Cost Effectiveness of Automated Multichannel Chemistry Analyzers

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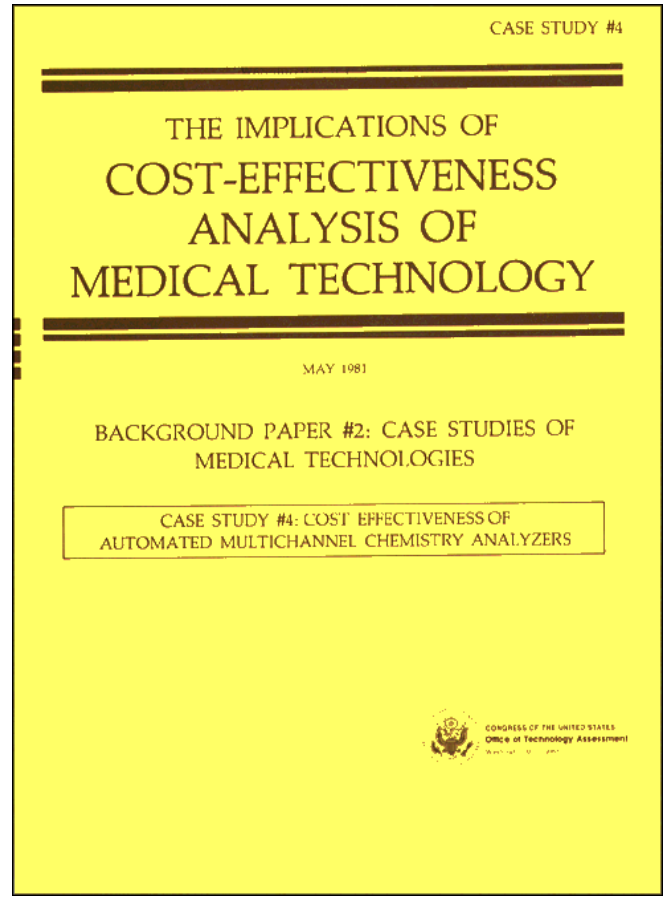

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THE IMPLICATIONS OF COST-EFFECTIVENESS ANALYSIS OF MEDICAL TECHNOLOGY

MAY 1981

BACKGROUND PAPER #2: CASE STUDIES OF MEDICAL TECHNOLOGIES

CASE STUDY #4: COST EFFECTIVENESS OF AUTOMATED MULTICHANNEL CHEMISTRY ANALYZERS

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OTA Background Papers are documents that contain information believed to be useful to various parties. The information undergirds formal OTA assessments or is an outcome of internal exploratory planning and evaluation. The material is usually not of immediate policy interest such as is contained in an OTA Report or Technical Memorandum, nor does it present options for Congress to consider.

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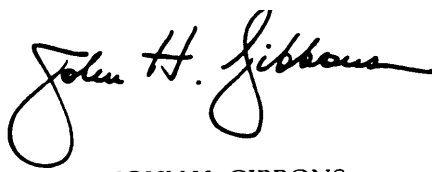
Foreword

This case study is one of 17 studies comprising Background Paper #2 for OTA's assessment, ***The Implications*** of ***Cost-Effectiveness Analysis*** of ***Medical Technology,*** That assessment analyzes the feasibility, implications, and value of using cost-effectiveness and cost-benefit analysis (CEA/CBA) in health care decisionmaking. The major, policy-oriented report of the assessment was published in August 1980. In addition to Background Paper #2, there are four other background papers being published in conjunction with the assessment: 1) a document which addresses methodological issues and reviews the CEA/CBA literature, published in September 1980; 2) a case study of the efficacy and cost-effectiveness of psychotherapy, published in October 1980; 3) a case study of four common diagnostic X-ray procedures, to be published in summer 1981; and 4) a review of international experience in managing medical technology, published in October 1980. Another related report was published in September of 1979: ***A Review*** of ***Selected Federal Vaccine and Immunization Policies.***

The case studies in ***Background Paper #2: Case Studies*** of ***Medical Technologies*** are being published individually. They were commissioned by OTA both to provide information on the specific technologies and to gain lessons that could be applied to the broader policy aspects of the use of CEA/CBA. Several of the studies were specifically requested by the Senate Committee on Finance.

Drafts of each case study were reviewed by OTA staff; by members of the advisory panel to the overall assessment, chaired by Dr. John Hogness; by members of the Health Program Advisory Committee, chaired by Dr. Frederick Robbins; and by numerous other experts in clinical medicine, health policy, Government, and economics. We are grateful for their assistance. However, responsibility for the case studies remains with the authors.



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Preface

This case study is one of 17 topics being issued that comprise Background Paper #2 to the OTA project on the *Implications of Cost-Effectiveness Analysis of Medical Technology.* * The overall project was requested by the Senate Committee on Labor and Human Resources. In all, 19 case studies of technological applications were commissioned as part of that project. Three of the 19 were specifically requested by the Senate Committee on Finance: psychotherapy, which was issued separately as Background Paper #3; diagnostic X-ray, which will be issued as Background Paper #5; and respiratory therapies, which will be included as part of this series. The other 16 case studies were selected by OTA staff.

In order to select those 16 case studies, OTA, in consultation with the advisory panel to the overall project, developed a set of selection criteria. Those criteria were designed to ensure that as a group the case studies would provide:

- examples of types of technologies by function (preventive, diagnostic, therapeutic, and rehabilitative);
- examples of types of technologies by physical nature (drugs, devices, and procedures);
- examples of technologies in different stages of development and diffusion (new, emerging, and established);
- examples from different areas of medicine (such as general medical practice, pediatrics, radiology, and surgery);
- examples addressing medical problems that are important because of their high frequency or significant impacts (such as cost);
- examples of technologies with associated high costs either because of high volume (for low-cost technologies) or high individual costs;
- examples that could provide informative material relating to the broader policy and methodological issues of cost-effectiveness or cost-benefit analysis (CEA/CBA); and
- examples with sufficient evaluable literature.

On the basis of these criteria and recommendations by panel members and other experts, OTA staff selected the other case studies. These 16 plus the respiratory therapy case study requested by the Finance Committee make up the 17 studies in this background paper,

All case studies were commissioned by OTA and performed under contract by experts in academia. They are authored studies. OTA subjected each case study to an extensive review process. Initial drafts of cases were reviewed by OTA staff and by members of the advisory panel to the project. Comments were provided to authors, along with OTA's suggestions for revisions. Subsequent drafts were sent by OTA to numerous experts for review and comment. Each case was seen by at least 20, and some by 40 or more, outside reviewers. These reviewers were from relevant Government agencies, professional societies, consumer and public interest groups, medical practice, and academic medicine. Academicians such as economists and decision analysts also reviewed the cases. In all, over 400 separate individuals or organizations reviewed one or more case studies. Although all these reviewers cannot be acknowledged individually, OTA is very grateful for their comments and advice. In addition, the authors of the case studies themselves often sent drafts to reviewers and incorporated their comments.

These case studies are authored works commissioned by OTA. The authors are responsible for the conclusions of their specific case study. These cases are not statements of official OTA position. OTA does not make recommendations or endorse particular technologies. During the various stages of the review and revision process, therefore, OTA encouraged the authors to present balanced information and to recognize divergent points of view. In two cases, OTA decided that in order to more fully present divergent views on particular technologies a commentary should be added to the case study. Thus, following the case

*Office of Technology Assessment, U.S. Congress, *The Implications of Cost-Effectiveness Analysis of Medical Technology.* GPO stock No. 052-003-00765-7 (Washington, D.C.: U.S. Government Printing Office, August 1980).

studies on gastrointestinal endoscopy and on the Keyes technique for periodontal disease, commentaries from experts in the appropriate health care specialty have been included, followed by responses from the authors.

The case studies were selected and designed to fulfill two functions. The first, and primary, purpose was to provide OTA with specific information that could be used in formulating general conclusions regarding the feasibility and implications of applying CEA/CBA in health care. By examining the 19 cases as a group and looking for common problems or strengths in the techniques of CEA/CBA, OTA was able to better analyze the potential contribution that these techniques might make to the management of medical technologies and health care costs and quality. The second function of the cases was to provide useful information on the specific technologies covered. However, this was not the major intent of the cases, and they should not be regarded as complete and definitive studies of the individual technologies. In many instances the case studies do represent excellent reviews of the literature pertaining to the specific technologies and as such can stand on their own as a useful contribution to the field. In general, though, the design and the funding levels of these case studies was such that they should be read primarily in the context of the overall OTA project on CEA/CBA in health care.

Some of the case studies are formal CEAs or CBAs; most are not. Some are primarily concerned with analysis of costs; others are more concerned with analysis of efficacy or effectiveness. Some, such as the study on end-stage renal disease, examine the role that formal analysis of costs and benefits can play in policy formulation. Others, such as the one on breast cancer surgery, illustrate how influences other than costs can determine the patterns of use of a technology. In other words, each looks at evaluation of the costs and the benefits of medical technologies from a slightly different perspective. The reader is encouraged to read this study in the context of the overall assessment's objectives in order to gain a feeling for the potential role that CEA/CBA can or cannot play in health care and to better understand the difficulties and complexities involved in applying CEA/CBA to specific medical technologies.

The 17 case studies comprising *Background Paper #2* short titles and their authors are:

Artificial Heart: Deborah P. Lubeck and John P. Bunker
Automated Multichannel Chemistry Analyzers: Milton C. Weinstein and Laurie A. Pearlman
Bone Marrow Transplants: Stuart O. Schweitzer and C. C. Scalzi
Breast Cancer Surgery: Karen Schachter and Duncan Neuhauser
Cardiac Radionuclide Imaging: William B. Stason and Eric Fortess
Cervical Cancer Screening: Bryan R. Luce
Cimetidine and Peptic Ulcer Disease: Harvey V. Fineberg and Laurie A. Pearlman
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Elective Hysterectomy: Carol Korenbrot, Ann B. Flood, Michael Higgins, Noralou Roos, and John P. Bunker
End-Stage Renal Disease: Richard A. Rettig
Gastrointestinal Endoscopy: Jonathan A. Showstack and Steven A. Schroeder
Neonatal Intensive Care: Peter Budetti, Peggy McManus, Nancy Barrand, and Lu Ann Heinen
Nurse Practitioners: Lauren LeRoy and Sharon Solkowitz
Orthopedic Joint Prosthetic Implants: Judith D. Bentkover and Philip G. Drew
Periodontal Disease Interventions: Richard M. Scheffler and Sheldon Rovin
Selected Respiratory Therapies: Richard M. Scheffler and Morgan Delaney

These studies will be available for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. Call OTA's Publishing Office (224-8996) for availability and ordering information.

Case Study #4

Cost Effectiveness of Automated Multichannel Chemistry Analyzers

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We also thank Harry Marks, who shared his knowledge of the automated chemistry analyzer industry. Finally, we thank Clyde Behney and Chester Strobel of the Office of Technology Assessment and numerous reviewers who gave us helpful suggestions in the final stages of writing.

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Case Study #4:

Cost Effectiveness of Automated Multichannel Chemistry Analyzers

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SUMMARY

General Findings

1. While the unit cost per chemistry determination has fallen considerably since multichannel analyzer technology first came into widespread use, the number of determinations and total costs have increased.

2. Automated multichannel chemistry analyzers are most efficient, relative to alternative methods, at high test volumes. This is because such analyzers tend to decrease variable costs per determination while increasing fixed costs for equipment and labor.

3. The cost effectiveness of multichannel analyzers depends on the incremental health benefits derived from the additional determinations that are required to make multichannel analyzers economically efficient compared to alternative methods. An important issue, not yet resolved, is whether it is necessary to demonstrate the cost effectiveness of multichannel chemistry screening (hospital or outpatient) in order to demonstrate the cost effectiveness of multichannel analyzers, or whether multichannel analyzers are the most efficient testing method even if such high-volume uses are excluded.

Product and Industry Characteristics

4. There are two classes of multichannel analyzers: continuous-flow analyzers and discrete-sample analyzers. One difference is that discrete-sample analyzers perform only the specific tests requested, whereas continuous-flow analyzers perform all tests on every sample. Many manufacturers produce discrete analyzers, but only one makes analyzers that use the continuous-flow process.

5. New developments in multichannel technology are likely to include the availability of more tests, more flexibility, and more automation of sample input and data output functions. Processing speed is no longer a major concern, largely because machine startup time, sample collection and coding time, and reporting time are now rate-limiting steps in the laboratory.

6. The rate of product turnover in this industry is rapid; industry representatives suggest that the state of the art is advanced significantly every 4 to 7 years. This high rate of product development contributes to equipment costs. The increase in fixed costs, despite the role of innovation in reducing variable costs per test, may or may not be desirable given society's interest in containing health care costs. The appropriate role of reimbursement policies in encouraging or discouraging product innovation and capital investment needs to be examined.

Quality of Measurement

7. The quality of measurement (i.e., accuracy and precision) in multichannel analyzers is generally regarded as quite good for most tests, although high interlaboratory variations have been reported for some tests. This consensus holds, despite the problem of sample cross-contamination. It is incumbent on those who interpret test results, however, to be aware of the range of interlaboratory variation.

Diagnostic Value

8. Diagnostic value depends not only on the sensitivity and specificity of the test in question, but also on the prevalence of the condition for which the test is performed. Where multichannel analyzers are used to screen for unsuspected abnormalities, the prevalence of each condition screened for will be quite low; therefore, the predictive value of any positive test will be quite poor. This state of affairs has led to increased induced costs for subsequent tests to rule out diagnoses following falsely positive test results.

Clinical Efficacy

9. Clinical efficacy of a laboratory test depends on the ability of the test results to influence a subsequent treatment decision and on the health benefits to be derived from such a decision. Evaluation of the clinical efficacy of the multichannel analyzer depends, therefore, on its uses. The clinical efficacy of routine chemistry profile screening is controversial, although some patients clearly benefit from such screening.

Economic Efficiency

10. The economic efficiency of any configuration of laboratory equipment may be defined as its ability to respond to a specified pattern of test orders at the lowest cost. Multichannel equipment is most efficient at high test volumes and in cases where the average number of determinations required per sample is high.

11. The economic efficiency of any particular number of channels, or of any particular combination of tests to occupy those channels, has not been analyzed systematically from a societal perspective.

Cost Effectiveness

12. A complete evaluation of the cost effectiveness of multichannel analyzers depends on cost effectiveness of each individual test for each of its major uses. Such analysis is feasible with use of decision-analytic methods.

