this patient population. Most of them also had a high probability of predicting the outcome of the brain scan from the signs and symptoms alone.

Cluster 1 included 44% of the patients studied. To meet the criteria for Cluster 1 (Figure 4), a patient would have to have all three primary attributes (i.e., no evidence of a cortical deficit, no history of a previous neoplasm and a scan which was not predicated upon the results of a previous test), and at least one of the 6 secondary attributes (i.e., under age 44, headache, seizure, history of trauma, no motor deficit or no visual field defect). Previous tests in this study were limited to skull films, cerebral angiography, and pneumoencephalography. Any one of these secondary features, in addition to all of the primary features, was requisite for being included in this group of patients. The probability of a normal scan in this group of patients was .993. Thus, a patient fulfilling these criteria could be anticipated to have a normal brain scan with considerable certainty. There were no surprises in this series, i.e., no patient who fulfilled these criteria had an abnormal brain scan in the series of patients studied. That is not to say that at some time a patient with these attributes may not have an abnormal brain scan, but the probability of such a result is .007. Thus, we can reliably predict a normal outcome without doing the brain scan in 44% of patients who were felt to have indications for a brain scan at the institution studied. The use of the brain scan in these patients would seem to be of limited value.

Cluster 3 was the third largest segment of patients, representing 9% of the patient population studied. Each patient had attributes which included no history of trauma, no history of headache, and the decision to request a brain scan was not based on a previous diagnostic test,in addition to one or more of the secondary features seen in Figure 5. In this instance, the probability of a normal scan was .97. Thus, brain scans done on patients fulfilling the criteria of Cluster 3 have a slightly greater probability of yielding an abnormal result than the patients in Cluster 1. In both of these clusters the _apriori_ ability to predict the normal outcome of the scan suggests that the brain scan has limited diagnostic efficacy in these patient populations.

To go slightly further down the scale of predictive probability, Cluster 8 (Figure 6) represents a group of patients in which the probability of a normal scan decreases to .93. These patients were men over 40 who had no history of a visual field defect, seizure, or sensory abnormality. 4% of the total patient population studied fell into this category.

On the other hand, in Cluster 9, representing 3% of the patients studied, the probability of a normal scan fell to .12. That is, in this population of patients, a high probability of an abnormal scan can be anticipated prior to performing the procedure. These patients were males who had no alteration of the brain stem function and no history of seizure but did have either one or more of the following criteria: visual field defects, indication of the scan by a previous test, history of trauma, cortical deficit, motor deficit, or no sensory abnormality. In this population of patients, the brain scan is probably diagnostically efficacious. The probability of anticipating the results (outcome) prior to the procedure is less than in Cluster 1 and 3. Equally important, since an abnormal scan could be anticipated with some certainty, the type of brain scan abnormality predicted by the signs and symptoms is not certain. Thus the scan could yield more specific clues resulting in alterations in the management of the patient.

Cluster 11 represents a similar group. The probability of a normal scan in this cluster is .14. These patients were females with no history of trauma and no sensory abnormality, but who had either one or more of the following: history of neoplasms, indication of the scan by a previous test, a cortical deficit, a visual field defect, alteration of brain stem function, or headache. Three percent of the patients studied fulfilled these criteria. Again, a brain scan would have considerably greater efficacy by our definition when used with these patients than when used with a patient in Cluster 1 or Cluster 3.

The entropy minimax program allows each patient to fit into only the cluster of highest probability. Thus, if a patient fits into Cluster 1, they are excluded from all other clusters.

Discussion

The availability of so many new diagnostic procedures neccessitates a better understanding of the relative merits of their use in patients presenting with common symptom complexes. Investigators seeking to evaluate the merits of alternative diagnostic procedures have used many different criteria. We feel it is reasonable to develop a more standard approach to study diagnostic efficacy. This concern relates to the socioeconomic implications in defining an optimal diagnostic strategy. We must better understand the merits of all options in order to design the most effective and efficient management of a patient's problems.

