Year 2 Progress Report
(5/26/98-5/15/99)
to the Whitaker Foundation

Personal Sensors for the Diagnosis and Management of Metabolic Disorders

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a grant under the Whitaker/NSF program on
Cost Reducing Health Care Technologies (CRHCT)

Contents:

Objectives (from grant application):

- To develop a widely applicable, inexpensive technology for clinical analyses of the key biochemicals important in the diagnosis and management of metabolic disorders (Technology)
- To develop an efficient, understandable, decision-tree-based economic model suitable for making successively refined estimates of economic impacts of technology for:
  1. the screening and diagnosis of metabolic diseases, and
  2. the empowerment of patients and providers in the management of chronic metabolic diseases. (Economics)
- To develop education activities for the bioengineering, medical, and industrial communities to enable them to apply the model to their biomedical technology R and D activities (Education).
- To utilize the economic model to focus our biochemical technology development on those inborn errors of metabolism with the greatest cost reduction potential, using galactosemia for the initial case study.
- Using the economic model, to prioritize future technology developments based on their cost reduction potential.

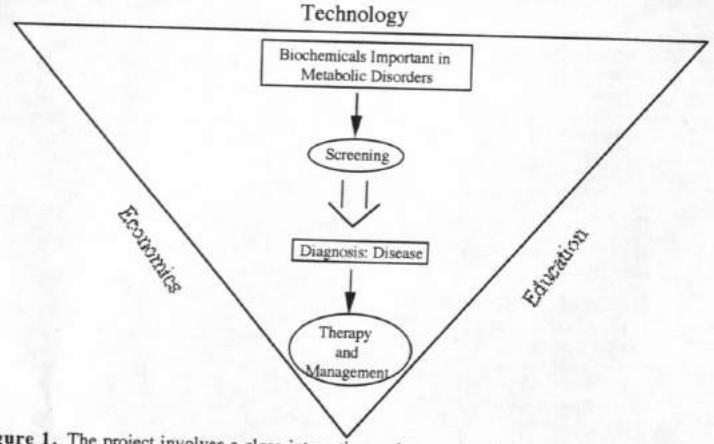

Figure 1. The project involves a close interaction and synergism between biomedical engineers (technology), economists (economic analysis), and educators (education).

Organization, Management, and Advisory Boards:

The grant began on July 1, 1997. The project is managed by an Executive Committee, consisting of J.D. Andrade as Chair and PI, R. Huefner and N. Waitzman as Co-PIs for the economics component, and S. Kern as Co-PI for the education component. Andrade also serves as Co-PI of the technology component. The Year 2 budget was allocated and expended as follows: 34% Technology; 28% Economics; 28% Education; 10% Advisory Boards. The Year 2 budget included some additional funds for expanding the education area. Each component of the project meets at least weekly; the Executive Committee meets monthly.

The local Clinical Advisory Team (CAT) consists of 7 members and meets every 3-4 months. The National Advisory Board (NAB) consists of 7 members and meets annually. The first meeting was held at the University of Utah on March 16, 1998. The second meeting was held on March 15, 1999 at the University of Utah. The report of the first NAB meeting was included in the Year 1 Progress Report and is available on the project website: www.healthtechcost.med.utah.edu. A summary of the first meeting is attached as Appendix A. The complete report of the second meeting is included as Appendix B. The third meeting will be held in mid-March, 2000.

The membership lists of the CAT and NAB are in Appendix C. Project staff, CAT, and NAB communicate regularly via e-mail using the Project's web site (http://www.healthtechcost.med.utah.edu).

Progress to Date and Plans for Year 3:

° Technology (Andrade)

The group decided to focus its technology development efforts on two fairly well known and understood inborn errors of metabolism: galactosemia, an enzyme deficiency which results in elevated galactose levels; and phenylketonuria (PKU), a deficiency which results in elevated levels of phenylalanine, an essential amino acid (1).

PKU is screened in all fifty states and galactosemia is screened today in most of the states. The reason for the lower incidence of screening in galactosemia is because of its lower incidence (1 in 50,000 to 1 in 100,000) as opposed to the 1 in 10,000 incidence for PKU. Although both diseases are treated by tight dietary management, galactosemia is a problem because galactose is endogenously produced from glucose. Thus galactosemics have severe chronic manifestations of their disease, even with good dietary control. Of course, their problems are even more severe if they do not strictly control their diets. Although we continue our activities in the development of sensors for galactose, our economic analysis and cost/benefit activities have prioritized our activities toward PKU.

PKU is difficult to manage since phenylalanine is an essential amino acid. PKU patients should be tested weekly for phenylalanine to empower them to maintain tight dietary control. There is considerable clinical concern with dietary compliance and management. Simple, home based, or other forms of inexpensive monitoring are not available. This has been most recently recognized in a series of European studies which have recommended that PKU be managed similarly to the management of chronic diabetes (2). This study demonstrated that if patients "see" their phenylalanine levels regularly, they voluntarily maintain stricter, more effectve dietary management.

Thus we are developing a bioluminescence based enzyme analytical system which is directly applicable to the quantitative analysis of key low molecular weight metabolites. The general background and rationale to the approach is presented in the chapter "Toward Dollar Devices for Measuring Metabolic Biochemistry" (3) included in Appendix E. Basically any enzyme-based reaction which can directly couple to the consumption or production of ATP (adenosine triphosphate) can be quantitatively measured using firefly luciferase based bioluminescence as the signal.

Galactose is readily and specifically phosphorylated using the enzyme galactokinase and its co-substrate ATP. The depletion in ATP as the result of this reaction is measured by the firefly luciferase reaction. The measurement of galactose for the diagnosis and management of galactosemia not only serves an important clinical need, but provides a model system or platform for the potential development for sensors for other metabolites which involve ATP-based reactions.

The rationale for the technology portion of the project was to select an analyte which can serve as a model for ATP-based sensing and at the same time could serve an important and presently unmet clinical need; hence galactose and galactosemia (1, 3).

The other key analyte selected was phenylalanine (1-3). Phenylalanine can be analyzed using the enzyme phenylalanine dehydrogenase. This enzyme uses NAD+ as a co-substrate, producing NADH and other products. NADH (nicotinamide adenine dinucleotide) is another key coupling agent in bioenergetics. It is very "convenient" that nature has also provided a bioluminescent reaction with which to measure NADH concentration. In this case it is the bioluminescence reaction present in several species of marine bacteria (4-6). This actually involves a two step reaction in which NADH is used, via an oxidoreductase enzyme, to produce $FMNH_2$, reduced flavin mononucleotide, which then, in the presence of an aldehyde and bacterial luciferase, produces light. This reaction, too, has been widely used for analysis purposes over the last thirty years (5).

The selection of phenylalanine and PKU provides us with the opportunity to develop a generic NADH sensing platform which can be immediately applied to the phenylalanine problem through the use of phenylalanine dehydrogenase. However, there are literally dozens of other specific dehydrogenase enzymes which will allow the measurement and monitoring of many other specific analytes. Indeed, one can envision the analysis of all common amino acids by this process.