13. A major consideration in evaluating the economic impact of the multichannel analyzer is the induced cost for diagnosis and treatment of patients with abnormal test results. Induced costs include costs of repeat chemistry profiles and individual tests, more specific laboratory tests to confirm a diagnosis, radiographic and other diagnostic tests, and therapeutic interventions. In the evaluation of cost effectiveness, these induced costs must be combined with the cost of the initial chemistry tests. However, many of these induced costs may be the result of inappropriate (i. e., cost ineffective) decisionmaking in response to abnormal test results; if so, the cost effectiveness of initial chemistry tests may depend on whether or not one assumes cost-effective decisionmaking will follow from the results.

14. The cost effectiveness of the multichannel analyzer depends on whether its uses at volumes sufficient to render the analyzer efficient are, themselves, considered cost effective. If health care resources are to be allocated optimally, the judgment as to whether a particular use is cost effective at the margin should depend on society's cost-effectiveness criterion value (i. e., the cost per unit of health benefit it is able or willing to pay, given the limit on total resources and competing health-care demands for those resources). The marginal, low-yield uses of chemistry tests, therefore, are cost effective only if resources are sufficiently plentiful to accommodate a high cost-effec-

tiveness criterion. Thus, paradoxically, the cost effectiveness of the multichannel analyzer may rest on whether we, as a society, are willing to pay enough for diminishing incremental health benefits to justify sufficient volumes of testing to permit us to afford the reduction in unit testing costs that multichannel analyzers offer.

Cardiac Enzymes

15. Three cardiac enzymes—creatine phosphokinase (CPK), lactic dehydrogenase (LDH), and aspartate aminotransferase, also called serum glutamic oxaloacetic transferase (SGOT)—and their isoenzymes were selected as examples of chemistry tests that are frequently ordered on multichannel equipment. CPK, LDH, and SGOT tests are available on all major multichannel analyzers; isoenzymes of CPK and LDH are becoming available on the equipment of at least one manufacturer. Their major use is to diagnose ("rule in/rule out") myocardial infarction ('[heart attack"). In the emergency room, they are used to decide whether to admit a patient to the hospital; in the coronary care unit, they are used to monitor a patient's condition and to decide when to discharge the patient to the general ward.
16. The diagnostic value of cardiac enzymes is difficult to evaluate, because the levels of these enzymes are themselves used to define the diagnosis of myocardial infarction. No published study has examined the incremental diagnostic information value of any single enzyme test, given the other two; of two, given the other one; of the enzymes, given the isoenzymes; or of the isoenzymes, given the enzymes. Such evaluations could lead to cost savings if some of the tests were found to provide information largely supplied by other tests in the management of myocardial infarction.
17. The clinical efficacy of tests measuring cardiac enzymes and isoenzymes depends ultimately on the risks associated with failing to hospitalize a patient with myocardial infarction, or on the incremental risk associated with complications suffered outside a coronary care unit. Even if these tests improved the accuracy of diagnosis, or even prognosis, the value of this clinical information would be nil unless treatment made a difference in health outcome. The efficacy of coronary care units and of hospitalization of patients with myocardial infarction is a matter of much controversy and is not likely to be resolved soon. Therefore, the health benefits to be derived from a more sensitive or specific diagnosis of myocardial infarction remain uncertain.
18. As long as coronary care and hospitalization are standard practice, the greatest value of cardiac enzyme and isoenzyme measurement may be induced economic savings. To the degree that these tests improve the sensitivity of the diagnosis, physicians may be more willing to rule out myocardial infarction on the basis of negative findings. To the degree that they improve specificity of diagnosis, they are less likely to lead to hospital admission of patients without myocardial infarction. An economic evaluation of the impact of enzyme and isoenzyme measurements is feasible and may be sufficient to demonstrate their cost effectiveness given actual practice, although it is difficult to assess the cost effectiveness of such measurements in ideal practice because of the uncertainty surrounding the benefits of intervention.

INTRODUCTION

. . . In recent years, the economic and technologic development of laboratory operations seem to have had a greater influence than the physician on trends in laboratory utilization (17).

The Problem

Since 1963, when Technicon Corp. began to market the first automated chemistry analyzer that could perform more than one test on a

single sample of serum, this technology has had a profound economic impact on the U.S. health care system. The question still being debated among industry officials, health services researchers, hospital administrators, laboratory directors, and clinical chemists and pathologists is whether this technology has been, on balance, an economic dream or nightmare.

Evidence is strong on both sides of the question. On the one hand, largely as a result of automation and especially as a result of multiple-channel technology, the cost per chemistry determination has fallen dramatically during the past decade. This cost reduction has resulted, in large part, from increased productivity of laboratory personnel as measured by the number of determinations per labor-hour. One British study showed a tripling of laboratory output per technician-hour between 1955 and 1966 in a hospital that had begun to use a 12-channel analyzer during that interval (55). A U.S. study showed a doubling of laboratory output per labor-hour from 1961 to 1970, during which time multichannel analyzers were purchased by three of the five hospitals in the study (30).

The importance of such savings in labor costs is underscored by studies that indicate that direct labor costs constitute 50 to 65 percent of the total direct costs of hospital-based, clinical chemistry laboratories (30,35,53,55). Comparisons of different studies indicate that the average direct cost of a chemistry determination was approximately $1.25 in 1969 (in hospitals that had not adopted a 6- or 12-channel analyzer) (30), $0.70 in 1971 (35), and $0.30 in 1974 (32). This trend has persisted despite a 35-percent increase in price levels from 1969 through 1974. On the basis of the continued decline in prices of reagents and consumables per test (10,23,46) and the increased labor productivity made possible by the availability of 20- and 30-channel analyzers, one can conclude that the real cost per test has continued to decline.

The problem is that, despite the dramatic reductions in unit costs, total expenditures on clinical chemistry tests have risen dramatically. Between 1971 and 1975, the number of chemistry determinations performed in the United States increased by 67 percent—from 2.9 billion to 5 billion. During that period, charges (not true costs) for these tests increased from $5.6 billion to $15 billion (34). These figures do not reflect the concomitant increase in costs of tests (other than chemistry) induced by unexpected results and required to rule out or confirm a diagnosis.

Underlying this alarming trend in laboratory costs is the increased frequency with which physicians order multiple-test profiles to be performed on automated equipment, rather than just individual tests needed for the immediate diagnosis. If, at one extreme, all of the tests had clinical value equal, on average, to the tests that would have been ordered without the availability of test panels, then the cost per unit of health benefit would have clearly decreased as a result of multichannel technology. If, at the other extreme, most of the additional determinations had no clinical value, then the cost per useful determination—hence, the cost per unit of health benefit—would have increased as a result of multichannel technology.

The truth, no doubt, lies between these extremes. Therein lies the dilemma in evaluating the cost effectiveness of multichannel chemistry analyzers. In essence, their cost effectiveness depends on the way they are used in clinical practice. It depends not only on their ability to reduce costs or improve efficacy of tests that would have been performed by other methods in their absence, but also on the benefits of new, high-volume, uses of the chemistry lab (e.g., hospital admission screening) induced by having more tests at low incremental, but high fixed, cost.

Scope of the Case Study

The remainder of this case study is in four parts. In the first part, by way of background, we offer a brief review of the history of multichannel clinical chemistry technology; we also describe several analyzers that exemplify the technology as currently marketed in the United States. Next, we present an analytic framework for evaluating the cost effectiveness of the multichannel analyzer, pointing out in the process the methodological problems inherent in evaluating a diagnostic technology that consists of many

elements, each of which may have many clinical uses. Within this analytic framework, we survey the evidence that bears on the question of cost effectiveness. Third, we review the available data concerning the costs of multichannel chemistry analysis. Finally, we use the analytic framework to examine the evidence concerning the cost effectiveness of using the cardiac enzymes and isoenzymes (for which tests are becoming more commonly available on multichannel analyzers) in the diagnosis of myocardial infarction. The review of the data on cardiac enzymes has more general implications for evaluation of not only the cost-effective use of the individual tests that can be performed with multichannel analyzers, but also the cost effectiveness of developing multichannel capability to perform such tests.

This case study touches on only some of the aspects of technology assessment that might be undertaken with respect to multichannel chemistry analyzers. Thus, for example, we pay only passing attention to the question of test precision and accuracy, one that has received considerable attention in the literature (5,28) and in the regulatory activities of the Food and Drug Administration. Moreover, we do not consider the impact of multichannel chemistry analyzers on the organization of laboratory services or health care institutions. Rather, we concentrate on the issues of cost and cost effectiveness of multichannel chemistry analyzers.

For purposes, of this case study, we ***consider*** only instruments designed to yield more than one chemical determination on a single blood sample. Thus, for example, the study excludes the centrifugal fast analyzer, which (despite its ability to process from 15 to 39 samples at a time at very high speed) is technically a single-channel analyzer., Evaluation of the centrifugal fast analyzer technology as an alternative to the multichannel analyzer technology would be of great value at this early stage of its diffusion, but is beyond the scope of the present study.

DESCRIPTION OF MULTICHANNEL CHEMISTRY TECHNOLOGY

Overview of the Industry

Development of the first continuous-flow analyzer, begun by Leonard T. Skeggs in 1950, led to the introduction of Technicon's Auto-Analyzer to the U.S. market in 1957. At about the same time, the first discrete-sample analyzers, the Robot Chemist and the AutoChemist, were marketed in the United States by American Optical and AGA, respectively (l). Continuous-flow and discrete-sample remain the two types of multichannel chemistry analyzers available today, although considerable sophistication and versatility have evolved.

The selling feature of a multichannel analyzer is its ability to per-form numerous tests simultaneously on one blood sample. This feature distinguishes multichannel analyzers from dedicated machines, which can run only one test at a time, and from centrifugal fast analyzers, which currently perform only one test at a time, although at very high speeds.

Although there is a large and growing market for automated multichannel analyzers (sales in 1978 were estimated at $170 million) (23), the field is dominated by a small number of firms. The undisputed market leader is Technicon; probably one-third to one-half of all automated multichannel analyzers in use are Technicon instruments.[1] Other firms that manufacture automated multichannel analyzers include Abbott Laboratories, American Instrument, American Monitor, Beckman Instruments, Chemetrics, Coulter Electronics, E. I. du Pont de Nemours, Inc. (Du Pont), Gilford, Hycel, Micromedic Systems, Ortho Diagnostics, Perkin-Elmer, Union Carbide, and Vickers.

Figures on market **shares** are not available [illegible] the public. [illegible] Mark research [illegible] firms provi[illegible] this kind [illegible] information for substantial [illegible] the results are available only [illegible] their clients, Our estimates [illegible] conversations with individuals familiar with the industry, [illegible] Hyce *1978* report [illegible] the Security Exchange [illegible] Commissi[illegible] *(23)*, and on Schwartz's discussion [illegible] data from the Center [illegible] from Disea Control *(42)*.

This study concentrates on the products of three firms: Technicon, Hycel, and Du Pont. These firms differ both in size and in the importance of automated chemistry analyzers in their overall sales pictures. Although they do not exhaust the market, their products exhibit enough variety to give a good sense of the market. Basic product information for the instruments reviewed below is shown in table 1.

Continuous-Flow Analyzers

General Description

Details of the continuous-flow process are described clearly by Schwartz (42). The process used today is a modification developed by Leonard Skeggs in the 1950's. In brief, one serum sample is split into numerous aliquots (parts) separated by air bubbles. The partitioned sample passes through separate incubation and detecting modules. Samples and reagents are drawn through the system by a pump. The flowing reactants are mixed as they pass through glass tubes in the form of concentric helixes.

In addition to dividing the sample, the air bubbles regulate the flow and clean the tubes between sample portions. Reagents are added in the required sequence, and everything flows along to the module where the appropriate measurements are taken at the endpoints of the reactions. The results are recorded on a strip chart recorder and may a I so be sent to a computer. Every chemical test is run every time a sample passes through the system; hence, reagents are consumed whether or not a test is requested or reported. It is possible, however, to deactivate one or more channels on any particular day, thus reducing the number of tests run.

Technicon Corp.

Technicon is the only manufacturer of continuous-flow analyzers. It purchased the original rights to the process from Leonard Skeggs in 1954. Since the introduction of its AutoAnalyzer in 1957, Technicon has held patents that preclude the use of the continuous-flow technique by other manufacturers. That technique is used in all of Technicon's multichannel analyzers, which ***are*** all variants of the Sequential Multichannel Analyzer (SMA), introduced in 1965.

Four of Technicon's multichannel instruments, the SMA 6/60, SMA 12/60, SMA II, and Sequential Multichannel Analyzer with Computer (SMAC), are described below.[2] Purchase prices and other specifications are given in table 1. In all, 23 tests are available on any of Technicon's machines (see table 2).

Technicon's primary business is the development, production, marketing, and servicing of automated analytical systems, including reagents. Technicon is generally agreed to be the

[2] Technicon's Auto Analyzer 11 is not discussed in this report. That analyzer is available in two- and three-channel models, as well as a basic single-channel model.

Table 1.—Multichannel Analyzers Produced by Three Major Manufacturers

Manufacturer	Model	Number of channels	Number of tests available	Number of samples processed per hour	List price
Technicon Corp.	SMA 6/60	6	23	60	$ 52.000
	SMA 12/60	12	23	60	99,500
	SMA II	12	23	90	138,600
	SMA II	18	23	90	173,250
	SMAC	20	23	150	271,000
Hycel, Inc.	Super-17	17	18	60	75,000
	SKS-60	17	15	60	120,000
	Hycel-M	30	24	120	225,000
E. 1. du Pont de Nemours & Co.	ACA-I	30	29	97[a]	49,000
	ACA-II	30	38	97[a]	69,000
	ACA-II	60	38	97[a]	89,000
	ACA-III	625[b]	38	97[a]	120,000

[a] Number of determinations per hour.
[b] Refers to software capabilities.

SOURCE: Personal communications and marketing materials from the manufacturers (10,24,46).