The criteria physicians use to initiate a diagnostic procedure relates to what they are taught are the appropriate indications for the procedure and to the physician's personal experience with the diagnostic study in managing patients with similar symptom complexes. This experiential learning becomes part of the physician's system of indications for a diagnostic procedure. The physician's personal experience is almost always insufficient to develop a reliable estimate of the potential for the diagnostic test to yield significant information. The effect of diagnostic information on the management of the patient or even on physician's behavior has not been subjected to in-depth investigation. What would happen to a patient if the "indicated" test were not performed? Obviously, the answer to this question varies with the diagnostic test under analysis; however, in the case of radionuclide brain scans, the answer would probably be that it often does not make much difference.

The measurement of diagnostic efficacy has been difficult, and as one might anticipate, a number of measurement techniques have been developed, ranging from "use rate" to "log likelihood ratio." Perhaps a brief discussion of the alternative methods of estimating diagnostic efficacy would be helpful in order to place the entropy minimax approach to diagnostic analysis in context.

Current PSRO and legal standards of health care relate in part to the "use rate" of a diagnostic procedure. That is, the medical and legal standards of care are in part established by whether or not the procedure is commonly performed by other physicians when faced with a similar problem in patients. Use rate alone, however, is a poor estimate of the diagnostic efficacy. Many studies have shown that some procedures are used for reasons other than to benefit the patient. Studies on the use of the skull x-ray in pediatric head injuries support this contention.[(3)] The decision on patient management is not based upon the results of the x-ray, rather it depends upon other clinical manifestations. Yet, emergency skull x-rays continue in use because of the physician's concern for the legal implications were he to fail to get a skull x-ray on a person with a head injury. Defensive medicine has increased the use of diagnostic procedures which are not helpful in decisions regarding patient management.

A second criteria, widely applied in estimating the value of new diagnostic technology, has been termed the "marginal substitution rate." In this instance, the new diagnostic procedure is evaluated on the basis of its capacity to replace a prior diagnostic modality. An example of this approach relates to the advent of computer tomography, CT, scanning and its capacity to decrease the use of the radionuclide brain scan. Inasmuch as the radionuclide brain scan has not previously been evaluated in terms of efficacy, i.e., its effect on outcome of the patient's problem, the use of marginal subsitution rate to indicate the clinical efficacy of the CT scan is not reasonable. Even if CT were to replace radionuclide brain scans we still would not know whether or not CT scanning benefits patients. Thus, the marginal substitution rate <u>per se</u> is limited in its use as a criteria for diagnostic utility and should not be recommended as the principal rationale for using a new diagnostic modality.

Historically, in diagnostic radiology and nuclear medicine the most typical criterion evaluated is the pathologic correlation. In this regard the merits of alternative diagnostic procedures are tested on their accuracy in correlating with what the pathologist sees at autopsy or what the surgical specimen revealed. While this has been the principle criteria for developing and testing new diagnostic modalities in medicine, it is quite apparent that the mere fact that a diagnostic procedure can be well correlated by pathologic observation does not necessarily speak to the question of whether or not this procedure benefits patients.

An alternative set of criteria could relate to the question of whether or not the use of a diagnostic procedure had an effect on the course of the patient's disease. Ideally,one would seek to measure the ultimate effect of a diagnostic test on the patient's sense of well being. Does the use of a diagnostic test ultimately improve the quality of the patient's life? Although these criteria remain the ultimate objective in developing a measure of diagnostic efficacy, these outcome states are extremely difficult to measure. Until we can reliably ascertain the effect of a diagnostic procedure on the course of the patient's disease, other measures of diagnostic efficacy will have to be used.

One recently applied technique to analyze the diagnostic decision process relates to the ability of the diagnostic procedure to change the physician's subjective probability of a specific diagnosis. This "log likelihood" approach is being used in the American College of Radiology study on diagnostic efficacy of radiologic procedures performed in the emergency room. This method of analysis essentially hypothesizes that it is necessary to change the physician's subjective probability of naming a disease in order for a diagnostic test to be efficacious. While this is a reasonable approach to diagnostic efficacy, particularly in view of the difficulty in measuring outcome states, the technique is limited in two respects. First, it is entirely subjective (e.g., appraising the physician's personal probability change). Second, the outcome being tested relates to the physician's capacity to name the disease rather than to the question of whether or not naming the disease could affect what happens to the patient.