Most of the Year 2 technical work has continued to focus on the development of the ATP sensing platform using galactose and galactokinase and the NADH sensing platform using phenylalanine and phenylalanine dehydrogenase (6). The work to date on both platforms has focused on optimum conditions for a homogeneous type sensor, meaning that the various biochemical reactions are occurring in the same volume simultaneously and competitively. Although this works reasonably well in the case of the galactose/galactokinase/luciferase system, the phenylalanine/phenylalanine dehydrogenase/bacterial luciferase system may require a heterogeneous type sensor, wherein the phenylalanine reaction is spatially separated from the bacterial luciferase detection reaction as the two reactions have quite different pH requirements (6). This is not a major problem but does require some appropriate optimization and design considerations. Considerable progress has been made on both systems. The homogeneous phenylalanine system does work and has resulted in a paper now in press (6). This is the major Ph.D. work of Dong J. Min. Mr. Min has expressed both bacterial luciferase and oxidoreductase, both incorporating a polyhistidine segment for efficient purification and a BCCP (biotin expressing) domain for rapid, stable immobilization. Mr. Min will defend his Ph.D. dissertation this summer and join the project as a postdoctoral associate during Year 3.

Dr. Thomas Baldwin, Professor of Biochemistry at Texas A&M University, was a visiting Whitaker CRHCT seminar speaker during Year 1. He spoke on the bacterial bioluminescence system and its potential as a component of enzyme based assays. He spent the entire day with the project staff and provided considerable insight and input into recombinant bacterial luciferases and oxidoreductases. He serves as a member D.J. Min's Ph.D. supervisory committee. Dr. Baldwin will visit again in August, 1999 for Mr. Min's Ph.D. defense and to spend a day consulting with us on bioluminescent enzymes.

Progress has also been made on the simpler galactose system. During Year 2 we have worked on the galactose-1-phosphate (G-1-P) sensor, as the clinical community needs to measure both galactose and G-1-P. Mr. Chris Eu is doing his Ph.D. work on this system. During Year 2 he completed a rather extensive modeling and simulation of these sensing reactions; that work is now in press. (7) He is now working (which will continue into Year 3) closely with Dr. R. Stewart, Asst. Prof. of Bioengineering on the expression of galactokinase in E. coli. Galactokinase is an expensive and somewhat labile enzyme. He is modifying our existing firefly luciferase plasmid (8)

for this purpose, hopefully resulting in galactokinase with a BCCP (biotin expressing) domain and a polyhistidine tail, which will permit direct immobilization and one step purification, respectively. The availability of such a unique galactokinase will greatly simplify sensor development and fabrication.

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The first year progress on both sensor systems was presented at the 10th International Conference on Bio and Chemiluminescence, September 4-8, 1998. Short papers were published in the conference proceedings (Appendix E).

The preliminary assessment of the feasibility of a creatinine sensor, potentially for the direct monitoring by patients of the status of their renal transplant, was briefly discussed in the Year 1 report. This problem was brought to our attention by Dr. John Holman, a renal transplant surgeon with whom we now have an active collaboration. Creatinine is readily converted to creatine by a creatinase enzyme and then creatine is phosphorylated with creatine kinase to creatine phosphate. The consumption of ATP via the phosphorylation reaction is detected by the firefly luciferase sensor. The reactions were modeled and simulated using multiple reaction enzyme kinetics software. A set of optimum conditions was estimated from the simulation and then a preliminary set of experiments were conducted. The general conclusion was that such a sensor is indeed feasible and merits development.

This simple example shows the power of the technique and the technology. Once we have functioning platforms for ATP analysis and NADH analysis, it is, in principle, a fairly "simple" matter to apply a new enzyme "front end" to impart the specificity needed for a particular analyte.

During Year 2 we added Mr. Rupert Davies, a Bioengineering graduate student, to the group to focus on the creatine/creatinine sensors. Mr. Rupert has completed a far more complete simulation and is now beginning the analytical experiments. His work will continue through Year 3. Since the creatinine sensor utilizes a creatine sensing channel, his work also provides a creatine sensor, an important metabolite with its own clinical analysis needs and applications. If time is available, he will perform a simulation and feasibility experiments directed toward a urea sensor as well. This work will allow the development of multichannel panels to more thoroughly and fully diagnose and manage kidney diseases.

Another important technical effort in Year 2 was the preliminary evaluation of the galactose assays in blood and urine.

Working closely with our industrial collaborator, Protein Solutions, Inc. (PSI), we have reconsidered the design of the dipstick sensor, opting for an intensity-based system using a small, hand held, inexpensive luminometer, analagous in size and operation (and eventual cost) to the current generation of hand held glucometers for home glucose monitoring in diabetes (see www.jdfcure.com and www.diabetes.org). This change in sensing philosophy was in part due to our increasing realization that the medical community is moving more and more towards the need for – and insistence on – recorded data which can be transmitted to and reviewed by the physician or other health are provider. This requires an instrument to store, analyze, and transmit data to the health care provider. These topics and concepts were extensively discussed at a recent home health workshop funded by the FDA and the National Science Foundation (NSF). See

www.hctr.be.cua.edu and click on home health workshop. PSI is now developing a hand held luminometer which will measure both intensity and spatial position of luminescence, providing a robust and accurate detection method for our dipstick sensors. (see www.proteinsolutions.com).

Another significant development is the move, lead by the diabetes community, to develop truly minimally- and even non-invasive means for sample collection. Techniques and technologies are becoming available for the collection of interstitial fluid (ISF) from the epidermal/dermal region without drawing blood or activating pain receptors. Such small volumes require a very sensitive analytical method. Our bioluminescence assays are nearly ideal for analysis of ISF samples. We are beginning to interact with firms developing ISF collection methods and expect to test such samples for galactose, phenylalanine, and creatinine during Year 3. The use of ISF, rather than blood, will significantly enhance patients' willingness to undergo optimum testing schedules. Andrade's brief position paper on this topic, prepared for the home health workshop noted above, is included in App. E.

A few months ago we initiated a paper study of aminoacyl-tRNA synthetases, the enzymes responsible for loading specific amino acids onto tRNA for protein synthesis purposes. The reaction of the specific amino acid with its specific tRNA is ATP dependant (see enzyme class (6.1.1). For 17 of the 20 common amino acids the amino acid—ATP—enzyme reaction does NOT require the presence of the specific tRNA. The specific synthetase thus binds the specific amino acid AND binds ATP. We hope to use the specific synthetase as the "front end" of an amino acid sensor. The consumption of a known initial amount of ATP is then detected by our ATP sensor. This approach is exactly analagous to the galactose sensor, which also works via ATP depletion. The beauty of the synthetase approach is that there is a synthetase for EACH individual amino acid, making it possible to develop a sensor for each (or for all) of the amino acids. Mr. Anureg Maheshwari, a chemical engineering graduate student , has already completed a preliminary analysis of the Phenylalanine and Tryptophan synthetases. His simulation indicates that the reaction will indeed work for amino acid analysis via ATP bioluminescence. The experimental work will begin this summer. We do not have the resources on this grant to do more than a preliminary feasibility study. Assuming the study indicates feasibility, then we will seek University and Federal grant funds for the continued work.

During Year 3 we will continue to implement the galactose and phenylalanine assays in a dipstick, machine readable format. We will also continue to study the sensing reaction in both urine and blood environments with particular attention to potential interferences which may need to be considered. We will compare and contrast the bioluminescent assay with more classical and traditional assays of galactose and phenylalanine based on colorimetric and photometric detection. Prototype dipstick sensors for both galactose and phenylalanine should be available for pre-clinical testing by late Fall, 1999, and hopefully incorporated into a small clinical trial in early 2000, about half-way through Year 3. This small trial will involve a segment of Utah's PKU and, possibly, galactosemia population. We are now writing the Institutional Review Board (IRB) protocols for this study.