Table 2.—Chemical Determinations Available on Technicon, Hycel, and Du Pont Multichannel Analyzers

	Technicon (continuous-flow)	Hycel (discrete-sample)			Du Pont (discrete-sample)		
Test	All models	Super-17	SKS-60	Hycel-M	ACA-I	ACA-II	ACA-III
Acid phosphatase					X	X	X
Alanine aminotransferase (SGPT)	X	X		X	X	X	X
Albumin	X	X	X	X	X	X	X
Alkaline phosphatase	X	X	X	X	X	X	X
Alpha-hydroxybutyrate dehydrogenase				X	X	X	X
Ammonia						X	X
Amylase					X	X	X
Aspartate aminotransferase (SGOT)	X	X	X	X	X	X	X
Bilirubin, total	X	X	X	X	X	X	X
Bilirubin, direct	X			X	X	X	X
Bilirubin, neonatal						X	X
Calcium	X	X	X	X	X	X	X
Carbon dioxide	X			X	X	X	X
Cerebrospinal fluid protein					X	X	X
Chloride	X	X		X	X	X	X
Cholesterol	X	X	X	X	X	X	X
Creating phosphokinase(CPK)	X		X	X	X	X	X
Creatine phosphokinase-MB (CPK-MB)						X	X
Creatinine	X	X	X	X	X	X	X
Ethanol					X	X	X
Gamma-glutamyl transferase	X			X		X	X
Glucose	X	X	X	X	X	X	X
Iron	X			X	X	X	X
Lactic acid					X	X	X
Lactic dehydrogenase(LDH)	X	X	X	X	X	X	X
Lactic dehydrogenase, liver					X	X	X
Lipase						X	X
Magnesium					X	X	X
Phenobarbital						X	X
Phenytoin						X	X
Phosphorus, inorganic	X	X	X	X		X	X
Potassium	X	X		X			
Primidone						X	X
Protein, total	X	X	X	X	X	X	X
Pseudocholinesterase					X	X	X
Salicylate					X	X	X
Sodium	X	X		X			
Triglyceride	X	X	X	X	X	X	X
Urea nitrogen(BUN)	X	X	X	X	X	X	X
Uric acid	X	X	X	X	X	X	X

SOURCE: Personal communications and marketing materials from the manufacturers (10.24.46

market leader, responsible for perhaps 40 to 50 percent of all sales of automated multichannel chemistry analyzers in the United States. "Clinical systems" represented 57 percent of its total **1978** revenues of more than **$275** million. Another 27 percent of Technicon's 1978 revenues were contributed by sales of reagents and consumables.

SMA 6/60 and SMA 12/60.—These noncomputerized analyzers are descended directly from the SMA 12 "Hospital Model" that was introduced in **1965.** Their names indicate that they have 6 and 12 channels, respectively, and that each is capable of processing 60 samples per hour. Both analyzers are equipped with aflame photometer for analyzing serum electrolytes. The manufacturer estimates that at least 2,000 SMA 6/60s and 5,000 12/60s (first sold in 1969) are currently in place (46).

SMA II.–The SMA II was first sold in 1977, and the manufacturer estimates that several hundred SMA IIs are now in place. Two different models are available, one with 12 channels (SMA II-12) and the other with 18 (SMA

11-18). The SMA 11 has a computer that can be used for extensive report production. A flame photometer is used for analyzing serum electrolytes. Both models process **90** samples per hour. The SMA II requires smaller sample sizes than do the SMA 6/60 and 12/60. In the SMA 11-18, which is, in effect, composed of **a 6-**channel and a 12-channel module, reagent economy is improved somewhat, since only the modules that contain tests included in the test order are activated.

SMAC.—SMAC is the largest of Technicon's automated multichannel analyzers. It has 20 channels and can process 150 samples per hour. SMAC is computerized, allowing for extensive report preparation, computerized verification that all operations are occurring in their appropriate sequence, and selective reporting of abnormal results, among other functions. Since the first sale in **1974,** more than 1,000 SMACs have been sold. This analyzer offers more specific chemical methods than previous Technicon instruments. Electrolytes are analyzed by an ion-selective electron method instead of by the traditional flame photometer.

Discrete-Sample Analyzers

General Description

Discrete-sample analyzers, in effect, replicate the manual process of testing. These devices perform a number of tests sequentially on one sample. Opinion is divided on whether the speed, accuracy, and precision of discrete-sample analyzers are comparable to those of the continuous-flow analyzers **(42,43).** Increasing sales indicate, however, that these analyzers fill what many clinical laboratory directors perceive to be a need.

A discrete-sample processor is a collection of relatively independent, general purpose channels that are run in parallel. The channels are tied together at three points: 1) sample presentation, made in sequence to successive channels; **2)** sample transport, at several reaction temperatures; and 3) data acquisition, accomplished through a computerized system that reads dedicated detectors in each channel. Users may select only those tests whose results are needed; other tests will not be run,

The prototypes for the discrete sample analyzers were American Optical's Robot Chemist and AGA's AutoChemist. Today, there are many models available. The models of two manufacturers, Hycel and Du Pent, are discussed below.

Hycel, Inc.

Hycel is primarily a manufacturer of clinical chemistry analyzers. This company derives a large share of its revenues from sales of automated analyzers and related reagents. In 1978, 37 percent of Hycel's total revenues of almost $39 million were from the sale of clinical systems and 39 percent were from sales of reagents to be used with automated analyzers (23).

Among Hycel's products are three multichannel chemistry analyzers: the Super-Seventeen, the SKS-60, and the Hycel-M. These analyzers range in price from **$75,000** to **$225,000** (see table 1). The prices of the machines differ depending ***on*** the ***number*** of channels and tests available, output as measured in test results per hour, and the test methods used.

Super-Seventeen. —Introduced in 1975, the Super-Seventeen is a computerized, programmable multichannel analyzer with 17 channels that is capable of performing 18 tests (see table 2). The Super-Seventeen uses a flame photometer to measure electrolytes. It is capable of processing 60 samples per hour, yielding 1,020 determinations. Patient data are stored on cassettes.

SKS-60.—First sold in 1978, the SKS-60 has 17 channels and is capable of performing 15 tests (see table 2). In place of the traditional calorimetric methods used by most analyzers, the SKS-60 employs newer, more specific enzymatic test methods that are thought to provide more reliable results because of reduced interference. The following functions are under computer control: reagent dispense timing, incubation, calculation of chemistry results, and system calibration. If the appropriate tests are selected, globulin, AG ratio, and BUN/creatinine ratio are calculated and printed out automatically. The SKS-60 can process. 60 samples per hour, yielding 900 determinations.

Hycel-M.—The Hycel-M is Hycel's newest automated analyzer at this writing. This computerized analyzer has 30 channels and is capable of processing 120 samples per hour. Twenty-four tests are now available (see table 2). Any combination of individual tests, panels, or profiles may be selected by the operator. The machine is equipped with a microprocessor that processes samples and another processor that manages data.

E. I. du Pont de Nemours & Co.

Du Pont is a large firm with many interests and sources of revenue, among which automated chemistry analyzers and reagent sales are relatively much less important than they are to Technicon and Hycel. Nonetheless, Du Pont's Automatic Clinical Analyzer (ACA) line is being expanded and refined, and sales are considerable in terms of market penetration. The company estimates that **30** to **40** percent of hospitals wit h more than 100 beds have an ACA in the clinical laboratory; about **70** percent of the ACAs are thought to exist alongside other manufacturers' equipment. Du Pont emphasizes small-batch processing, so its equipment is often used to complement the larger processors. The ACA was first sold in **1970;** ACA sales recently passed the 2,000 mark (10).

Du Pont manufactures three multichannel analyzers: the ACA-I, ACA-II, and ACA-III. The number of channels and tests, output speeds, and purchase prices are shown in table 1. All three machines are mechanically similar. Each operates with an individual test pack for each analysis. The analyzer is loaded with a number of samples and, for each sample, the correspondin g test packs containing the appropriate reagents, The test pack serves as both reaction chamber and cuvette for photometric analysis. Either standard or enzyme methods can be incorporated into the test packs. Under computer control, the proper amounts of sample and diluting agent are injected into the test packs. Temporary seals around the reagents in the packs are broken with hydrostatic pressure. The analyzer then mixes the reagents, waits a predetermined amount of time, and measures the outcome of the reaction. One test pack is accepted every 37 seconds, so a total of 97 determinations can be made per hour.[3]

The number of channels refers not to physical apparatus, but to the maximum number of tests that can be programed into the machine at any one time. The ACA works best in a lab that runs only a few profiles or many individual tests each day, or in a lab needing fast, accurate emergency or small-batch test processing. It would not compete with a multichannel instrument in a lab where dozens of multiple-test profiles were run each day.

ACA-I.—This analyzer has 30 channels and can perform 29 different clinical tests (see table 2). It produces a report slip that has two parts: a photographic reproduction of the handwritten sample identification card, and a computer-printed list of the test names and numerical results.

ACA-II.—The ACA-II is available in a 30- or a 60-channel version. Thirty-eight test methods can be selected by the purchaser (see table 2). One of these, the CPK-MB, has been "technically released" (i.e., it is not yet universally available). Results are provided by the ACA-II in the same format as results provided by the ACA-I.

ACA-III.—This machine is similar in many respects to the other ACAs. The main difference is that it contains a microprocessor, which makes it programmable and thus very versatile. The ACA-III can be programed to run tests on as many as **625** channels in sequence. At pres-

[3]Althou the AC is, **strictly speaking, a** multichann **analyzer, because it** automatical **withdraws the** appropria amount **sample** fro **a sample** cup to perform mar tests, function in many respects like a single-channel analyzer. Differe tests are fully contain within the consumable test packs and passed throu the machine e a conveyor-be manner. The e fir te pack enters the e fir preheat area within the temperature chamber followir It\ associated sample cup. Thirty-seven second later, the e conveyo is s indexed forwar **and the** e fir **test pack** mov s **the** e secor preheat area a wit n the temperature chamber, while the secorI te pack mov s in the e fir preheat area. Anoth 37 7 secon later, the system indexes s forwar movn **the** fir **test pack** **the next** t statio **the** e secor **pack** **the** second prehe area, a the third test pack the e fir preheat area. The proce s continu s a th **way, with the** e fir **test pack eventually reaching the** e photomet where the results are react. In n anoth 37 secon that t te resu t is printed a t and the e secor test pack ente the e photomet area. Thus, a determination is **made every** 37 7 secon

ent, only 38 chemistry tests are available (see table 2). But since Du Pont has been introducing new tests (or methods) at a rate of four or five per year, the enormous expansion capability of the ACA-III may eventually be useful. The microprocessor can also reprogram the machine to accept new methods for performing existing tests; provide the flexibility to run adult and pediatric sample sizes simultaneously; and produce a more extensive printout of results, including an indication that a particular result is abnormal, along with the range of normal values for the test, the units of measure for the test results, and the time of day the test was run.

Centrifugal Fast Analyzers

Centrifugal fast analyzers were developed at the Oak Ridge National Laboratory. The first commercial machine was sold in 1970. These analyzers are designed to run a single test on a large number of samples—the reverse of the multichannel concept of running a large number of tests on a single sample. The commercially available centrifugal fast analyzers today include the GEMSAEC (Electronucleonics, Inc.), the CentrifiChem (Union Carbide), and the Rotochem II (AMINCO). These analyzers do not compete directly with the high-speed, multichannel analyzers such as SMAC and Hycel-M at present, but they may within the next few years.

Design Issues and Tradeoffs

Accuracy and Precision

For both continuous-flow and discrete-sample analyzers, there is a tradeoff between speed and reduced variable cost, on the one hand, and accuracy and precision, on the other. The tradeoff has been most clearly recognized in the design of continuous-flow analyzers; the problem of "carryover" from one sample to the next in the common tubing of these analyzers has been studied at length (s). There are also problems of sample cross contamination in discrete-sample analyzers. Companies have directed their product improvement efforts (e.g., in Technicon's SMA II and SMAC) to minimizing the carryover problem; despite this problem, however, the accuracy and precision of multichannel instruments have long been recognized to be superior to those of manual methods (54).

Another theoretical problem with continuous-flow analyzers and certain discrete-sample analyzers has to do with the timing of reactions. If reactions are all required to be synchronized, then suboptimal accuracy must be tolerated for the slower reactions, or a reduction in the overall processing rate must be made to accommodate the slowest reactions, or additional channels must be created to split the fastest reactions into two or more parts.

Speed

The ability of automated equipment to analyze specimens rapidly is increasing to the point where the speed of analysis is no longer the rate-limiting step in the overall testing process (28). Limits in the ability to speed up the specimen input and coding system and to record and report results make further increases in equipment speed of little value. This is reflected in the relatively modest sales in the United States of the Vickers M300, which can analyze 300 samples per hour on 20 channels, yielding 6,000 determinations per hour. Concerns for future development of automated equipment will shift to improved versatility and reliability, as evidenced by Technicon's development of the more flexible, intermediate-sized SMA II and Du Pont's development of increased test selection in the ACA-II and ACA-III.

Selectivity y

Discrete-sample analyzers have an apparent cost advantage over continuous-flow analyzers, because they have the capability of performing only those tests desired for each sample, thus not only saving reagents, disposable, and channel maintenance, but also minimizing the number of unsolicited tests. On the other hand, the reagent cost per test is so low with the available continuous-flow instruments that this advantage may be more theoretical than real.[4]

[4]See review of cost data below in the part of this case study on the economics of the multichannel analyzer.

Future Trends

Instruments

The rate of product turnover in the market for multichannel chemistry analyzers is rapid. Manufacturers, in their user cost estimates, suggest that machines be depreciated over 4 to 7 years, although the machines' useful life could be much longer (1,22). High corporate expenditures on product development -e.g., in 1978, Technicon and Hycel spent 7.4 and 8.7 percent, respectively, of their sales revenues on research and development **(23,45) —** undoubtedly contribute to the rapid rate of turnover. That Technicon spent $7 million to develop SMAC (34), which must be recovered in the purchase price of equipment, further suggests possible inefficiencies in the equipment replacement rate.

The rapid growth of centrifugal fast analyzers in this market cannot be ignored. Despite their single-channel capability, such analyzers are already competing successfully in the same market as the multichannel instruments.

Chemistry Tests

A number of chemistry tests that have heretofore been rather expensive and had to be performed manually will be available in the near future on multichannel analyzers, especially on discrete-sample systems. Examples include isoenzymes of creatine phosphokinase (CPK-MB), high-density lipoproteins, renin, and vanillylmandelic acid (VMA). If added to multichannel equipment, each of these will undoubtedly increase in use, and the possible implications for clinical practice in the areas in which these tests are used (e.g., diagnosis of myocardial infarction and coronary disease, diagnosis and treatment of hypertension) should be examined carefully.

FRAMEWORK FOR COST= EFFECTIVENESS EVALUATION

Efficiency and Cost Effectiveness

There are at least two levels of questions one might ask concerning the cost effectiveness of the automated multichannel analyzer. The question at the simpler level is whether, for a given pattern of test ordering (i. e., for a specified number of each type of test ordered per unit of time), a Particular class of automated multichannel analyzers can produce results at lower cost than (and with accuracy and precision at least equal to) alternative methods. This may be called the question of economic efficiency. An evaluation of the economic efficiency of multichannel analyzers for any particular pattern of utilization would be straightforward, given data on the various components of testing costs. [s]

Even with information on the most efficient means of producing a specified set of test results over time, however, it would remain to be determined whether any particular pattern of utilization, and therefore any particular analyzer, is cost effective. This determination would require answers to a more complex set of questions, which concern not only the costs of testing, but also the induced costs and health benefits attributable to the many available chemistry tests in their various clinical uses.

One important limitation of the analytic framework described below ought to be mentioned. The analytic approach is designed to permit evaluations of the cost effectiveness of discrete clinical chemistry technologies (e.g., automated analyzers v. manual, multichannel v. single channel)—not of the cost effectiveness of configurations of equipment in a clinical laboratory. Although evaluation of the latter would surely be the more realistic basis for policy, we offer this more microlevel approach as a necessary step toward that complex undertaking.