The technique used in this study (entropy minimax) determines whether or not the additional data gleaned from a diagnostic procedure would change the information (knowledge state) of the physician concerning the probability of a specific outcome. Multivariate analysis, e.g., entropy minimax, provides an opportunity to predict the information which could be anticipated from a diagnostic procedure in any specific cluster of signs and symptoms the patient presents to the physician. This technique essentially measures whether or not the additional data gleaned from the diagnostic procedures changed the entropy of the clusters of analysis variables in an n-dimensional matrix. Heretofore, this technique has not been widely applied to medical decision analysis. Ideally, this method would be used to determine the probable information provided by diagnostic procedure in relation to its effect on the course of the patient's disease. If we were to use as an outcome a change in the course of a patient's disease or a patient's sense of well being, this method would be a means to compare the merits of alternative procedures available to address a specific symptom complex.

However, until we have better measures of the ultimate outcome, we can obtain useful information on the ability to predict the outcome of the diagnostic procedure prior to embarking upon its performance. While this approach does not allow one to determine the effect of the procedure on the course of the patient's disease, it seems reasonable to suggest that if one can reliably predict that a test will be normal prior to its performance, that that procedure would have little efficacy in providing information which the physician can use to manage a symptom complex.

We recognize that many physicians are fully aware that in many instances, diagnostic procedures are used which have little chance of affecting the management of the patient. In many patients, the physician, can anticipate with reasonable certainty that the procedure will be normal prior to its use. Physicians continue to use the procedures, however, frequently because they are either looking for the 'surprise' or are seeking to confirm normality. We would suggest that if normality can be reliably confirmed on the basis of the symptom complex alone the procedure would have little efficacy. In the study described here, the physicians could have anticipated with considerable certainty that in 44% of the patients the procedure would have yielded a normal radionuclide brain scan. It would seem that continued application of the brain scans in this group of patients would not necessarily benefit the patients. Thus, a method has been described whereby it is possible to anticipate the probability of a normal diagnostic procedure prior to its use with sufficient degrees of accuracy to warrant the conclusion that the use of a diagnostic procedure will yield little information that the physician can use to manage the patient. 44% of patients having brain scans in this series have filled criteria whereby one could anticipate with a probability of .993 that the brain scan would be normal.

Summary

The efficacy of radionuclide brain scanning, defined in terms of probability as to whether or not the scans will yield information relavant to the management of the patient, has been studied in a

series of 139 patients undergoing radionuclide brain scans in a university hospital setting. Patterns of diagnostic attributes were clustered and the probability of each outcome was calculated using the entropy minimax approach to diagnostic decision analysis.

In this series it was shown that patients who had no cortical deficit, no history of previous neoplasm, and no indication of the scan by a previous test, and in addition, one or more of the secondary attributes (headache, seizure, age under 44, history of trauma, no motor deficit or no visual field deficit), would yield a normal brain scan with probability of .993 prior to performing the test. We conclude that in this population of patients the brain scan has limited potential diagnostic efficacy in affecting the management of the patient inasmuch as the outcome of the test, i.e., normality, can be predicted prior to embarking on the procedure.

Other clusters were identified with varying capability for predicting whether or not the brain scan would be normal. Patient's presenting with symptoms suggesting the need for a brain scan can now be tested to determine whether the physician can predict the results of the test with sufficient certainty to warrant eliminating the test from the diagnostic protocol in selected patients.

This approach toward diagnostic decision analysis is equally applicable to a study in the efficacy of the cerebral computed tomography where the population of patients appears to be quite similar to the population referred for radionuclide brain scans. It is apparent that increasing emphasis on diagnostic efficacy studies is essential in view of the current social, economic and medical responsibilities of physicians required to choose among alternative diagnostic tests.