Finally, we are now convinced, in part due to discussions at the home health workshop (noted above), and due to our own growing experience and confidence in metabolite analysis, largely the result of this grant, that the time is right to begin to design and implement a Metabolite Chip. The "M" Chip would be a multichannel, bioluminescence-based analytical device to sense and quantitatively measure about 100 metabolites; such a chip would, literally, quantitatively "image" metabolism. The image of a PKU patient's metabolism would be dramatically different from that of a galactosemic patient, or a diabetic. The ability to measure – to IMAGE, in chemical terms – metabolism would be a great asset to research as well as to clinical and preventative medicine. But the major benefit of such a chip will be reduced cost. Using the ubiquitous microprocessor as a metaphor, Metabolite Chips could be manufactured by the millions, thus greatly reducing the cost per chip. A physician or patient need not use all the data generated, but

merely focus on the several channels of immediate clinical need and interest. The other channels could simply be ignored by the custom programmable device, much as is now the case with microprocessors used for specific, embedded, applications. We expect to further develop this concept during the early months of Year 3. Of course, analysis of phenylalanine and the other amino acids, galactose, G-1-P, creatinine, creatine, and ATP – all activities of this grant – would be important and critical components of a Metabolite Chip.

° Economics (Huefner, Waitzman)

The economic impact analysis is concerned with how assessments of economic costs, economic returns, and policy issues may be used for guiding research and development of cost reducing health care technologies. Year I focused on four topics:
(1) obtain and assemble needed information and data;
(2) begin more complete benefit-cost analysis of the technology under development;
(3) apply the economic impact analysis to the specific area of research; and
(4) begin development and use of an iterative model.

The first of these efforts was completed in the first year, with the selection of PKU as the primary focus for our research and development activities. The second year effort has focused on the remaining three matters.

Development of Cost-Benefit Analyses:

Our goal is to estimate the potential cost-effectiveness associated with introducing a home monitor for Phenylalanine (Phe) levels for use by PKU patients and their care-givers. Maintaining Phe levels within a recommended range through strict dietary management is critical to reducing the adverse side effects of the disease. The hypothesis underlying a home monitor is that more frequent and patient-controlled testing will translate into better dietary management of the disease, lower Phe levels, and better health. The estimate of cost reduction by the use of home monitors depends on:

the expected reduction of Phe levels through home monitoring; and
the reduction in the health costs of PKU associated with such reduction in Phe levels.

Our research in year two has focused on developing estimates on both accounts.

Regarding the expected reduction in Phe levels through home monitoring, we have pursued a dual strategy with respect to estimating the potential responsiveness of patient management of their condition and their Phe levels using a home monitor:

1) Multivariate Analysis of Frequency of Phenylalanine Testing.

One strategy was to focus strictly on the expected increase in frequency of testing that would be made available through a more convenient device. No previous analysis to date has been conducted on this issue. We developed a multivariate analysis based on data collected on sixty-four PKU patients from 1984 through 1997 at four clinics (Las Vegas, Reno, state of Utah) collected for previous FDA-sponsored research. The data consist of 6,400 observations (Phe test results) on those patients as well as the interval since the last test, severity of condition, demographic characteristics of patients, site of test, and whether the patient was an experiment or control subject for the original study (experimental subjects received free low-protein food during specified periods of time). The results of our multivariate logistic analysis (test reading above/below recommended target) shows a very powerful and robust direct relationship between

interval of testing and Phe level; the longer the interval, the lower the probability that the test result is within the recommended range. A final draft of this analysis is being prepared for submission to the American Journal of Public Health (App. F).

A second analysis of the effects of frequency of testing is slated to be undertaken in Year 3, based on a prospective trial where a group of PKU patients will receive daily Phe monitoring at a Utah clinic.

2) Questionnaire to Utah PKU Patients on the potential Value of a Home Monitor.

We have developed and are currently piloting a questionnaire to PKU patients and their parents regarding the current difficulties associated with their current dietary management and the potential usefulness of a home monitor in facilitating easier management. While the questionnaire will elicit "willingness-to-pay" estimates (that is a measure of the monitor's potential value from a prospective patient viewpoint) the questionnaire is also designed to help address the extent to which a home device might decrease the intervals between tests, an essential element, combined with 1) above, to assessing the extent to which such a monitor may reduce Phe levels in patients with PKU.

An analysis of the cost of PKU as a function of Phe level is critical to the estimate of cost reduction associated with the home monitor. An accurate estimate is difficult because of the low incidence of the condition and because many of the co-morbid conditions, for which PKU patients are treated, do not have the condition code recorded on each record of service. We therefore pursued special Medicaid data, the so-called State Medicaid Research Files (SMRF), which were vast enough, and longitudinal in design, to fit our needs. Unfortunately, our request for a fee waiver as well as our appeal for the SMRF files was denied based on the potential commercial returns of the device (which we unsuccessfully argued would be minimal). We therefore have pursued, as of April, 1999, an equally (if not more) attractive data set through Kaiser Permanente, Southern and Northern California regions. We are working with Rebecca Mardasch, MD, who directs the Southern California metabolic clinic. She is optimistic that our request for data will be filled. The data, with observations of over 300 patients with PKU followed over five years, will include a comprehensive profile of medical care utilization. In year three, we will construct a utilization and cost profile of PKU from these data which will serve as the basis for the cost reduction analysis component of our study

Integration of economic and developmental research.

The integration of the economic impact analysis with the technology development work continues through meetings of the principal investigators and other project staff, meetings of the Clinical Advisory Team during the year, and the annual meeting of the National Advisory Board. Again this year, principal topics of discussions at these meetings have been the economic and policy considerations, along with related detailed discussions of the nature of the conditions, monitoring, and treatment of PKU. The work on the connection of the economic analysis and developmental research also continues its consideration of patient involvement in the monitoring and treatment of chronic conditions, with special attention to the treatment of children. This has led to consideration of master clinician teams interfacing with both tertiary care facilities and home-based care (App. B).

"Progressive Precision": An iterative model for the Application of Cost-Benefit Analysis to Technology Development Research

The integration of economic and policy analysis to the selection of appropriate technology for research and development is an ongoing activity. Our iterative approach has been expanding in

scope to suggest the value of employing basic analytic tools as ways of thinking, rather than as decision rules. Neither the tools nor their understanding need be sophisticated to use, thus making them accessible to bioengineers interested in the cost effectiveness of their technologies. More importantly, such use allows both earlier and more continuous analysis and questioning of the direction to be taken in research and development efforts. Finally, our interactions are producing ideas and interest in building more flexibility and exploration into research and development activities.

We are drafting a paper on successive iterations, addressing three evolutions in our emphasis. It is exploring how to stage analysis through simple uses of cost-effectiveness, benefit-cost, present value, decision trees, etc. We presently are crafting the article to show such uses and to simultaneously serve as a very brief and fundamental primer for the basic concepts of these tools. Some aspects of our experience in integrating economic and policy analysis with research and development may lead us to expanding elements of the present draft to separate reports. Presently under consideration are papers on technology and patient participation in their health care and on the search for cost-saving technology in an incomplete market.