Economic Efficiency

Available data concerning the question of economic efficiency in the production of test results are reviewed in the part of this case study on the economics of the multichannel analyzer.

These are [illegible] the part [illegible] this case [illegible] on the [illegible] the [illegible] analyze

Here we offer a conceptual framework for analysis of the efficiency question.

Fixed and Variable Costs

Both economic theory and cost-accounting principles offer methods of classifying costs for purposes of analysis. One distinction that is central to the evaluation of multichannel analyzers is that between costs that do not vary with the volume of testing (fixed costs) and costs that vary in direct proportion with the volume (variable costs). A major economic effect of automation in the laboratory, generally, and of multichannel analyzers, in particular, has been to transform costs that had previously been variable into fixed ones (4,35). The result is that increasing automation becomes economically more attractive at higher volumes of use.

Among the costs that are typically considered to be fixed, that is, independent of the number of samples analyzed, are equipment costs, insurance, maintenance, laboratory supervision, and overhead (including administration, space, utilities, etc.). Variable costs, that is, those roughly proportional to the number of samples analyzed, include reagents, and consumables and supplies. Automation reduces the variable costs of reagents and supplies per test, while increasing the fixed costs of equipment, insurance, and maintenance.

Direct labor, the most important economic element, is not yet reflected in this typology of costs. Labor costs for technician and technologist time do not fall neatly into either category. Some aspects such as sample collection, coding and preparation, and reporting of results are more variable than fixed. Other aspects, especially sample processing and analysis, are more nearly variable if tests are performed manually, but more nearly fixed if automated equipment is used. An additional fixed labor cost with automated equipment is training of technicians. Thus, a major impact of automation has been to transform many labor costs from variable to fixed (35).

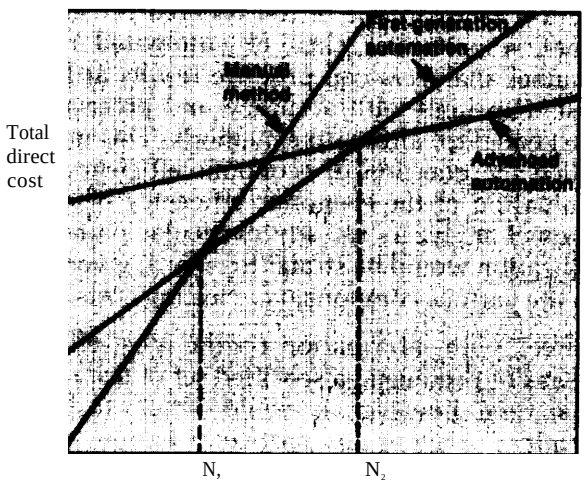
One common misperception is that automation reduces the need for highly skilled professional labor and thus reduces unit labor costs. Commenting on this, Mather points out that the training and skill required for adequate quality control and supervision are no less with sophisticated instruments than with manual methods (28).

The validity of all cost estimates is, of necessity, compromised by market imperfections in both the production process and the hospital. As in virtually all benefit-cost and cost-effectiveness analyses, one must settle for proxies for "true" costs, recognizing that biases may exist and endeavoring to adjust for the most important and obvious of these,

The Cost Envelope

The problem of selecting the most efficient technology for producing a specified number of tests has been formulated by several authors (4,11,35). If the assumption is made **that determinations** are undifferentiated and that the only variable affecting cost is the number of determinations performed, the picture may be represented as in figure 1. This figure displays total direct costs, as a function of test volume, for three prototypical technologies: manual, first-generation automated, and advanced auto-

Figure I.—Cost Envelope for Three Alternative Clinical Chemistry Technologies



mated. The slope of each cost line represents the variable cost per test; the intercept on the vertical axis represents the fixed cost. In reality, of course, the fixed cost for manual determinations is not zero, although it is much smaller than for automated technologies. Note that the more advanced technologies exhibit greater fixed costs but lower variable costs.

For any specified number of tests, the most efficient technology is the one with the lowest total cost at that test volume. Thus, for test volumes less than N_1, the manual method is most efficient; for volumes between N_1 and N_2, first-generation automation is most efficient; and for volumes above N_2, the advanced technology is most efficient. This is a well-known result: Automated chemistry technologies are economically most advantageous at higher test volumes. '

The cost envelope in figure 1 is characterized by decreasing incremental costs per test as the test volume increases. This reflects the cost characteristics of the underlying technologies. The technologies with lower variable costs (but higher fixed costs) become relatively more efficient as the number of tests increases.

Multichannel Efficiency Issues

The questions of economic efficiency become more complex when one takes into account the multichannel aspect of the technology. For one thing, the simple distinction between fixed and variable cost no longer suffices. There are some costs that depend on the number of samples tested, but not on which determinations are run on each sample; and there are others that depend both on the number of samples and the number and identity of determinations performed.

Although the distinction may be unimportant for continuous-flow instruments once they have been designed and purchased (since all tests on the machine are run on every sample), it is very important when equipment design decisions are made. Specifically, two questions have important efficiency implications: 1) how to select the particular tests to include in the 12, 20, *or* 30 channels; and 2) how to ascertain the most efficient number of channels. At this point, we are still assuming that the number and distribution of tests ordered have been specified; hence, the economic analysis depends on the test-ordering pattern.

Optimal Selection of Channels.—With the objective of minimizing costs, the selection of channels in a multichannel analyzer ought to depend on the frequency with which determinations are requested, individually and in groups. In the extreme case, if a particular test were always ordered alone, it would probably not be efficient to include it among the channels of a multichannel continuous-flow analyzer. At the other extreme, if certain profiles were always requested together, they would be more logical choices for automation.

Taylor contends that the key economic consideration in deciding which tests to automate is the number of aliquots of sample to be processed by the lab technician (44). He reports that, prior to the introduction of an SMA 12/60 in his hospital, the average number of aliquots required per specimen was 1.98. (Ideally, the average would be 1.00, the number that would obtain if all multiple-determination specimens could be accommodated by the multichannel analyzer.) With the SMA 12/60, the optimal combination of tests yielded an aliquot rate of 1.42 per specimen. The 20-channel SMAC, optimally configured, would reduce this rate to 1.21 per specimen, given the test-ordering pattern at this investigator's hospital (44).

In principle, it might be desirable to exclude a relatively common test from the multichannel analyzer if it were usually ordered alone. In the study cited above, for example, the optimal set of 12 tests in the SMA 12/60 excluded calcium, inorganic phosphorus, and cholesterol, even though these tests are ordered more often than some tests that were included in the efficient set.

Optimal Number of Channels.—Our review of the literature revealed no studies evaluating the most efficient number of channels to build into a multichannel analyzer, given a particular test-ordering pattern. Specifically, the merits of

"Data confirming this point are reviewed below in the part of this case study [illegible] the multichannel analyzer.

6, 12, or 20 channels have not been evaluated. Assuming any specified test-ordering pattern, the question of whether to add a channel to the design of a continuous-flow multichannel analyzer ought to depend on the following factors:

1. the fixed cost of the new channel;
2. the variable cost of using existing channels when the test on the new channel is ordered alone;
3. the variable cost of using the new channel when only tests on existing channels are requested;
4. the differences, for the new channel, between the variable cost per test on multichannel equipment and the cost per test on dedicated equipment or by manual methods; and
5. the cost savings for aliquot preparation for orders involving the new channel and at least one existing channel.

Only if there exists a test for which the cost increases described by items 1 through 3 are outweighed by the cost reductions described by the items 4 and 5 is it efficient to add a channel to the design.

Further complicating the problem of evaluation is the fact that test-ordering patterns differ from institution to institution. Hence, equipment-design decisions must be based on aggregates across the range of institutions that constitute the potential market for the instrument.

Of course, multichannel analyzers may induce changes in test-ordering behavior which may alter the initial findings from analyses that are conducted before the instrument is in place. Under such circumstances, the question is not merely one of economic efficiency, but of the clinical cost effectiveness of the additional tests ordered.

Cost Effectiveness

Overview

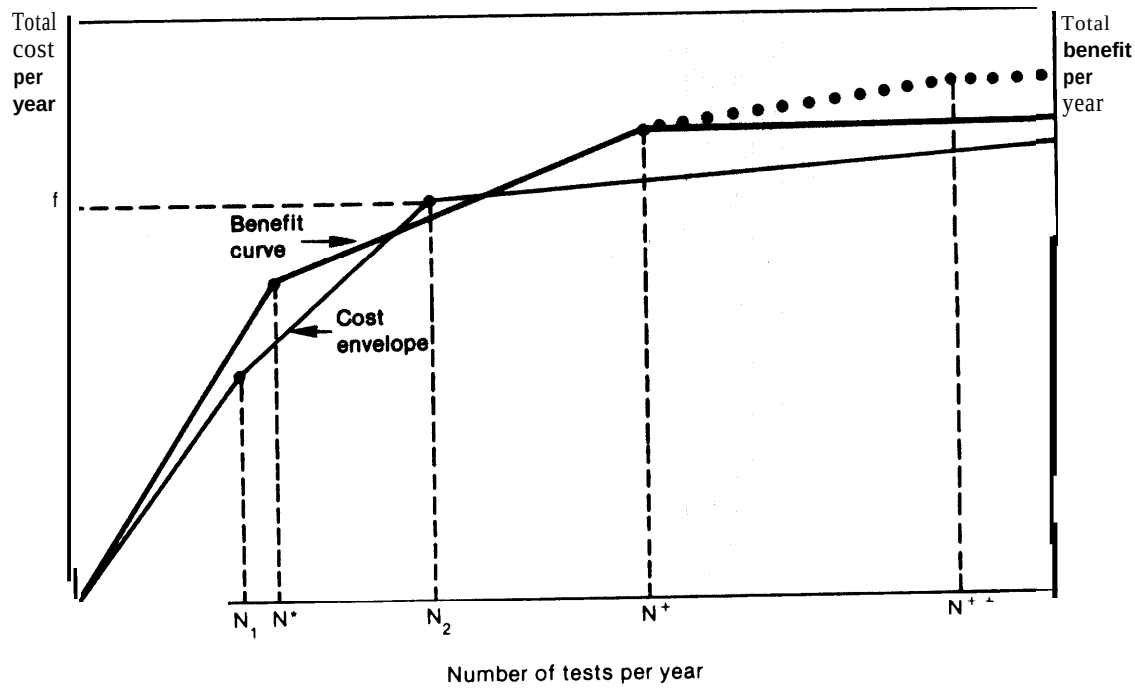
For the second, more complex question, concerning the cost effectiveness of alternative technologies, we present a framework that can be used to evaluate the cost effectiveness—in the broader sense—of automated multichannel analyzers. This framework is based on more detailed presentations available elsewhere (11,50, 51,52) and on research in progress.

As stated earlier, cost analyses have shown that the more advanced analyzers are cost effective at high test volumes, but not at lower ones (35). This result can be seen in figure 1. As the number of samples to be analyzed increases, the incremental cost of additional tests falls. This situation, known to economists as “diminishing marginal cost, ” is juxtaposed with “diminishing marginal benefit. ” That is, additional tests ordered are decreasingly beneficial from the clinical perspective (assuming that physicians are already making the best use of the level of testing they utilize). This juxtaposition necessitates explicit channel-by-channel and use-by-use analysis of individual chemistry tests to evaluate ‘the overall cost effectiveness of the automated multichannel analyzer.

The complexity of this situation is illustrated in figure 2. Let us suppose that costs and health benefits have been measured on the same scale. This could be done by valuing each year of life saved by the opportunity cost of saving a year of life by alternative means (i. e., by some specified cutoff value of a cost-effectiveness ratio) (52). This assumption will be relaxed later on. In the present formulation, however, the difference between the height of the curve measuring the total cost and the height of the curve measuring total benefit is the variable of interest—it represents the net benefit of testing. The segments of the benefit curve represent decreasingly beneficial uses of the test as the number of available tests increases. The slopes of these segments represent the expected value per test. The segments of the cost curve (as in figure 1) represent successively more advanced technologies exhibiting diminishing incremental, but increasing fixed, costs.

By inspection of figure 2, we see that at the point of switchover to the most advanced technology (where the number of tests is N_2), the slope of the benefit curve becomes steeper than that of the cost curve; incremental benefits exceed incremental costs. This does not necessarily mean that it is cost effective to use the ad-

Figure 2.—Hypothetical Analysis of the Cost= Effective Level of Testing



vanced technology to test beyond this level. To take advantage of this low variable cost, we must pay the high fixed cost, F. If the incremental benefit continues up to the level N^{+}, and then flattens out as the beneficial uses of the test are exhausted (solid line in the figure), then society is actually better off testing at level N* with the intermediate technology than at N^{+} with the advanced technology. At N*, the net benefit is maximized. If, however, the incremental benefit of testing continues all the way up to N^{++} (dotted line in the figure), then it would be best to use the advanced equipment for this larger number of tests.

The above remarks relate only to evaluation from a societal perspective, in which the costs of health care resources are considered. From the perspective of patients, considered here not as payers for their own health care, it would be best to test at the highest possible level at which benefits accrue to the patient. This would occur at N^{+} if the solid benefit curve were to obtain, a result that would be at odds with the societal interest **(1 1).**

Thus, the cost effectiveness of multichannel technology depends on the slope of the benefit curve as the number of tests increases. This, in practice, depends on the value of such tests in screening patients who are asymptomatic for the conditions being tested. It is not clear whether the most advanced multichannel analyzers can pay for themselves, in efficiency terms, without increasing the use of the chemistry laboratory for screening purposes. If they cannot, then the evaluation must turn to the issue of clinical efficac$_y$ of such uses.

Levels of Evaluation of Clinical Efficacy and Cost Effectiveness

The cost effectiveness of multichannel analyzers can be considered at each of four levels: 1) technical quality of measurement; 2) diagnostic value of test results; 3) clinical efficacy, in terms of expected impact on-treatment decisions and patient outcomes; and 4) overall cost effectiveness.

Technical Quality of Measurement.—The technical quality of measurement in automated

analyzers may be described in terms of precision (absence of test/retest variability) and accuracy (absence of bias or systematic departure from the true value). The precision and accuracy of the major automated analyzers are generally regarded as quite good, largely because such analyzers eliminate human error in measurement (5,28,54). For some tests, however, although within-laboratory reliability is excellent, between-laboratory variations may be important. Between-laboratory variations have been noted especially in relation to cholesterol and SGOT determinations (12).

Furthermore, there is a tradeoff between accuracy and speed because of the problem of contamination of results from one specimen to the next. This tradeoff also arises when the rate-limiting reaction among, say, 17 or 20 tests is accelerated beyond optimal rates to keep step with the others. In weighing this tradeoff from a cost-effectiveness point of view, the costs of repeat measurements induced by lack of accuracy must be considered.