PATIENT POPULATION

Patient Sex	Number
Male	66
Female	63
Total	139

Age Range (Years)	Number of Patients
0 - 20	35
20 - 40	28
40 - 60	37
60 - 80	32
Over 80	7
Total	139

Result of Scan	Number
Normal brain scans	127
Confirmed abnormal brain scans	12
Total	139

FIGURE 1 CHARACTERISTICS OF THE PATIENT POPULATION

ANALYSIS VARIABLES

Attributes	
Sex of patient	M/F
Age of patient	Years
Scan indicated by previous test	Yes or No
Headache	" "
Seizure	" "
Previous history of neoplasm	" "
History of trauma	" "
Cortical deficit	" "
Motor deficit	" "
Sensory abnormality	" "
Visual field defect	" "
Alteration of brain stem function	" "

Outcomes

Normal scan

Abnormal scan

FIGURE 2 VARIABLES USED IN THE DATA ANALYSIS

FIGURE 3 TYPICAL PAGE FROM THE BRAIN SCAN QUESTIONNAIRE

1. Headache---------------------------- O yes O no

   a) Duration------------------------ O < 1 Week
      O 1 Week to 1 Month
      O 1 Month to 3 Months
      O > 3 Months

   b) Continuity---------------------- O Continuous
      O Intermittent

   c) Severity------------------------ O Mild
      O Moderate
      O Severe

   d) Location if diffuse------------- O Bilateral
      O Unilateral

   e) Location if focal--------------- O Retroorbital
      O Frontal
      O Temporal
      Parietal
      O Occipital

2. Seizure----------------------------- O yes O no

   a) Number of Episodes-------------- O Single (First)
      O Multiple < 10
      O Multiple > 10 (Long-standing)

   b) Location------------------------ O Generalized
      O Focal

   c) Type---------------------------- O Major Motor
      O Minor Motor
      O Temporal Lobe
      O Other

   d) Is Seizure Pattern Changing?---- O Yes
      O No

   e) Pertinent Family History of Seizures--------- O Yes
      O No
      O Unknown

3. Neoplasm---------------------------- O yes O no O suspect

   a) Location------------------------ Brain
      O Lung
      O Breast
      O Other

   b) Pertinent Family History of Neoplasm----- O yes
      O no
      O unknown

4. History of Trauma------------------- O yes O no

CLUSTER NO. 1

Primary features (all of the following)	
Cortical deficit	No
History of neoplasm	No
Scan indicated by previous test	No
Secondary features (one or more of the following)	
Motor deficit	No
Visual field defect	No
Headache	Yes
Seizure	Yes
Age under 44	
History of trauma	Yes
Estimated probabilities	

P (normal scan) $= .993 \, {}^{+.000}_{-.016}$

P (abnormal scan) $= .007 \, {}^{+.014}_{-.000}$

A TYPICAL CASE FROM CLUSTER NO. 1 PRESENTED WITH ALL OF THE PRIMARY ATTRIBUTES AND:

Headache
Seizure
History of Trauma
Visual Field Defect

FIGURE 4 ANALYSIS RESULTS FOR THE MOST SIGNIFICANT CLUSTER

CLUSTER NO. 3

Primary features (all of the following)	
History of trauma	No
Headache	No
Decision based on previous test	No
Secondary features (one or more of the following)	
Cortical deficit	Yes
History of neoplasm	Yes
Age greater than 62	
Motor deficit	Yes
Visual field defect	Yes

Estimated probabilities

$$P(\text{normal scan}) = .97\,^{+.00}_{-.07}$$

$$P(\text{abnormal scan}) = .03\,^{+.07}_{-.00}$$

A TYPICAL CASE FROM CLUSTER NO. 3 PRESENTED WITH ALL OF THE PRIMARY FEATURES AND:

Visual Field Defect
Cortical Deficit

FIGURE 5 ANALYSIS RESULTS FOR THE THIRD MOST SIGNIFICANT CLUSTER

CLUSTER NO. 8

Primary features (all of the following)	
Male over age 40	
Visual field defect	No
Seizure	No
Sensory abnormality	No
Secondary features (one or more of the following)	
Cortical deficit	Yes
Scan indicated by previous test	Yes
History of neoplasm	Yes

Estimated probabilities

P (normal scan) $= .93^{+.01}_{-.13}$

P (abnormal scan) $= .07^{+.12}_{-.01}$

A TYPICAL CASE FROM CLUSTER NO. 8 PRESENTED WITH THE PRIMARY FEATURES AND:

Headache
Cortical Deficit
Alteration of Brain Stem Function
Motor Deficit

FIGURE 6 ANALYSIS RESULTS FOR THE EIGHTH MOST SIGNIFICANT CLUSTER

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