° Education (Kern)

During this year our objectives for education and communication included:

teaching a course for bioengineering students on health care cost issues related to medical device development;
continuing to communicate issues related to technology costs through conference sessions and publications; and
continuing to provide project information via the project Website

Class Development

We offered a class entitled Medical Device Development: Ideas to Profit in a Cost-Conscious Environment. This one semester course was an introduction to the operation of the medical device business in the current cost-conscious environment. It presented the interrelationships among the disciplines necessary to bring good ideas from concept to product and on the impact of external forces on the ability of the product to be successful. The course gave the student a view of the diverse and complex issues involved in developing a successful medical product. The influences of technical challenges as well as marketing, financial, regulatory, legal, and political concernswere all addressed. Special attention was given to the impact of technology on healthcare costs and on the new challenges bioengineers must face in the era of cost-consciousness.

The course lectures were:

1. Overview and Principles of Health Care Costs
2. The Product Development Program
3. Project Management
4. Iterative Cost Effectiveness Analysis
5. Design Development
6. Regulatory Overview
7. Gateway Review
8. Clinical Trials
9. Intellectual Property Issues
10. Financials, Budgeting, Accounting
11. Scale Up and Manufacturing
13. Product Launch and Technical Marketing
14. Post Product Launch Support

Class handouts and other information are posted on the grant website. Some of the lecture overheads are available there as PowerPoint presentation files. The class was well received by the bioengineering students enrolled and will be offered on a biannual basis.

The lectures on Principles of Health Care Costs and Iterative Cost Effectiveness Analysis are currently being written up for submission to EMBS Engineering in Medicine and Biology journal. We are also investigating the potential of coordinating a theme issue for a journal that would focus on health care technology cost issues.

Dr. Huefner and Dr. Kern will develop a course for next year on Decision Analysis and Decision Making, which will discuss and show methods for making complex decisions, providing bioengineering students with tools for quantitatively determining the best paths to pursue for cost effective technology development.

Annual BMES Meetings

We organized a session at the 1998 BMES Meeting in Cleveland on Cost Reducing Health Care Technologies. The session involved current and past recipients of these grants. The participants presented information on their respective technologies and their measured or hypothesized impact on health care costs. The focus of the session was to emphasize how one goes about building a model for analysis of the cost impact of a given technology and on how to obtain the data with which to analyze the model. The session included the following presenters:

Greg Cooper, MD, PhD University of Pittsburgh Medical Informatics
Ray Ideker, Ph.D. University of Alabama Bioengineering
Miklos Gratzl, Ph.D. CWRU Bioengineering
Steve Kern, Ph.D. University of Utah Bioengineering
Mark Saltzmann, Cornell University Chemical Engineering

The session was part of the Special Symposium on Growing the Medical Products Industry and was well attended.

We are organizing a session for the October, 1999 joint EMBS/BMES meeting in Atlanta. Dr. Kern will chair a session on Technology Assessment, make presentations on Iterative Technology Assessment, and present information on beginning a Student Design Contest for Cost Reducing Health Care Technologies at the October, 2000 BMES meeting in Seattle. The session schedule will be finalized in June and posted with titles and abstracts on the grant website. The session will be chaired by Dr. Kern. Please note that the Year 3 Budget of our grant includes funds for a Student Design Prize.

Other Conference Participation

We have proposed two sessions for the annual American Association for the Advancement of Science (AAAS) meeting in Feb., 2000 in Washington D.C. The two sessions follow on themes addressed in our National Advisory Board meetings. Several members of the Board will make presentations if the sessions are approved. We anticipate hearing about these sessions in early June. The proposed sessions are:

Session I

Health Care, Economics, and Technology: An Evolving Balance.

Synopsis: Economic and policy issues increasingly influence health care technology solutions as we wrestle with keeping health care quality high while keeping costs under control. The health care system is also undergoing rapid change brought about by managed care, shifting care to team providers in an outpatient or home environment. The development of health technologies under new market arrangements needs to be examined so that quality of care and cost are not at odds. This symposium will highlight the interrelationships between these components and discuss how they influence what is defined as a health care problem, the development of solutions to these problems, and the implementation of payment for these solutions.

Proposed Participants:

Robert Huefner, D.B.A.. Professor of Political Science, University of Utah, Salt Lake City, UT

Technology Forecasting in an Uncertain Era of Health Care.
Recent refinements of cost-effectiveness analysis by the Public Health Service and others increase the reasonableness and comparability of economic analysis of health care technology. But progress in using technology to reduce the costs of health care depends upon integrating (more) preliminary (doable and timely) economic analyses with research and development activities, and upon changes in incentives to encourage the development of truly cost-reducing technologies. (Participation confirmed)

Ken Keller, Ph.D. Professor of Science and Technology Policy, Hubert H. Humphrey Institute and former President, University of Minnesota

Issues in the Development and Adoption of Health Care Technology
Scientists and engineers committed to the application of health care technology must not only deal with the challenging complexities of biological systems, but also recognize the equally complex realities of human society, with its political, social, cultural, and economic values and structures. To the extent that scientists can anticipate these complexities, they can work constructively to help society balance these challenges. (Participation tentative)

Burton Weisbrod, Ph.D. Professor of Economics, Northwestern University, Evanston, Illinois

Technology, Incentives, and Health Care Costs
Incentives matter, and society sets them - although often unwittingly- in a manner which influences technology development in health care. Society should not simply respond to tomorrow's technology, we should actively shape its direction with incentives. (Participation confirmed)

Philip Lee, M.D. Institute for Health Policy Studies, San Francisco, California, and former Assistant Secretary of Health and Human Services

From Policy to Incentives to Technology
We must develop a rational health care technology policy which provides the incentives to develop solutions to problems that relate to and correlate with societal needs. Without this we risk creating barriers rather than incentives to effective health care technology solutions. (Participation confirmed)

Session II

Children and Chronic Diseases: Incentives for Solutions to Lifelong Problems.

Synopsis: Children are disenfranchized in the current health care economic debate, yet solutions to problems that are unique to them are critical to controlling costs to society over time. Problems in childhood, some known and some unknown, may be large indicators of future health care needs because they define the trajectory over which our future generations will travel in their individual states of health. This symposium will discuss the challenges of treating chronic disease conditions in childhood, of creating incentives for the primary development of appropriate technology solutions to these conditions rather than waiting to treat them in adulthood or applying "adult" solutions to these conditions.