Finally, although minimizing human error, machines suffer from fatigue and are prone to systematic failures that must be monitored closely by liberal interspersing of controls in each batch of tests (5,28). The costs of these controls must also be considered and compared to those for manual testing, because they compromise both the unit cost reduction attributable to automation and the effective rate of testing (28).

Diagnostic Value.—There are many possible measures of the diagnostic value of a test (31). These include its predictive value positive and predictive value negative (49). The former is the proportion of positive test results that truly correspond to disease or abnormality; the latter is the proportion of negative test results that truly correspond to the absence of disease.

The diagnostic value of a test can only be measured in the context of how the test is used. It is well known that the predictive value positive of a test depends not only on the properties of the test (i.e., its sensitivity and specificity y),[7] but also on the prevalence of the disease in the tested population. The lower the prevalence, the lower the predictive value of a positive result. As the number of tests run on a multichannel analyzer increases, most determinations will be performed despite the absence of any particular suspicion of abnormality; hence, the prevalence in the tested population of the conditions being tested for will be very low. It follows that the probability that any single positive result will be a true positive is very low.

One example cited in the literature relates to the use of the serum calcium value to screen for parathyroid cancer (12). Suppose that the prevalence of this tumor in the screened population were 1 per 1,000. Suppose also that the probability that a patient with no parathyroid abnormality had a 5-percent chance of having an elevated serum calcium level, according to the usual definition of normal limits. Then, the probability that a patient who tests positive will actually have a parathyroid tumor is calculated as follows:

$$\text{Tumor}|\text{Ca}^{++}\text{high}] = \frac{\text{Ca}^{++}\text{high}|\text{Tumor}] \times P[\text{Tumor}]}{\text{Ca}^{++}\text{high}|\text{Tumor}] \times P[\text{Tumor}] + \text{Ca}^{++}\text{high}|\text{No Tumor}] \times P[\text{No Tumor}]} = \frac{(1)(0.001)}{(0.001) + (0.05)(0.999)} = 0.02$$

Forty-nine of 50 patients who screen positive would have no tumor. Many of these would eventually be ruled out on the basis of repeated blood and urine tests. Some might be subjected to biopsies that prove to be negative.

As the number of tests increases, the number of false positives also increases. If 20 independent tests, each with a false-positive rate of only 5 percent, are run on a normal patient, odds are nearly two-to-one (64 percent) in favor of observing at least one positive result. That positive result must then be verified and possibly followed up at some cost. The induced costs that result from positive tests generally—and false positives in particular—must be considered carefully in evaluating the overall economic impact of multichannel analyzers.

It is not clear what the physician's attitude should be with respect to unexpected positive results (25). If the result is so unexpected that the

[7] Sensitivity is the proportion of positive tests among diseased patients; the specificity is the proportion of negative tests among undiseased patients.

physician considers an option to be simply to ignore it, then perhaps the test should not have been ordered. If, on the other hand, the test is available at virtually zero incremental cost on a multichannel profile, then should the physician discard the information? This issue, the appropriate inference to be drawn from test results in the context of a multiple-test panel, is unresolved both in theoretical and practical terms.

Clinical Efficacy.—The clinical efficacy of the multichannel analyzer also depends on the pattern of its utilization. One might differentiate between its clinical efficacy in optimal usage (defined, perhaps, by cost-effectiveness criteria) and that for actual usage (i. e., its effectiveness). Evidence for the former requires analysis that because of both data limitations and methodological obstacles has not yet been undertaken (50). There is, however, some fragmentary evidence concerning the latter.

One measure of effectiveness, albeit imperfect, is the degree to which test results contribute to altering or confirming an existing treatment plan. Dixon and Laszlo (8) reported that only 5 percent of automated chemistry tests ordered by house officers in their study were used in this way. These investigators found that, on average, only 3 of the 12 chemical values provided by the analyzer were actually wanted by the house officers. After an intervention in which the physicians were restricted in the number of tests they could order, the percentage of test results that contributed to altering or confirming the course of treatment increased from 5 to 23 percent.

A study by Durbridge, et al. (9) corroborated these findings. They found that the effects of introducing hospital admission screening with a multichannel analyzer were to increase the number of tests during the patients' hospitalization by **78** percent (not including the screening profile itself), to increase consultations by 25 percent, and to increase laboratory costs by 64 percent. These effects had no measurable health benefit to any patient in the study.

Other studies have found multichannel chemistry screening to have appreciable value, however. Carmalt, et al. (7), in evaluating a 14-test screen on hospital admission, reported that new or additional diagnoses were found in 16.9 percent of patients. An additional 21.6 percent had "unexplained abnormal" results, such as hypercholesterolemia or hyperuricemia. Of all patients tested, 1.4 percent were found to have deteriorating or newly discovered renal disease, a finding that led to treatment in four patients.

Belliveau, et al. (3) found clinical value in an 18-channel chemical admission screen in a community hospital. In 7.4 percent of patients screened, test results indicated or "possibly" indicated a new diagnosis. These included: 21 cases of diabetes mellitus, **9** of gout, **6** of cirrhosis, 5 of hypercholesterolemia, and 1 of myeloma. Tests most often found to be abnormal were uric acid (15.1 percent), SGOT (13.5 percent), and LDH (12.3 percent). In all, nearly half (43.2 percent) of patients had at least one abnormal result, leading in most cases to retesting and further diagnostic workups.

Thus, the evidence as to the effect of chemistry screening on treatment decisions is mixed. There are undoubtedly some treatable conditions discovered as a result of such screening, but the value of early intervention in those conditions must be examined. Clearly, better measures of clinical effectiveness of tests and their uses are needed, as are studies of the benefits of individual tests in the full range of their clinical uses. The methods of decision analysis may be useful in carrying out such evaluations, using expected improvement in patient outcome as the ultimate measure of effectiveness (19,51).

Cost Effectiveness.—Weinstein and Fineberg (51) describe an analytical approach for evaluating the cost effectiveness of an individual chemistry test in one of its uses. The methodological problems of cost-effectiveness analysis increase dramatically, however, when one moves from an individual test in a single use (e. g., VMA in the diagnosis of pheochromocytoma in an asymptomatic hypertensive patient) to an instrument that performs multiple tests, each of which may have several clinical uses.

The problem is complicated further because it would be inappropriate, in analyzing the cost effectiveness of state-of-the-art multichannel in-

struments, to compare them with fully manual testing. It is, however, appropriate to ask: 1) whether it is cost effective for a particular test to occupy a channel in any such instrument, and 2) under what circumstances the reduced variable cost of an instrument justifies its increased fixed cost relative to alternative equipment.

The cost of any diagnostic technology largely depends on the costs induced by test results. These include the costs of repeat tests required to compensate for measurement error or to confirm presumptive diagnoses. Running more tests generates more positive results, leading to greater induced costs to verify these findings (9). These induced costs must be balanced against the decreasing cost per test in laboratories that use multichannel analyzers at high volumes. The issue of induced costs must also be considered in evaluating the relative cost effectiveness of continuous-flow (unselective) and discrete-sample (selective) analyzers. Technicon's SMA 11 and SMAC systems address this concern by automating a function that many hospital laboratories have provided all along: selective reporting of only those tests requested by the clinician.

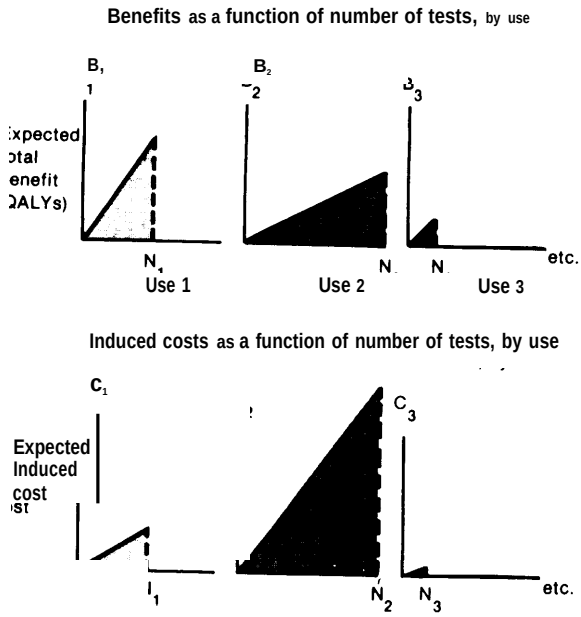
One of the authors of this study (Weinstein), under a grant from the National Center for Health Services Research, is now developing an analytical model for cost-effectiveness analysis (CEA) of the multichannel analyzer. The model addresses two questions: 1) What is the cost effectiveness of a test in each of its clinical uses? and 2) Given the answer to that question, what is the cost effectiveness of automating a particular test? The model is used here to analyze the marginal value of a single test. Methods to evaluate the joint cost effectiveness of many tests remain to be developed.

The analysis proceeds in several steps. The first is to estimate the cost envelope for the test, i.e., the cost of testing as a function of the number of tests ordered per unit time, assuming the most efficient testing technology at each level (this was shown in figure 1). The next step is to specify the clinical indications for the test, including the possibility of using it for screening. Estimates of the frequencies with which these indications arise must also be obtained.

Next, for each clinical indication or use, the expected value of clinical information (EVCI) is estimated using a decision-analytic framework. The EVCI is a measure of the average amount of health benefit (e.g., quality-adjusted life years saved (QALYs) **(52))** per test. Also, for each clinical use, the expected induced costs per test are estimated. Methods for performing both of these analyses have been demonstrated (51).

Assuming that the first indication occurs in N, patients per year in a particular setting, that the second indication occurs in N_2 patients per year, and so forth, the aggregate expected benefit and aggregate expected induced cost can be plotted as a function of the number of tests for each use (see figure 3). Each curve is actually a line segment whose slope is the benefit or induced cost per test, and which extends from the origin to the maximum possible number of tests (N_1, N_2 etc.). For screening, the corresponding segment may be replaced by an open-ended ray, assuming that there is no limit to the number of potential candidates for screening. Alternatively, the limit for a hospital may be the total num-

Figure 3.—Analysis of Cost Effectiveness for a Test With Multiple Uses



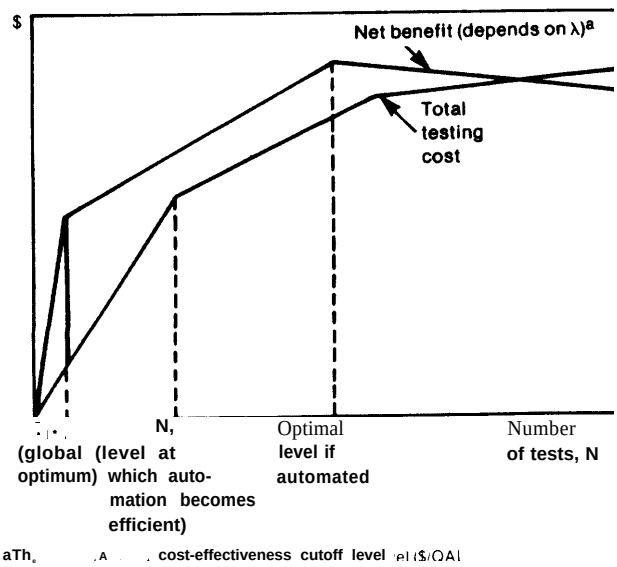
ber of hospitalizecl patients, less the number with some specified indication.

The next step in the analysis is to construct a net benefit curve for each possible cost-effectiveness cutoff level. This cutoff level, λ, might range from $1,000 per QALY to arbitrarily high values of cost per unit of health benefit. For each value of λ and for each clinical use, the net benefit per test is calculated as:

$$B_i^{Net}(\lambda) = \lambda B_i - C_i$$

Bi is the expected benefit per test (in life years or QALYs), Ci is the expected induced cost per test, and λ is the cost per unit of benefit. A net benefit curve, analogous to that in figure **2,** is then constructed by concatenating line segments with slopes $B^{Net}(\lambda$ and with horizontal spans Ni, in decreasing order of their slopes. This is shown in figure 4. For each cost-effectiveness cutoff value, λ the optimal level of testing, $N^*(\lambda)$ can be found as the point of maximum vertical distance between the net benefit curve and the testing cost curve.

Figure 4.—Composite Analysis of the Cost-Effective Level of Testing



aTh. A cost-effectiveness cutoff level el($/QAL

For the hypothetical illustration in figure 4, automation is not cost effective at this particular cutoff level. For sufficiently high values of ^, reflecting the ability to pay more per unit of benefit despite scarce resources, the cost-effective level of testing will shift to the right and into the domain in which automation is efficient.

Concluding Observations Based on the Conceptual Framework

The foregoing conceptual framework for evaluating the efficiency and cost effectiveness of the multichannel automated analyzer suggests that the cost effectiveness of automation cannot be assessed independently of the level of resources in the health care system, nor of the price society is able and/or willing to pay for the diminishing incremental benefits to be derived from marginal indications for testing. In order to reach volumes at which multichannel instrumentation is efficient, for example, we must be willing and able to pay for relatively low-yield uses of tests. If resources were truly scarce, however, we would be able to afford only the most essential uses of tests—and these would be most efficiently performed by manual methods. In summary, the question may be whether or not we, as a society, really wish to pay enough for diminishing incremental health benefits to justify sufficient levels of testing to justify, in turn, the reduction in unit testing costs that the multichannel analyzers offer.

The empirical question, yet to be analyzed, is at what point on the spectrum of clinical uses for each test the multichannel analyzer becomes efficient. Is it necessary to adopt hospital admission screening or well-patient ambulatory screening to render the multichannel analyzer efficient? Or does the level of testing necessary to render the multichannel analyzers efficient (i.e., N_2 in figure 1) occur well before we exhaust the generally accepted and cost-effective indications for testing? In the answer to this question may lie the answer to the overall question as to the cost effectiveness of multichannel analyzers in our health care system.

ECONOMICS OF THE MULTICHANNEL ANALYZER

Overview

In this part of the case study, we review the available data concerning the costs of performing chemistry tests on multichannel equipment. The data reviewed are intended to answer the question of economic efficiency: What is the cost of producing test results according to a specified pattern?

In the first section, we review data pertaining to each component of chemistry laboratory cost that may be influenced by the choice of equipment. These cost components, reviewed separately below, are as follows: 1) direct nonlabor costs (equipment, service and maintenance, reagents and consumables); 2) direct labor costs; and 3) indirect costs.

Data on direct nonlabor costs were obtained from manufacturers as the prices charged to institutional purchasers (10,24,46). For purposes of this review, we concentrate on the following products: Technicon's SMAC and SMA 12/60, Hycel's Super-Seventeen, and Du Pont's ACA II.