Proposed Participants:

Edward B. Clark, M.D. Professor and Chair of Pediatrics, University of Utah, Salt Lake City, UT

Resources and Technology for Children with Chronic Disease
The goals for the next 30 years for targeted child health research, education and advocacy will define and expand the role of technology in the advancement of care for children with chronic disease. If achieved, this investment in our future generation can produce immense societal benefits. (Participation confirmed)

Brent James, M.D. Executive Director, Intermountain Health Care Institute for Health Care Delivery Research and Vice President for Medical Research, Salt Lake City, UT

Outcomes Assessment for Projecting Future Technology Needs
Outcomes assessment is usually reserved for assessing the benefit of existing health care technology. It can also be used to project the needs for future technology solutions in health care based on problem areas identified in the analysis. Examples with reference to chronic disease management will be discussed. (Participation confirmed)

Norman Waitzman, Ph.D., Associate Professor of Economics, University of Utah, Salt Lake City, UT

Policy and Economic Incentives for Lowering Barriers to Technology Development
Incentives matter in generating interest in the development of technology solutions where the market is perceived as too small for attention. To facilitate development of these "orphan" technologies, economics and policy need to focus on issues pertaining to rare diseases. This is particularly challenging in a managed care environment that tends to focus on higher prevalence conditions. (Participation confirmed)

Joseph D. Andrade, Ph.D., Professor of Bioengineering, University of Utah, Salt Lake City, UT

Personal Sensors for Chronic Metabolic Disorders
Health care cost concerns are driving a growing interest in point of care-based technologies for screening, diagnosis, and even treatment of many disorders. Innovations and enhanced technologies in meter-less chemical analysis devices make it possible for individual patients to

monitor virtually any metabolic analyte of interest. There is an evolving trend in encouraging and empowering consumers and potential patients with greater education, awareness, and responsibility for their own health care. (Participation confirmed)

Web Site (http://www.healthtechcost.med.utah.edu)

The grant web site is continuing to be developed. It includes progress reports and information from our grant meetings. It also includes Power Point presentations for lectures given at our National Advisory Board meetings and for most of the lectures presented in our class. Other technical presentations and links to the technology development effort have also been incorporated. We will continue to expand and enhance the site in the final year of the grant.

Budget:

The expenses in the second year to date have been essentially identical to the categories and amounts in the proposal budget. The only substantive difference has been the use of some post doctoral funds for graduate students and slightly less than anticipated expenses for seminar speakers and visitors. We also arranged to video tape the entire proceedings of our March 16, 1998 and March 15, 1999 National Advisory Board meetings and plan to edit those into a concise 20-30 minute summary tape which we can then use in later presentations. We estimate that this will require $5,000-8,000 for editing services later this summer. We have harbored the funds carefully and intentionall underspent. We expect to ask for a no cost six month extension to extend the grant period through Dec. 30, 2000. This will enable us to fully participate in the Oct., 2000 BMES and the July, 200o World Congress (in Chicago). We therefore request that any unexpended funds as of June 30, 1999 be carried over. We anticipate that those unexpended funds will be about 20% percent of the total Year 2 budget.

Our plans for the Year 3 budget are identical to that in the grant application: $172,050 direct and $85,165 indirect for a Year 3 total of $257,215, plus the unexpended carry over of Year 1 and Year 2 to be used as noted above.

It is important to note that shortly after the grant was awarded the University of Utah College of Engineering provided an equipment grant of $10,000 for the acquisition of the equipment necessary to set up the web site and to provide for appropriate communication and dissemination of the project results. This includes a computer, a projection system, a CD production system, and related equipment. No equipment funds were budgeted in the grant application.

The relevant Year 3 budgets from the original grant application are enclosed for your information (Appendix G).

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Appendices

A. Summary – National Advisory Board (NAB) Meeting of March 16, 1998
B. Report – NAB Meeting of March 15, 1999
C. NAB and Clinical Advisory Team (CAT) Membership
D. Conferences and Meetings – Attended and Planned
E. Papers Published and in Press
F. Papers Submitted, in Advance Preparation, and Planned
G. Year 3 Budget

Appendix A

The 1998 NAB MEETING: SUMMARY AND PERSPECTIVES

The first meeting focused on Patient Empowerment and was organized in four discussion areas:
III. Patient Empowerment;
IV. Technology for Cost Reduction
V. Cost/Benefit Issues; and
VI. Policy Issues.

PATIENT EMPOWERMENT:

There are many driving forces for patient empowerment. Some of the characteristics of an empowered patient are demand for information, a demand for choice, desire to take control, a certain degree of skepticism, and a desire for convenience.

The patients do, indeed, want to be empowered. Patient empowerment must consider effective empowerment. Many patients are utilizing the Internet and in many cases getting inappropriate or incorrect information. It is important to create communities of information. Physicians and other professionals could work with various patient and patient advocacy groups to help provide the community of information and the authority assurance which is needed. Security and information are opposites; the information community must be activists with respect to validating and insuring the appropriateness of information.

Patients often ask two key questions: "Are you listening to me?" and "Do you understand my condition?" The importance of using patient discussion and support groups was noted, and the importance of using physicians who have or have had the disease in question to over come the us verses them gap. Patients and physicians could collaborate in a guided or cooperative empowerment by forming a team, including physicians and nurses, and physicians who have personally experienced the disease or problem in question. John Wennberg's prostate study was noted, in which physicians who were afflicted with a prostate problem were part of the patient advisory team and helped develop the educational and other materials used in the study.

The processes of prevention and care must directly involve the patients themselves. Home glycometer and glycosylated hemoglobin monitoring and the importance of the patient in taking and processing the data was noted. Such chemically based "bio-feedback" is apparently very effective in helping the patients control their disease. It was noted that patients need a sense of control, a sense of choice.

TECHNOLOGY FOR COST REDUCTION:

Technology is imbedded in the care delivery process. There are two models with which the patient can deal with their diseases or ailments: the free, independent access model and the mediated or guided process model. The patient taking control is important, convenience is important, immediacy and relevance to the patient is important.

Interest in managing a disease state is related to its importance to the patient. Can the technology or the monitoring lead to a change in treatment or therapy? Can it lead to a change in ultimate outcome? If not, then there is little interest or incentive in attempting to monitor.

Technology will continue to evolve. How systems respond to technology is a function of the incentives in place. Premature policies can inhibit technology development.

COST/BENEFIT ISSUES:

Both implicit and explicit costs were noted. Who has the incentive to decrease costs? Who benefits from new technology? Who bears the cost of that technology?
Whose value system is being represented? Is it the provider, the receiver of services (the patient), or the whole population?". Who pays, for example, for PKU diets? Is this part of social services or part of health care costs?

There are three factors which drive policy: budget, oversight, and information. Policy tends to change incrementally. Costs and benefits are really outside the current market mechanism.

The issue of outcomes analysis was discussed. All outcomes are intermediate outcomes. When should assessment be done. If it is done too prematurely, it may inhibit development.

POLICY ISSUES:

Public empowerment is also important, as well as individual patient empowerment.

There is a need for innovation in economic analysis. Analysis in the very early stage of technology development is needed, rather than relying solely on technology assessment or analysis after the technology is highly developed and already being applied. The concept of progressive precision was discussed; as the technology and its applications develop, the analysis can be made with greater precision.

Appendix B

UNIVERSITY OF UTAH/WHITAKER FOUNDATION
PROGRAM ON COST REDUCING HEALTH CARE TECHNOLOGIES:
PERSONAL SENSORS FOR THE MONITORING AND MANAGEMENT OF CHRONIC METABOLIC DISEASE

NATIONAL ADVISORY BOARD

SECOND ANNUAL MEETING MARCH 15TH, 1999.
SALT LAKE CITY.

The meeting was called to order at about 8:40 AM in the Alumni House at the University of Utah by Dr. Ed Clark, Chairman of the National Advisory Board (NAB).

Dr. Clark welcomed all attendees, each of which introduced themselves.