Data on direct labor costs are the most difficult to obtain, because estimates of these costs require estimates of worker productivity in laboratories with various configurations of equipment. Later in this case study, we will refer to two published studies in an effort to derive approximate estimates of the magnitude of labor costs and their sensitivity to the availability of automated equipment. Unpublished data on labor costs obtained by the College of American Pathologists were not available to us in performing these analyses, but could be of great value in cost-effectiveness analyses (CEAs) to be performed in the future.

No published studies suggest that indirect costs are affected by the types of equipment used. In the review below, therefore, we discuss this component of cost only briefly.

In the section following the review of cost data, we suggest analyses to address the following two efficiency questions, applied to currently available multichannel equipment. First, what is the relation between the unit cost per determination and test volume, assuming a fixed number of determinations per sample? (These cost functions may be compared to unit costs with dedicated equipment or manual methods to determine breakeven test volumes.) Second, what is the relation between the unit cost per determination and the number of determinations per sample, for various types of analyzers? The published data on labor costs are too fragmentary to allow us to resolve these questions, but we do suggest an analytic framework for their resolution.

In the third section below, we discuss the cost implications of R&D policies in this area and of the rate of product turnover. Then we restate the problem of induced costs and repeat tests and give some indication of the magnitude of their economic impact. Finally, in the last section, we make some observations on the economic incentives faced by hospital laboratories, given the current regulatory and reimbursement environment.

Review of Cost Data

Direct Nonlabor Costs

Equipment.—Equipment prices are shown in table 1. The prices for the instruments to be reviewed here are as follows:

Technicon SMAC	$271,000"
Technicon SMA 12/60	99,500
Hycel Super-Seventeen	75,000
Du Pont ACA II	69,000[9]

These are list prices, obtained directly from the manufacturers (10,24,46).

The annual cost of owning a machine depends on its useful life and the interest rate. Assuming a 7-year amortization period (22) and a real interest rate of 5 percent (after inflation), the annual equipment costs, in constant 1979 dollars, are:

Technicon SMAC	$45,000

[illegible] an [illegible] $4, [illegible] it a test [illegible] than one [illegible] the 14 standard [illegible] is [illegible] y-channel [illegible]

Technicon SMA 12/60 16,500
Hycel Super-Seventeen 12,400
Du Pont ACA II 11,400

Service and Maintenance.—Costs for equipment service and maintenance (including parts and labor) can be estimated from experiences of laboratories that perform their own maintenance, or from prices charged by manufacturers for full-service plans. One study reported annual maintenance costs in a hospital laboratory to be $6,100 in 1971, or slightly more than $10,000 in 1979 dollars (35). Others estimate that labor costs for maintenance amount to approximately 20 percent of direct labor costs **(32).**

Although the prices charged for full-service plans may overestimate true costs, many labor-a tories buy these plans. Technicon offers a plan that includes preventive maintenance, three emergency service calls per year, parts, and unlimited consultation. The annual prices are $25,000 for the SMAC and $7,900 for the SMA 12/60, or slightly less than 10 percent of their purchase prices.

Hycel's plan for the Super-Seventeen includes service and maintenance, plus all reagents, supplies, control samples, and other items. The price is based on test usage. For individual tests, it averages between 12 and 22 cents per determination, depending (in block-rate fashion) on the volume of usage and actual tests performed. For complete profiles, it averages between 4 and 17 cents per test, also depending on the volume of usage. Charges are determined by reading meters built into the reach inc.

Du Pont has two service plans for the ACA. One is a rental plan; the user does not buy the machine, but leases it from Du Pont. The fixed price of $1.13 per determination includes use of the machine, maintenance, unlimited emergency visits, parts, consultation, reagents, nonreagent consumables such as control and calibration products, and a training course for three technologists. Alternatively, customers who own their equipment may purchase a service contract for $6,200 per year. This covers parts, labor, unlimited emergency visits, 24-hour telephone consultation, replacement of mechanical and electrical parts as they are updated, and replacement of reagents lost as the result of instrument malfunction.

Reagents and Consumables.—For Technicon's equipment, the reagent prices per sample are shown in table 3.[10] Note that for these continuous-flow analyzers, all reagents (20 for SMAC and 12 for SMA 12/60) are consumed on each sample. Total reagent and consumable cost per sample for the SMAC is approximately $1.67; for the SMA 12/60, it is $1.26. Note the variation among reagent prices; the prices range from 36.8 cents per sample for triglycerides on

[illegible] Technicon's block-rate pricing these prices correspond [illegible] a user making a volume of 100 samples per day (**26,000** per year-). Unit reagent **prices** would **be** somewhat less t or **higher** volumes

Table 3.—Reagent and Consumable Prices for Two Technicon Analyzers

Item	Cost per sample SMAC	SMA 12/60
Reagents		
Albumin	**$0.011**	$0.022
Alkaline phosphatase	**0.036**	0.086
Calcium	**0.005**	0.009
Carbon dioxide	**0.021**	0.011
Chloride	**0.004**	0.011
Cholesterol	**0.022**	0.067
CPK	**0.266**	0.322
Creatinine	**0.003**	0.004
Direct bilirubin	**0.026**	0.023
Glucose (oxidase)	**0.070**	0.106
Inorganic phosphorus	**0.004**	0.013
Iron	**0.009**	0.016
LDH	**0.053**	0.147
Potassium	**0.015**	0.009
SGOT	**0.031**	0.041
SGPT	**0.040**	0.235
Sodium	**0.017**	0.009
Total bilirubin	**0.020**	0.022
Total protein	**0.005**	0.009
Triglycerides	**0.254**	0.368
BUN	**0.004**	0.005
Uric acid	**0.024**	0.051
Consumables		
Calibrators and controls	**0.332**	0.184
Other consumables	**0.430**	0.178
Total reagent cost per sample	**$0.91**[a]	$0.90[b]
Total reagent and consumable cost **per sample**[a]	**$1.67**	$1.26
Total reagent and consumable cost per determination	**$0.08**	$0.10

[a]Assumes SMAC contains tests except iron and direct bilirubin
[b]Assumes SMA 12/60 Contains the following: albumin, alkaline phosphatase, calcium, CPK, creatinine, glucose, inorganic phosphorus, LDH, SGOT, total bilirubin, total protein, BUN.

SOURCE: Personal communications and marketing materials from Technicon (46).

the SMA 12/60 to 0.3 cents per sample for creatinine on the SMAC. Consumables account for roughly one-half of variable costs per sample in the SMAC and for about one-third of variable costs per sample in the SMA 12/60. Reagent prices are lower for the SMAC than for the SMA 12/60, in part because of the smaller reagent volumes required for the SMAC.

Hycel's reagents and consumables are included in the price per sample under their maintenance plan for the Super-Seventeen, described above. Alternatively, they can be purchased separately at prices ranging from 10 cents per test for inorganic phosphorus to 23 cents per test for alkaline phosphatase, except for triglycerides, which are priced at 83 cents per test. Note that the Hycel analyzer, unlike Technicon's continuous-flow analyzers, consumes only the reagents for the tests requested.

Reagents and consumables for the Du Pont ACA are available on an individual basis for those who own the analyzer, but the "full-service" price of $1.13 per test includes reagents and consumables as well as equipment use and service.

Summary of Direct Nonlabor Costs.—On the basis of the data presented so far, the fixed and variable components of direct nonlabor cost can be calculated for a selection of instruments, service and use plans, and test configurations. Examples are shown in table 4.

Table 4.—Direct Nonlabor Costs for Selected Analyzers

Analyzer	Annual fixed cost	Variable cost Per sample
Technicon SMAC[a] with service plan.	$70,000	$1.67
Technicon SMA 12/60a with service plan.	24,400	1.26
Hycel Super-17 with service plan, full profiles only		
< 12,000 samples/year.	12,400	3.00
12,001-24,000 samples/year. .. .	27,400	1.75
24,001-36,000 samples/year. .. .	44,200	1.05
>36,000 samples/year.	55,000	0.75
Hycel Super-1 7 with service plan, individual [illegible]		
< 12,000 tests/year.	12,400	0.22 x Nc
12,001-120,000 tests/year.	12,760	0.19 x N
120,001-228,000 tests/year.	17,560	0.15 x N
>228,000 tests/year.	24,400	0.12 x N
Du Pont ACA II with rental plan. . .	0	1.13 x N

[illegible] test configurations given in legend to table —
[illegible] of [illegible] block-rate [illegible]
[illegible] of determinations per

SOURCE: Personal communications and marketing materials from the manufacturers (10,24,46).

Direct Labor Costs

Economic analyses of automated chemistry tests have consistently found that direct labor costs account for 40 to 60 percent of the total direct costs (30,32,35). McLaughlin, in a 1971 study at **a** hospital with a 12-channel analyzer, found the direct cost per determination to be 28 cents, or 51 percent of total direct costs (30). This would be 46 cents at 1979 price levels. Pegels, in a study based on 1971 data, found average direct labor costs of 21 cents per test, or 62 percent of total direct costs for operating a 20-channel analyzer (35).

The effect of increased analyzer speed on overall labor costs has not been studied in recent years. However, McLaughlin's study suggests that labor accounted for approximately **50** percent of direct costs both in hospitals with and without multichannel analyzers (30). The important effect of automation, however, may shift to certain labor costs from variable to fixed (4,35). Some labor costs (e.g., for specimen collection and coding) remain variable, irrespective of the method of analysis, and are relatively unaffected in magnitude **(4,28).** Others (e. g., operation) become fixed in the short run. The costs of some fixed components of labor (e. g., supervision and training) may be expected to increase (28,30).

There are insufficient recent data from institutions with automated analyzers on which to base quantitative estimates of the effect of multichannel technology on labor costs. Qualitatively, for analyses such as those presented immediately below, it may be reasonable to assume that: 1) the variable component of labor is proportional to the number of samples tested (not determinations), and 2) the fixed and variable components are roughly in the same proportion to each other as are the fixed and variable components of nonlabor direct costs, The second assumption reflects the observation that supervision and training requirements tend to increase as a function of the complexity of in-

strumentation (and, hence, fixed capital and maintenance costs). Studies of laboratory productivity are needed to validate these assumptions and to provide more reliable quantitative estimates.

Indirect Costs

No recently published data are available on indirect costs of clinical chemistry laboratories. Moran suggests a rule of thumb that indirect costs (space, administration, utilities, etc.) may add 25 percent to direct costs (32). In any event, it is unlikely that multichannel analyzers have had much impact on indirect costs, compared to other automated analyzers or even manual methods.

Hypothetical Analyses of Efficiency

The available data on labor costs are inadequate for performing realistic analyses, but it is possible to suggest the kinds of analyses that can be used to evaluate the need for automated multichannel equipment as a function of the number of tests required per serum sample,

For purposes of these hypothetical analyses, we assume that the fixed and variable components of labor are each equal to the fixed and variable components of nonlabor direct costs for each equipment configuration. This assumption is consistent with the finding that labor costs consistently account for about half of total costs. The variable component of labor is assumed to be proportional to the number of sample aliquots that the technologist must prepare.

The following analysis is based on the cost data for the SMA 12/60. The question is: How large an annual demand for tests (determinations) is required to justify purchase of an SMA 12/60? Unlike some previous analysts who have addressed this question in the past, we adopt the societal interest in minimizing true cost, not the laboratory director's interest in maximizing net revenues.

Suppose that the average number of determinations required per sample is two. (This is consistent with the data of Taylor, cited above (44).) The direct fixed costs for the analyzer are assumed to be **$24,400** for nonlabor items (see table **4),** plus $24,400 for the fixed component of labor. The direct variable costs are **$1.26** per sample, or $0.63 per determination, plus $0.63 per determination for labor. Hence, total cost (TC) is given by the expression:

$$TC = \$48,800 + \$1.26N$$

where N is the number of determinations. Average cost per determination is equal to:

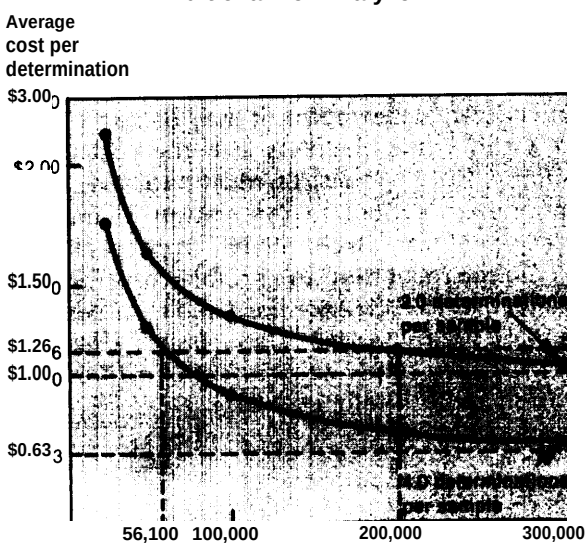
$$AC = \frac{TC}{N} = \$1.26 + \frac{\$48,800}{N}$$

As shown in figure 5, the average cost declines as the number of determinations increases.

Suppose that the next best alternative method has a unit cost of $1.50 per determination. (This figure is consistent with data from Pegels, adjusted for inflation (35).) Then, as shown in figure 5, the analyzer is efficient, provided that at least **200,000** tests on 100,000 samples are performed per year.

If, instead of two determinations per sample, four per sample were requested, then the breakeven volume would be only 56,100 determinations on only 14,000 samples. Thus, we con-

Figure 5.—Hypothetical "Breakeven" Analysis for a Multichannel Analyzer



elude the efficiency of multichannel analyzers at lower test volumes is very sensitive to the number of determinations performed per sample. Their cost effectiveness, therefore, depends critically on the benefits to be derived from those additional determinations.

Fixed Costs of Production and the Rate of Innovation

From societal perspective, the price of equipment to the purchaser overstates the actual incremental cost of production. It includes a significant component that reflects the fixed, hidden costs of product research, development, and marketing (22). For example, development costs for Technicon's SMAC alone were $7 million (34). Allocated among 1,000 machines sold, on average, 5 years later, and assuming an annual interest rate (not inflation-adjusted) of 10 percent, these costs alone would account for $11,400 in the $271,000 purchase price of SMAC. Furthermore, as Holy points out, product development is but one of many costs in the process from product conception to marketing (22). Patent protection costs perhaps $100,000 or more for a major product and several thousand dollars for each patented component; engineering documentation for production may cost $250,000. Perhaps the largest hidden costs are those that a company must absorb for research and development of ideas that never reach production (22).

From society's viewpoint, it maybe appropriate to factor these elements into the cost of a technology. But the question must be asked: Are the resources devoted to innovation in multichannel analyzer technology appropriately spent? Do the reductions in variable costs justify the fixed costs that finance the rapid turnover in cost-saving innovations? These issues deserve study, and they apply to the cost-effectiveness evaluation of technologies ranging far beyond the realm of clinical chemistry analyzers.