J. Andrade, Project Principal Investigator, gave a brief background on the organization and status of the project and a very brief review of the deliberations of the first annual meeting, held March 16th 1998. That meeting was on the subject of patient empowerment. A brief summary is included as Appendix "A". A complete set of notes of the first annual meeting is available on the web site:
www.healthtechcost.med.utah.edu

Dr. Clark's talk, From Birth to Old Age: Resources and Technologies for Children with Chronic Disease, is posted on the web site. He emphasized that infants with acute disease often become children and adults with chronic disease. He noted that biomedical technologies tend to deal with the acute conditions and much less research and development has gone to technologies for chronic conditions. He noted that there are three minorities in Health Care today:

1. Ethnic minorities;
2. Females; and
3. Children.

Of these, children are the most disenfranchised, as they have little direct voice or vote. He emphasized that the needs of children are different from those of adults. In the United States children only consume about $ 1,000 per year for health care needs, whereas adults cost $2,200 and adults over 65 approximately $7,000. He also noted that children served under Medicare were allocated only 2/3rd of that available via Medicaid for adults for the same services. He further noted that 20 to 30% of all children have some chronic condition.

He said that the challenges for academic pediatrics today are to investigate, translate, educate, and advocate for children. He emphasized that children are therapeutic

orphans. There is considerable need for point of care and home based technologies for their chronic treatment and management. For example, a respirator dependant child costs $4,000 per day in the hospital, $1,220 today in the home, with 24 hour nursing service, and $700 per day in a skilled nursing facility.

He noted the Barker Hypothesis (D. J. P. Barker, ed., Fetal and Infant Origins of Adult Disease, Brit Med. J. Publ., 1993) on the fetal origins of adult cardiovascular disease and other adult ailments. He presented the University of Utah plan for Master Clinician Teams interfacing with both tertiary care facilities and home based facilities. As part of his vision for pediatrics in 2020, he presented a technology wish list:

1. Home monitoring with central evaluation;
2. Non -Invasive monitoring;
3. Electronic Medical Records and their access;
4. Digital Health Data and Communications; and
5. Technologies which are appropriate for use by parents and other lay providers.

He concluded with a hope and vision for the future, noting that the present generation of children is the last generation of the current millennium and the first generation of the next millennium.

The complete presentation is available on the project web site.

The discussion began with Phil Lee asking about reimbursements for home technologies. There was a brief discussion of incentives for the development and application of technologies. Lee mentioned the Orphan Drug Act. Andrade noted that there is an orphan device component in the FDA. Joe also noted that FDA and the National Science Foundation are sponsoring a Home Health Workshop in Washington D.C., on April 7-9, 1999: Future Medical Devices: Home Care Technologies for the 21st Century, chaired by Jack Winters of the Biomedical Engineering Program at the Catholic University of America. Further information is available on the workshop web site (www.hctr.be.cua.edu/hctworkshop). There was considerable discussion on the fact that reimbursement and incentive policies focus on short-term needs and outcomes, rather than long-term. Zallen noted that it is time to change that policy.

Feldstein noted that there needs to be a payment mechanism to provide incentives. There was some discussion of the incentives within health plans. Although Intermountain Health Care in Utah, for example, has a very low member turnover, in some plans the turnover is 20% per year or higher, thus providing very few incentives for long term care. Sipes-Metzler noted that in Oregon there is a mechanism whereby a patient who changes health plans can stay with the same provider, thereby providing a longer-term incentive. Paula Julander, with the Utah State Senate, noted that such policies take a long time to change. She started bringing PKU needs to the attention of the State Legislature some 10 years ago; it was only quite recently that the Legislature mandated coverage for PKU diets and maintenance. Phil Lee noted that there are many disease-focused interest groups.

There was general consensus that there needs to be a national approach to invest in health infrastructure. Phil Lee said that the purpose of government is to take care of the most vulnerable. Carl Jaffe noted that, although reimbursement or payment mechanisms may not be in place, parents spend a great deal on their children and are very concerned for their children's health.

After a brief refreshment break, Carl Jaffe presented a short paper titled Technology, Information (Education), and Chronic Diseases. Dr. Jaffe's paper is available on his web site, (http://info.med.yale.edu/caim). He noted that in one year the World Wide Web has gone from 20 million to 80 million users, and that the elderly and women are the fastest growing groups. He talked about information as a "good" and an economic asset. He emphasized that there may be individual uniqueness and cited the evolving fields of pharmacogenomics and pharmacodynamics. He noted that every patient encounter should be a generator of information and not solely a consumer of information. He discussed the evolution of the computer and related devices as "information appliances". With respect to the development of analytic instrumentation, he noted that the display of information has to be tailored to the nature of the user. He gave some examples as to where sensing technology may be going, including sensing jewelry, sensing clothing and the possibility that even store bought foods might include a bar code or other means of presenting nutritional and related information. He emphasized the development of presentations and displays which reduce information clutter and emphasize actionable information. He suggested that the information generated and perhaps the actions initiated could be fed back to the individual user, to the social group, and to the health care providers. He emphasized that the need for and the benefit of technologies must be presented in a manner which is visible and identifiable to the users and beneficiaries. He suggested that pediatrics is a good area, because parents, and indeed society in general, feel responsible for children. There was some discussion about the visualization of data, i.e. the appropriate presentation of information, tuned to the users needs. Trend visualization was also discussed.

The discussion then continued, focusing on economic issues. Norman Waitzman used the analogy that the market functions as a homeostatic mechanism and that there is an economic tension. He used the example of the automobile versus highway and road investments, and compares that to the information highway, in which there has been investment in infrastructure and there now needs to be investment for its use. The question is: What are the economic incentives to develop and utilize the "automobiles" of the information highway? Carl Jaffe noted that Hewlett Packard has had interest in the home sensor arena.

There was some discussion of patient groups and patient support groups utilizing the Internet, including the Diabetes community, the PKU community, and even the Galactosemia community. See www.jdfcure.com, www.diabetes.org, www.galactosemia.org and www.pku.org

Chase Peterson, noted that the Internet gives access to facts, but not to context or to wisdom. That lead to a brief, spirited discussion on good and bad information on the web, the context for that information, and the opportunity to discuss and evaluate information with health care providers and other experts. Diane Stadler noted the responsibility of the patient and their family to critically review information. There was some discussion of government initiatives for the information super highway, including the Gore initiatives on education and libraries and possible political resistance to those initiatives. Andrade noted the new information technology initiative through the National Science Foundation. Phil Lee noted that there are two separate trust funds, one for education/library and the other for rural health and that Utah Senator Orin Hatch is on the appropriate committee and is well aware of these funds and initiatives; it might be appropriate to approach him regarding the issue of personal sensors for application to Telemedicine and related areas.

Owen Ash noted that the output from sensing and monitoring devices must be simple for the patients to read and interpret; this is difficult because disease management guidelines are in flux. Paige Sipes-Metzler noted that over a third of the hits on the Internet are health related and therefore there is a great opportunity to use the Net for medical and health related purposes. Carl Jaffe noted that it is unlikely that there would be much control of information on the Net and, as competition evolves for net exposure, good information should supersede bad information. Claire Leonard noted that patients often assume a diagnosis or ailment and do indeed get a lot of good information about the wrong diagnosis.

There was a brief discussion of the issue of low incidence diseases. How does one do outcome research when there are so few patients available? The Net and worldwide organizations of patients having rare diseases will help facilitate such studies.

Anne Prince noted that PKU is a "good" disease with which to test and evaluate these approaches. There was considerable discussion on the issue of rare or orphan diseases and the political process by which diseases or medical problems gain attention in Congress. Zallen suggested that one simply has to find Congressmen who have the disease of interest in their family. Another approach is to tie together a number of diseases and develop a generic label and political strategy for them, for example all metabolic diseases.

There was further discussion of the data generating process for various diseases and conditions and the expense of collecting such data. It was noted that it is difficult to do outcomes research if the data is not even being appropriately collected. An example of the Securities and Exchange Commission was brought up, and the means of generating the data from many sources in the economy for economic projections. There are apparently no such mechanisms available for medicine and health.

The afternoon session began with Dr. Claire Leonard's paper: A Case Study: PHENYLKETONURIA- From Infant to Adult. She presented a brief history of the discovery and the initial treatment methodology for PKU and summarized the outcomes

and problems. She noted that the level of Phenylalanine in the fetus is one and a half to two times that of the mother. She discussed the nature of and problems with PKU diets. She noted a number of the problems when children go off diet including attention span decreases, mood issues, and perhaps temper problems. She discussed the issue of monitoring, and then discussed a number of specific individual cases.

In the ensuing discussion, the issue of coverage and payment mechanisms for PKU treatment and diets were discussed. It was noted that most care is subsidized. Dr. Leonard noted that a chronic disease must be "owned" by the patient at a very early age, thereby providing both education and empowerment. As they move into adulthood they will then be empowered, functioning adults with respect to the management of their disease.

Stadler noted that the resources for the management of PKU are state dependent and some states have greater resources allocated then others. She said that the frequency of Phenylalanine monitoring is very important. Anne Prince noted a number of problems in monitoring and management, including the fact that generally blood samples require a week for the analysis and for the delivery of information to the care giver. She emphasized that both clinicians and patients need tools with which to deal with the disease.

Barry Zallen asked about the cost of dietary compliance. The general figure given was $5,000 to $7,000 per year or more for an effective diet. Claire Leonard noted that the major barrier to effective management is patient education and empowerment. Carl Jaffe noted that people are not long term motivated. They are basically short term motivated, and our policies and procedures reflect this perspective. It was noted that the management of PKU and related diseases in Europe is probably tighter and better than in the United States.

Anne Prince noted that the lack of a home test for Phenylalanine, or a rapid turnaround test, is a barrier to effective patient empowerment; such a sensor would be very helpful for empowerment. A variety of patient motivation mechanisms were discussed, including some sort of rebate if Phenylalanine level is maintained within a certain target range. There was also a discussion of incentives for technology development and application. It was noted that there is a need for a measure of integrated PKU status, perhaps analogous to the glycosylated hemoglobin test used for assessing long-term management of diabetes. The question was raised if any information might be available in hair. There was general agreement that some sort of long-term integrative measure would be very helpful, although there was no specific suggestion as to a possibility.

Claire Leonard presented a brief qualitative algorithm for patient empowerment and action, as a result of a PKU level target assessed by a home based sensor. Barry Zallen noted a comparison to asthma, where the patients do make the appropriate measurements at home and, based on those measurements, are empowered to manage their condition.

There was some discussion of other biochemical abnormalities in PKU, particularly other amino acid levels. It was noted that elevated phenylalanine levels actually inhibit the transport of other amino acids into the brain due to saturation of a common amino acid transporter system by the high phenylalanine concentration.

The discussion then focused on how to incentivize health plans in providing for long term effective management and care for PKU patients. How does one convince both the patients and the health plans that poor management may lead to lower I.Q, to mental health problems, and possibly depression? It was noted that depressed patients have a higher rate of service in all areas of medicine. How does one generate an economic analysis which includes short term as well as long term components? It was suggested that R. Huefner's progressive precision model for economic estimation needs to be applied to this kind of case. What is an estimate of the economic benefits of a now non-existent technology? What is the cost to the Health Care System of not developing a particular technology? Such questions are rarely raised and the methodology for answering them is not yet developed, and is indeed an objective of this particular grant and program.

A final discussion was on the subject of the third and final meeting of the National Advisory Board (NAB). Andrade suggested meeting as part of the American Association for the Advancement of Science Year 2000 meeting in Washington D.C. The Board could meet either just before or just after the AAAS meeting and participate in a number of AAAS symposia related to NAB topics. Although the group was very interested in possibly participating in the AAAS meeting, it was also concerned that the NAB's own discussions and deliberations might be compromised. The Board felt that their meetings have been so productive that it prefers to have an independent third meeting in Year 2000. It was decided to proceed with both meetings: the NAB meeting in Salt Lake in March, 2000 AND the AAAS meeting in Washington, D.C. in Feb., 2000, conditional on the acceptance of our Symposia proposal by the AAAS.

The meeting was adjourned at about 2:30 PM.

Summary - based in part on H. McQuarrie's input:

Ed Clark's team concept for managing chronic illness should be very effective and provides a good means for prediction of the need of and impact of appropriate technologies. Carl Jaffe's presentation provided the next link dealing with information transfer. Efficient and effective information transfer is vital if the Ed Clark vision is to succeed. Claire Leonard's presentation describes the limitations and inefficiency of traditional medical care in dealing with the rare disease, PKU, and the frustrations of trying to manage the disease without the communication and counseling tools necessary to alter the behavior of both patient and care giver. Clinical organizations and academic centers may be outmoded, possibly inefficient and unfocused, and may impede the team concept vision. The medical care system for managing chronic illness may need to be re tooled. Present technology and near future technologies may well be ahead of the current

Whitaker NSF Project on Cost Reducing Health Care Technologies (CRHCT)
Personal Sensors for the Management of Chronic Metabolic Disease
NATIONAL ADVISORY BOARD (NAB) Meeting
March 15, 1999 University of Utah
Final Agenda

7:15 AM	: NAB Breakfast at University Marriott Hotel. Welcome and Introduction	J. Andrade
8:15 AM	: Travel to University of Utah Alumni House Board Room	
8:30 AM	: Meeting overview and objectives; Summary of 1998 NAB Meeting	J. Andrade
9:00 AM	: FROM BIRTH TO OLD AGE: Resources and Technology for Children with Chronic Diseases	E. Clark, NAB Chair
9:45 AM	: DISCUSSIONS Technology Implications Economic Implications	 J. Andrade, Moderator N.Waitzman, Moderator
10:15 AM	Refreshment Break	
10:30 AM	: DISCUSSIONS Education Implications Health Policy Implications	 S. Kern, Moderator R. Huefner, Moderator
11:00 AM	: Open Discussion	
11:30 AM	: LUNCH	
12:15 PM	: A Case Study : PHENYLKETONURIA - From Infant to Adult C. Leonard, Dept. of Pediatrics	
12:45 PM	: DISCUSSION	E. Clark, Moderator
	Patient perspectives	J. Wennberg, P. Sipes-Metzler
	Health Provider Perspectives	C. Leonard, C. Peterson, S.Kern B. James, B. Zallen,
	Policy / Economics Perspectives	P. Lee, H. McQuarrie P. Feldstein, P. Lee,
	Technology Perspectives	R. Huefner, N. Waitzman J. Andrade, C. Jaffe, O. Ash,
		C. Brokopp, S. Kern
1:45 PM	: Other problems, Needs, and Challenges	B. James, E. Clark
2:00 PM	: Where To From Here ?	J. Andrade, R. Huefner
2:30 PM	: Adjournment, Transfer to Hotel or Airport	

medical care delivery system. We might need another project to fund the development of innovative modeling of clinical, healthcare systems.