Induced Costs

Given the ability of multichannel technologies to produce additional determinations at very low incremental cost, perhaps their induced costs make their greatest economic impact. These induced costs include repeat tests, additional laboratory tests required to rule out or confirm a diagnosis, radiographic or other diagnostic tests, and treatments.

Obviously, the magnitude of induced costs depends on the particular tests ordered, the clinical procedures followed, and the population tested. In one study of hospital admission screening, use of a multichannel analyzer led to a 78-percent increase in the number of other tests performed, a 64-percent increase in other laboratory costs, and a 25-percent increase in the number of consultations (9). Explicit decision analyses have indicated that induced costs can easily account for half of all costs attributable to laboratory tests, even in populations in which the proportion of patients with a condition requiring intervention is small (51).

The high rate of false positives in multichannel test panels can amplify this effect (12). Thus, even if the cost per determination can be reduced, one must consider the effect of multichannel technology on total costs, and ask whether these increases in "rule-out" costs are justified by the benefits. Clearly, further studies are needed in which the magnitude of induced costs attributable to particular chemistry tests is estimated.

Financial Incentives

It would be inappropriate to conclude a discussion of the economics of the multichannel chemistry analyzer without some discussion of the financial incentives faced by laboratory directors and other users of the technology. Typical third-party reimbursement rates for chemistry tests clearly exceed not only marginal costs but also average costs for most laboratories. If the sole concern of the laboratory director were to maximize net revenues, the obvious incentive would be to increase the number of tests, at low incremental cost but high incremental revenue (32).

Whether this incentive motivates laboratory directors in practice has not been shown, but that it does motivate them certainly seems plausible and is generally accepted as fact. On an aggregate level, society seems willing to per-

mit hospitals to use laboratory revenues to subsidize other meritorious, but low-income, services. The result, of course, has been to make multichannel analyzers even more attractive, because their costs per test decrease with increasing test volumes.

Other subtler financial and organizational incentives may also contribute to the adoption of multichannel analyzers. Mather points out that many hospital laboratories with only moderate volumes may purchase advanced multichannel equipment to shift costs from labor to capital, thus relieving pressure from the overburdened labor supply (28). This inefficiency can be rationalized to the hospital administration if the labor supply is relatively fixed and if added revenues can more than pay for the loss of efficiency.

The countervailing effects of government regulation of capital expenditures through certificate-of-need programs have been negligible. No instance of denial for multichannel analyzer purchase was found in the States surveyed by the authors. (At current price levels, only Technicon's SMAC and the new Hycel-M would be covered by such regulations in any case.) Other regulatory policies, including denial of reimbursement for certain uses of the laboratory (e.g. such as hospital admission profiles) may ultimately alter the financial incentives to acquire multichannel chemistry analyzers, but such measures are not likely to have much effect for several years.

COST EFFECTIVENESS OF CARDIAC ENZYMES IN DIAGNOSIS OF MYOCARDIAL INFARCTION: A STRUCTURED REVIEW

Overview

The analytical framework for cost-effectiveness analysis (CEA) of multichannel chemistry analyzers presented earlier strongly suggests the need for cost-effectiveness evaluations of the individual chemistry tests that constitute test panels. Such evaluations should consider not only the quality of measurement and diagnostic efficacy of such tests, but also the expected clinical value of the information obtained, the costs induced or averted as a result of the tests, and the costs of producing various quantities of test results on different chemistry analyzers. For a full evaluation of the cost effectiveness of automating a particular test, according to the methodology presented earlier, each clinical indication for its use must be considered separately before proceeding to an overall evaluation of the test.

In this part of the case study, we present a structured review of the information required to conduct such CEAs for three chemistry tests that are commonly used to diagnose myocardial infarction (heart attack). These tests are the cardiac enzymes: 1) creatine phosphokinase (CPK), 2) lactic dehydrogenase (LDH), 3) and aspartate aminotransferase, also known as serum glutamic oxaloacetic transferaese (SGOT). They are all available on the multichannel analyzers reviewed in this study. We also review information pertaining to the use of certain isoenzymes of these compounds. Some of these isoenzymes have been widely acclaimed for their diagnostic value in myocardial infarction, and some are being considered for use in improved multichannel analyzers. One (CPK-MB) is now available on a limited basis in Du Pont's ACA.

It should be emphasized that our review of the cardiac enzymes and isoenzymes pertains only to a single clinical use of these tests, namely, diagnosis (i.e., "rule-in/rule-out") of myocardial infarction in patients with symptoms suggesting it. A complete evaluation of these tests would consider other uses as well, including, for example, the use of LDH and SGOT to diagnose liver disease. (Tests for CPK, however, are probably performed almost exclusively in the diagnosis of myocardial infarction or screening for cardiac damage.)

The clinical properties of these enzymes and

isoenzymes are briefly reviewed in the first section below. In the next section, we structure a clinical decision tree for the typical "rule-in/rule-out" decision problem. We then proceed in the subsequent sections to evaluate the available evidence at each of the four levels of analysis described in the part of this case study on the framework for cost-effectiveness evaluation: 1) technical quality of measurement, 2) diagnostic value, 3) clinical efficacy, and 4) cost effectiveness. Our review concludes with a brief discussion of efficiency.

Clinical Properties of the Cardiac Enzymes[11]

Elevation of the serum level of either LDH, SGOT, or CPK suggests tissue damage, but not necessarily damage to the muscles in the heart wall (myocardium). Cardiac damage usually, but not always, causes all three enzymes to rise. LDH, however, may also be elevated in the presence of liver disease (such as hepatitis), pulmonary infarction, renal disease, muscular damage, shock, leukemias and lymphomas, and other cancers. SGOT may be elevated due to liver disease, skeletal muscle damage, brain damage, kidney disease, or shock. CPK may be elevated due to damage to skeletal muscles or the brain; it rises easily in the presence of even mild skeletal trauma, such as that following physical exercise. All three may be elevated due to congestive heart failure or trauma of thoracic surgery.

All three enzyme tests are typically ordered in the workup for myocardial infarction, either in the coronary care unit to determine whether to return the patient to a regular hospital bed (or possibly to discharge the patient), or in the emergency room to decide whether to admit the patient to the hospital. The three tests are usually ordered together because of their individual lack of specificity. If all three are positive, it helps to confirm the diagnosis, The enzyme tests are usually accompanied by an electrocardiogram (EKG), which is considered a very specific test if the classical signs of myocardial infarction are found. An equivocal or negative EKG, however, is usually not considered sufficient evidence to rule out a myocardial infarction, and the enzymes and patient history become the principal diagnostic tools.

If the tests are given too soon or too late following a myocardial infarction, they are likely to produce more false negatives than if given at the proper time intervals. LDH elevations typically appear within **24** hours of the myocardial infarction, peak between **48** and **72** hours, and return to normal 7 to 10 days later. SGOT elevations run a shorter course, beginning within **8** to 12 hours, peaking at 36 to 48 hours, and returning to normal 4 to 5 days after the myocardial infarction. CPK follows the shortest course of all. The elevations first appear in about 6 hours, peak around 24 hours, and return to normal levels in 3 to 4 days. Thus, a patient whose enzymes are measured within a few hours of the myocardial infarction is likely to show a normal LDH. A patient whose enzymes are measured **48** hours later may show a normal CPK. For this reason, these enzymes are usually measured for at least 3 to 4 days before a diagnosis is made. This practice, of course, can be costly, since it means prolonged hospitalization for many patients who will turn out not to have suffered a myocardial infarction.

Isoenzymes are slightly different molecular forms of an enzyme, all of which catalyze the same reaction. The difference between isoenzymes is important because the composition of total enzyme levels differs among body tissues. Some isoenzymes or isoenzyme profiles are quite specific for particular organs (e.g., heart or liver), and therein lies their diagnostic value. Methods for separating isoenzymes usually take advantage of their physical properties, and separation is often accomplished by electrophoresis. Measurement methods based on radioimmunoassay and on calorimetry have also been developed, and the latter are the basis for developments toward automation in multichannel analyzers.

The isoenzymes most valuable in the diagnosis of myocardial infarction are the isoenzyme CPK-MB and the enzymes LDH_1 and LDH_2. CPK has three isoenzymes: CPK_1 (or CPK-BB),

[11] Unless otherwise noted, most of the background material for this section is based on a review by Rapaport (36,37).

CPK_2 (or CPK-MB), and CPK_3 (or CPK-MM). CPK-MB is found only in heart tissue. Its presence in serum is thought to be a very specific indicator of cardiac damage. However, cardiac damage is not synonymous with myocardial infarction. Congestive heart failure, severe angina, myocardial ischemia, and cardiac surgery or chest trauma can also cause CPK-MB levels to rise in the blood, as can certain forms of muscular dystrophy, polymyositis, or significant myoglobinuria. While CPK-MB is quite specific for myocardial infarction, its clinical sensitivity is reduced by the time course of the elevation, typically less than that for total CPK.

LDH has five isoenzymes. Those that are useful in the diagnosis of myocardial infarction are LDH_1 and LDH_2. In particular, if the serum level of LDH_1 exceeds the level of LDH_2, then the number of diagnostic possibilities is reduced considerably. This "flipped LDH pattern" (so called because in normal serum the LDH_2 level exceeds that of LDH_1) may be observed in patients with a myocardial infarction, but also in those with acute renal infarction or hemolysis.

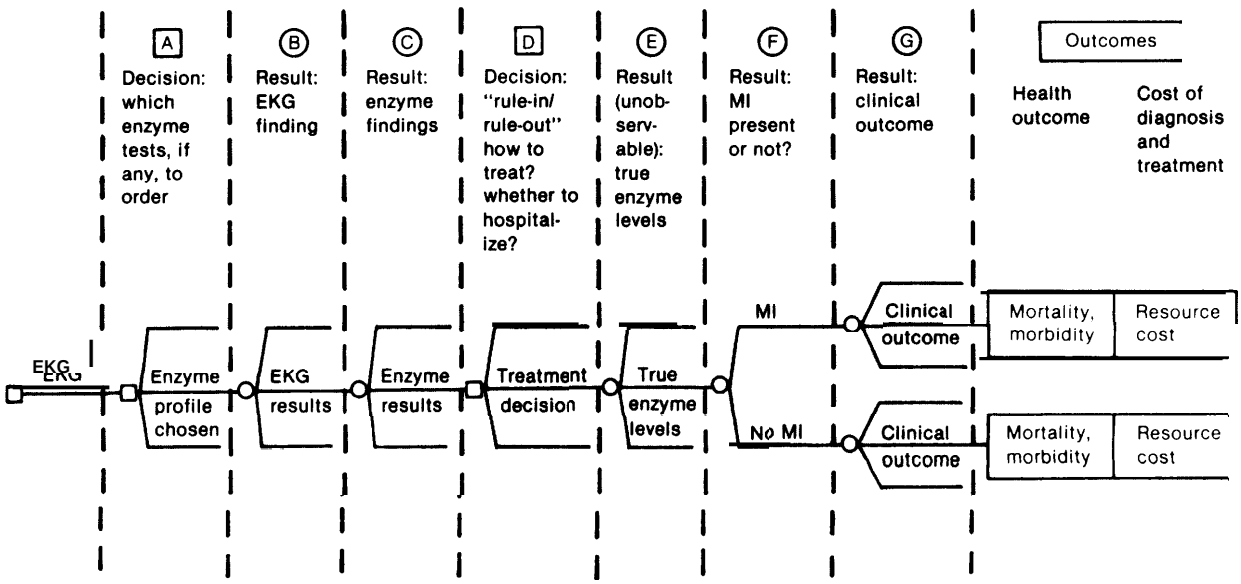
However, since elevated CPK-MB and flipped LDH have only one cause in common—myocardial infarction—the combination is extremely specific. Some enthusiasts claim that **80** percent of "rule-in/rule-out" tests for myocardial infarction cases can be resolved with virtual certainty on the basis of CPK and LDH isoenzyme results (15). These authors suggest that SGOT would have virtually no clinical value in the diagnosis of myocardial infarction if CPK and LDH isoenzymes were routinely available (15).

Structure for Decision Analysis

The structure of the decision whether to order enzymes and/or isoenzymes for the patient with suspected myocardial infarction is diagramed in the decision tree shown in figure **6.** The information required to complete the analysis consists of data on: 1) probabilities at chance nodes, and 2) costs and health outcomes at the end of each path.

The tree begins at the tar left with the ordering of an EKG. Next, at ❑ , is the key decision

Figure 6.—Structure of Decision Analysis for Evaluation of Enzymes in Diagnosis of Myocardial Infarction (MI)



under analysis: what combination of enzyme tests to order. At the first probability node, Ⓑ, the EKG results are obtained. At the next probability node, Ⓒ, the enzyme (and isoenzyme) results are obtained. The probability of any particular combination of test results depends, among other factors, on: 1) the conditional probability of this set of values, given the true enzyme levels that would be measured by a perfectly accurate and precise test; 2) the conditional probabilities of combinations of enzyme levels, given the presence or absence of a myocardial infarction; and 3) the prevalence of myocardial infarction in patients with similar histories and EKG results. This tree structure assumes that the EKG results are not available at the time of the decision whether to order enzymes; in some clinical situations, the order of nodes ❑ and Ⓑ may be reversed.

Next comes a decision, at node ❑ : whether to treat for or to rule out a myocardial infarction. The value of the tests, presumably, lies in their ability to inform this decision-and, in turn, in the value of a correct diagnosis of myocardial infarction, if present, or correct ruling out of myocardial infarction, if absent. The consequences of false negatives (inappropriate rule-out) may be added risk of complications or even death if the patient does not get proper bed rest or if the complication occurs outside the coronary care unit. The consequences of false positives (inappropriate rule-in) may be primarily economic costs in the form of prolonged hospitalization or prolonged in the coronary care unit.

Next, for purposes of analysis, estimates are needed of the probabilities of the true enzyme levels, given the measured values (a function of test precision and accuracy). These are incorporated at probability node Ⓔ. Given the enzyme levels, the next probability node, Ⓕ, indicates whether myocardial infarction was present or not. Finally, the clinical outcome unfolds at Ⓖ, given the treatment decision at ❑ and the true diagnosis as revealed t Ⓕ. The final outcomes are grouped, for purposes of cost-effectiveness evaluation, into two categories: health outcome (mortality and morbidity) and resource cost (for diagnosis and treatment).

The decision tree in figure 6 provides a structure for the review that follows in the remaining pages of this case study. The discussion of enzyme test measurement relates to the probabilities required at node Ⓔ, the conditional probabilities of true enzyme levels, given the measured values. The discussion of diagnostic value relates to the test result probabilities at node ❻ and their relation to the conditional disease-state probabilities at node@, the latter being the predictive values of the test results (e.g., the probability of myocardial infarction, given a particular set of test values). The discussion of clinical efficacy concerns the probabilities at node Ⓖ in relation to both the treatment decision at Ⓓ and the true condition as revealed at Ⓕ: Does intervention make a difference? The final section considers the cost data to be associated with each path of the decision tree and discusses the cost-effectiveness implications of altering the sensitivity and/or the specificity of the diagnostic workup by the addition or deletion of enzyme and isoenzyme determinations.

Quality of Measurement

Measurement errors for calorimetric determinations of CPK, SGOT, and LDH have been found to lie well within the bounds recommended by the College of American Pathologists, at least if the tests are carried out under ideal laboratory conditions. The coefficients of variation reported, however, depend on the laboratory.[12] An in-house evaluation by Technicon found coefficients of variation of approximately 5 percent for all three enzymes, with excellent linearity of response over the relevant range of values (41). Other studies have detected reliability problems in automated measurement of SGOT, however, with coefficients of variation closer to 10 percent (2,12). Even more serious than intralaboratory variation is interlaboratory variability, which has been reported to be as high as **25** percent for SGOT (12). Despite these caveats, however, the ability of existing technology to provide reliable

[12] The coefficient of variation in a sample of measurements is the ratio of the sample's standard deviation to the sample mean.

measurements of these enzymes is generally acknowledged.

Data on test precision and accuracy are available from the manufacturers for each of their instruments and can provide estimates of the probabilistic relations between measured and true values. These data may be viewed, however, only as lower bounds on variability in actual practice. Studies of laboratory performance are needed to provide more realistic probability estimates. Such data can be obtained from quality-control studies, which are performed by all laboratories under Federal law.

As for the quality of isoenzyme measurement, coefficients of variation for immunologic methods have been reported to be quite acceptable—approximately 5 to 10 percent for CPK-MB. Other, notably calorimetric, methods have been found to be less reliable **(6).** The new method used by Du Pont on its ACA, however, is said to be as precise as the best available manual methods, with coefficients of variation well under 10 percent (10). One problem in measuring CPK-MB is storage of samples, since CPK-MB may undergo chemical change at higher temperatures, leading to false negatives (reduced sensitivity) (33).

Overall, data relating to quality of measurement are readily obtainable. Published data to date suggest that measurement error is not a major consideration in the overall evaluation of cardiac enzymes.

Diagnostic Value

Several studies report estimates of the sensitivity and specificity of the cardiac enzymes and isoenzymes in the diagnosis of myocardial infarction. These results, based largely on hospital patients, are summarized in table 5. With a few exceptions, the results are quite consistent across studies. These data support the view that CPK, LDH, and SGOT are rather sensitive, but only moderately specific. In combination, considering a test positive only if all three are positive, the specificity improves considerably, but at some loss of sensitivity.

CPK-MB and the flipped LDH do appear to be rather specific, but probably not perfectly so. No data on the joint sensitivity and specificity of the isoenzymes were available, except for the study by Galen, et al. (15), the results of which are given in table **6.** They find that CPK-MB elevation and flipped LDH never occur together in the absence of myocardial infarction and that CPK-MB is always elevated in its presence. However, CPK-MB elevation and flipped LDH both occur in only **80** percent of myocardial infarction cases, and CPK-MB is elevated in 15 percent of nonmyocardial infarction cases.

The data reported in the literature are deficient in several respects. First, there are few estimates of probabilities of combinations of enzyme test results, Such data would be needed to evaluate the incremental diagnostic value of one test (e.g., SGOT), given that other tests are already available. It would be inappropriate to assume that the tests are conditionally independent, since many of the causes of serum enzyme elevation are not unique to a single enzyme. Assuming conditional independence would tend to overestimate the incremental diagnostic value of any single test.

A second, and more serious, deficiency in the data is that there is no independent definition of

Table 5.—Sensitivity and Specificity of Cardiac Enzymes, Isoenzymes, and EKG in the Diagnosis of Myocardial Infarction (MI)

Test	Sensitivity for MI	Specificity for MI
CPK	100%[38 39], 98%[20 40], 94%[48], 93%[28], 91%[47]	85%[40], 76%[28], 74%[47], 73%[20], 69%[26], 65%[38], 29%
LDH	98%[20], 96%[47], 91%[26]	80%[26], 77%[20], 23%[47]
SGOT	97%[20], 96%[36], 89%[47]	87%[20], 79%[47]
CPK and LDH and SGOT	86%[16]	94%[16]
CPK-MB	100%[15 16 20 39 40 48], 98%[26], 96%[38]	100%[38 39 48], 99%[40], 98%[20], 97%[26], 85%[15]
$LDH_1/LDH_2 > 1$	95%[27], 90%[40], 86%[26], 80%[15], 74%[16]	98%[15], 95%[16 40], 90%[26], 86%[27]
EKG	78%[20 38], 74%[16], 66%[26], 52%[47]	100%[16 18 20 38 40 47]

SOURCE: Sources of data are indicated by small superscript numbers next to percentages; see numbered list of references at the end of this case study.

Table 6.—Results of Galen, et al., on Joint Occurrence of Elevated CPK-MB Isoenzyme and Flipped LDH Isoenzymes

Finding	Probability, given MI	Probability y, given no MI
CPK-MB⁺, flipped LDH . . .	**0.8**	0
CPK-MB ⁺, normal LDH . . .	0.2	0.15
CPK-MB ⁻	0	0.85

SOURCE: R. S. Galen, et al., "(Diagnosis of Acute Myocardial Infarction: Relative Efficiency of Serum Enzyme and Isoenzyme Measurements," J.A.M.A. 232:145, 975.

myocardial infarction. In most studies, the tests being evaluated are also used to define the presence or absence of disease. This can lead to two scenarios, both of which lead to bias in the estimation process. One procedure is to restrict the population under study to those with overwhelming evidence of myocardial infarction or no myocardial infarction, either as confirmed by a positive EKG finding or as ruled out by the absence of enzyme elevations other than the one under study. Such a procedure overestimates test sensitivities and specificities by restricting the study population to those who may be most or least likely to show signs of myocardial infarction-the equivocal cases are thus excluded. The other procedure reported by some investigators is to use the enzyme values themselves to classify patients as having myocardial infarction or not. This obvious circularity also creates bias in the estimation process and will tend to overestimate sensitivities and specificities if the enzyme levels are conditionally dependent with positive correlations.

The resolution of this problem of evaluating the diagnostic value of tests which themselves provide the only basis for defining the disease state remains a topic of methodologic research. One promising approach may be to bypass the evaluation of diagnostic value, which is really only a way-station in the overall evaluation process, and to proceed directly to measures of clinical efficacy in terms of prognostic value and patient outcome. For example, one might estimate the survival curves and morbidity rates for patients with a particular pattern of test results. The rates would be conditional on the treatment alternative (e. g., hospitalized or not), but irrespective of any attempt to classify the patient as having had a myocardial infarction or not. The incremental value of any enzyme test would be measured in terms of its expected information value (calculated by averaging out an appropriate decision tree). This value would depend on the consequences to the patient of making the right or wrong treatment decision, in terms of patient outcomes, rather than in terms of the test's ability to classify patients into diagnostic categories.

A third limitation of the available data is that, for the most part, the data ignore the question of defining a positive or abnormal enzyme level. In actuality, enzyme levels are measured on a continuum, and the choice of a positivity criterion is itself a decision. By selecting a stringent criterion, one can gain specificity but at a loss of sensitivity; with a lax criterion, one gains sensitivity but loses specificity. In order to include these considerations in the analysis, one would need data on the probability distributions of values for **each enzyme** individually and in combination for patients with and without myocardial infarction, Data on the joint distribution of results are not available in the literature, although some data for individual tests have been reported (14).

The final missing datum needed for evaluation of diagnostic value is the prevalence of myocardial infarction in the population tested. As argued earlier, the prevalence, or prior probability of disease, has an important effect on the predictive value of a test result. Several studies agree that for patients hospitalized with symptoms suggesting myocardial infarction, the prevalence of myocardial infarction is approximately **50** percent (13,18). In patients with equivocal symptoms, who would be tested if cardiac enzymes were included in routine screening of hospital patients, the prevalence of myocardial infarction in the population tested would be much lower. Therefore, the predictive value positive would be lower than it would be among those with symptoms of myocardial infarction. Moreover, patients with myocardial infarction detected by screening would be more likely to have uncomplicated cases which would be less likely to benefit from prolonged hospitalization than would symptomatic cases (29).

Clinical Efficacy

The final piece of information on which the ultimate value of cardiac enzyme tests relies concerns the value of a correct diagnosis. Specifically, what are the consequences of "ruling out" a patient with myocardial infarction? What are the consequences of "ruling in" a patient without it? Since the consequences of a false "rule-in" (false positive) are largely economic, we defer most of the discussion of the latter question to the next section of this case study. It should be noted, however, that an erroneous "rule-in" may have the adverse consequence of diverting the physician's attention from the investigation of other, treatable causes of the patient's symptoms. The probability that such a treatable condition might be present would depend on the nature of the symptoms and the rest of the patient's history.

The consequences of a false "rule-out" (false negative) depend on the value of interventions, which may range from care in a coronary care unit, to hospitalization with bed rest, to bed rest at home. The value of bed rest, whether **at home** or in a hospital, during the first few days following a myocardial infarction, **when the** risk of ventricular fibrillation is greatest, is widely acknowledged. It is less clear whether bed rest can reduce the subsequent risks of reinfarction or arrhythmia and sudden death.

If bed rest were the only intervention of value, then the consequences of a false "rule-out" might be that the patient would not benefit from the reduction in risk afforded by that intervention. However, for patients with severe chest pain, or other symptoms bringing them to the hospital, bed rest is often the treatment of choice for other conditions they may have, such as acute ischemia. The intervention that has historically been specific for myocardial infarction is hospitalization, and in recent years, hospitalization in a coronary care unit. But the consequences of not hospitalizing a patient with myocardial infarction are a matter of some controversy, and therein lies the problem in evaluating the clinical efficacy of the enzyme tests used in the diagnostic workup.

A complete review of the evidence on the effects of prolonged hospitalization and intensive care units on mortality and morbidity of patients with myocardial infarction would constitute a case study in itself. A review of the literature reveals numerous studies, many of them British, indicating that home care is at least as effective as hospital care following myocardial infarction, and that shorter hospital stays are at least as effective as longer stays (21,29). Despite this evidence, the consensus in the United States is now at about 10 to 12 days hospitalization, possibly preceded by 3 to 7 days in the coronary care unit. Objective data supporting this practice are not available, however.

It is on this perceived benefit, measured as the difference in risk for myocardial infarction patients who are hospitalized and those who are not, that the clinical value of the diagnostic workup for myocardial infarction, including the enzymes, rests. If this difference were zero, the information value of the cardiac **enzymes** would be zero (excluding their purely prognostic value, independent of effects on health outcomes). The uncertainty surrounding this issue is the major obstacle to evaluation of the clinical value of cardiac enzyme and isoenzyme determinations in the diagnosis of myocardial infarction.

Cost Effectiveness

The diagnostic value of the cardiac enzymes lies in their ability to improve the predictive value in diagnosing myocardial infarctions. This involves reducing either the false-negative or false-positive rate,

Reducing the false-negative rate is tantamount to improving test sensitivity. If the cardiac enzymes are as sensitive as the literature reviewed above suggests, then their cost effectiveness would depend on the clinical value of identifying and treating a patient with myocardial infarction, compared with the added cost of diagnosis and treatment. As noted earlier, however, the health benefits from treatment in a hospital remain in doubt. Hence, the costs of the tests themselves, and the induced costs of hospi-

talization of patients "ruled-in," must be weighed against the hypothetical benefit of intervention.

Reducing the false-positive rate is tantamount to improving test specificity; it is in this domain that isoenzymes are said to have the greatest value. The value of improving the correct "rule-out" rate is largely economic; many patients may be spared unnecessary hospitalization, with ensuing savings both to society and to individual patients.

A study by Gerber, et al. (18) estimates the net economic savings that may be expected if the diagnostic test battery for myocardial infarction is expanded to include routine CPK-MB and LDH isoenzymes. Even imputing a cost as great as the institution's charge for these tests ($23 for each isoenzyme, $7 for each total enzyme, and $21 for an EKG) and assuming a complete work-up for each of 4 days in the hospital, the cost savings resulting from earlier discharge of the additional "rule-outs" easily outweigh the diagnostic testing costs (18). This appears to be a case where the induced savings in treatment costs exceed the direct costs of testing.

Gerber's analysis, however, assumes that the current practice of hospitalizing patients unless there is strong evidence against myocardial **infarction will prevail.** Given that state of affairs, whether clinically justified ***or*** not, the evidence seems to suggest that if physicians trust the specificities of EKGs and enzyme and isoenzyme tests, their net economic effect in symptomatic patients who are candidates for hospitalization may actually be to reduce costs. A limitation of the Gerber study for purposes of evaluating the enzymes and isoenzymes individually, however, is that the incremental contributions of the enzymes and isoenzymes to the overall cost savings were not reported. It could be that the EKG alone accounted for most of the savings. This study does suggest, however, that this would be a promising area for further research.

The net economic effect of enzyme determinations, if applied to patients asymptomatic for myocardial infarction, as distinguished from acute cases, is undoubtedly to increase costs, while the corresponding health benefit is questionable. Therefore, the overall cost effectiveness of this use of LDH, SGOT, CPK, and the isoenzymes rests on evidence not yet available on the health benefits of intervention in the natural course of myocardial infarction.

The overall cost effectiveness of automating any test must be based on an assessment of all of its principal clinical uses. It is possible that the uses of CPK, SGOT, and LDH in the diagnosis of myocardial infarction alone can justify automating these tests. If not, then one would have to examine as well the benefits and induced costs associated with other clinical uses, such as the use of LDH and SGOT in the diagnosis of liver disease.

Efficiency

Whether it is efficient, given a particular test-ordering policy, to reserve three analyzer channels for cardiac enzymes may depend on whether the machine to be used is a continuous-flow or discrete-sample analyzer. Reagent costs for CPK are among the highest of all tests (see table 3). Therefore, if CPK is requested for a sufficiently small proportion of samples, the costs of reagents consumed by continuous-flow analyzers could be considerable. For discrete-sample analyzers, this would not be a concern because reagents would be consumed only for those tests actually ordered. However, the fixed costs associated with a CPK channel and its maintenance would apply to both kinds of analyzers. Whether a continuous-flow multichannel analyzer, a discrete-sample multichannel analyzer, or single-channel equipment is the most efficient method of producing CPK, LDH, and SGOT results depends on the pattern of test ordering, and this pattern, in turn, would optimally depend on an assessment of the effectiveness and induced costs for each of their diagnostic uses.

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