Whitaker Cost Reducing Health Care Technology Grant National Advisory Board Meeting

Questions for the morning meeting session following the presentation by Dr. Clark.

Technology

1. Early intervention in the health of children with chronic disease conditions requires the adoption of health care technologies into the home or to local small healthcare facilities. What technologies are needed for decision support and diffusion of appropriate health information from the specialist to the clinic and to the home where health care management may occur on a day to day basis?

2. What would be an ideal technology wish list for health care outside of healthcare institutions? How do the needs differ for home care, modular clinic care, and other locations outside of major health care institutions?

Economics

1. How will the emerging health care market alter incentives with regard to the development and diffusion of health care technologies? Are there special challenges with respect to technology development for technology focusing on children?

2. The new structure of health care delivery will increasingly involve care outside of the hospital for chronic conditions. What will the new structure demand of technology; how might technology facilitate helpful changes in the structure of the health care delivery system? [e.g. To what extent will technologies for information transfer from patient to provider and back, and technologies to provide quicker and more accurate information, be useful or essential for integrated delivery teams?]

3. Are the crucial economic questions not entirely (or perhaps even substantially) related to the cost/effectiveness of the technologies -- but instead (or also) the costs and benefits of changing the structure and the practice patterns of the health care delivery system [i.e. to integrated delivery teams of multiple specialists and care givers and of patient and family].

Health Policy

1. What are the market inefficiencies which might be addressed to make the change to integrated delivery systems financially feasible and attractive? [e.g. The failure of the present market to provide rewards for long-term benefits of short-term investments and successes in health care. The high negotiation and information costs of integrated care delivered by independent providers.]

2. By what policies might these inefficiencies be addressed? [e.g. Development of single payers for specific conditions, as has been done for kidney failure. Capitated payments, at attractive rates made possible by reflecting long-term benefits, to integrated provider organizations.]

Education

1. To cost effectively manage chronic illnesses from childhood to adulthood, more patient care is being performed by paraprofessionals and lay people outside of hospital or medical centers. As technology diffuses outside of the hospital and into the home, what level of knowledge needs to be taught to users to effectively implement a technology? Who needs to be taught and how do we meet the need to do this? How do we assure that user education is sufficient to keep a useful technology from diminishing in effectiveness because of improper use?

2. How do we change the education of medical and premedical students to prepare them for the outward migration of more complex medical care beyond tertiary care centers? How do we assure that future health care workers are adequately trained to appropriately interact with technology as users or perhaps patients themselves?

Questions for the afternoon meeting session following the presentation by Dr. Leonard

Patient Perspectives

1. As health care becomes unentrenched from hospitals to the community at large, what role will web based patient education and support groups play in helping to disseminate therapies and solutions which are particularly effective or not effective?

2. How can patients and parents be optimally empowered to get the training, support and advocacy they need to manage their own or their family health conditions, some of which may last an entire life time?

Provider perspectives

1. How can providers who treat patients with rare diseases pool their experience base to share information on best practices? How do we most effectively create expert systems for defining best practices based on these pool experiences?

2. Will more extensive monitoring and screening help to identify the issues of most importance for treating low occurrence conditions? By gathering a more comprehensive picture of the patient's condition, will we potentially be able to better understand the issues of importance and hopefully offset the problem of less frequent incidence by gathering more information?

Policy/ Economic perspectives

1. Presume that most technological applications come through the search for applications of understood technologies (tools looking for a problem), but that new technologies may come from a search stimulated by a problem (a problem looking for tools). What market corrections or subsidies might be technically feasible and politically acceptable to stimulate the initial development of technologies: technologies which, once they are developed for a particular condition, might be expected to be easily transferred to multiple conditions? [e.g. Subsidies of technology development for specific diseases for which effective lobbies develop, as has recently occurred for AIDS and breast cancer. Subsidies for technology development showing promise for multiple orphan conditions. These two subsidies might be used together to direct the momentum of politically successful appeals toward a broader set of orphan conditions.]

2. How might technology and care for "orphan" conditions be promoted through:
   A. Market structure improvements including the elimination of inefficiencies [e.g. through regulated private or public monopolies for technology development and/or product marketing] and/or the capturing of externalities [e.g. establishing single payers for particular conditions or populations so that interests in long-term benefits are not erased by turnover in enrollees]?
   B. Subsidies, and of what form [e.g. government cost-sharing of care for orphan conditions, to reflect the externalities of benefits such as long-term savings in public and/or private expenditures related to the conditions].

3. Is net savings in health care costs the appropriate criterion for justifying prenatal care and other health promotion and condition management efforts? If not, what criteria are better?

Technology

1. How will our proposed technology solutions address the needs of patients with PKU? Will our efforts truly impact the quality management of this disease or merely add to the cost and confusion of managing this condition?

2. How do our perspectives compare to those of providers? To those of patients and parents of patient?

Appendix C

University of Utah Project on Cost Reducing Health Care Technologies: Personal Sensors for the Diagnosis and Management of Metabolic Disorders

CLINICAL ADVISORY TEAM (CAT)

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University of Utah Project on Cost Reducing Health Care Technologies: Personal Sensors for the Diagnosis and Management of Metabolic Disorders

NATIONAL ADVISORY BOARD (NAB)

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APPENDIX D: CONFERENCES AND MEETINGS – ATTENDED AND PLANNED
(see text of report for details)

J. Andrade, N. Waitzman, S. Kern, NSF/Whitaker Cost Reducing Health Care Technologies Grantees Meeting, Washington, D.C. July, 1998

S. Kern, Biomedical Engineering Society meeting, Cleveland, Oct., 1998

J. Andrade, NSF/FDA Home Health Workshop, Rockville, MD., April 7-9, 1999

R. Huefner, S. Kern, J. Andrade, , NSF/Whitaker Cost Reducing Health Care Technologies Grantees Meeting, Washington, D.C. July 8-9, 1999

J. Andrade, Nat. Inst. Dental Res Workshop, Saliva as a Diagnostic Fluid, Sept. 12-14, 1999, Bethesda, MD.

S. Kern and J. Andrade, Biomedical Engineering Society meeting, Atlanta, GA, Oct. 13-15, 1999

J. Andrade, Parents of Galactosemic Children meeting, Oct. 29-30, 1999 Columbus, Ohio

J. Andrade, S. Kern, N. Waitzman, R. Huefner and members of the NAB, American Assoc for the Advancement of Science, Feb.17-22, 2000, Washington, D.C.

J. Andrade, American Institute for Medical and Biological Engineering (AIMBE), Mar. 3-5, 2000, Washington, D.C.

S. Kern and J. Andrade, World Congress on Bioengineering, July 23-28, Chicago

S. Kern and J. Andrade, Biomedical Engineering Society meeting, Oct., 2000, Seattle

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Appendix E

Specific Immobilization of *in Vivo* Biotinylated Bacterial Luciferase and FMN:NAD(P)H Oxidoreductase

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Bacterial bioluminescence, catalyzed by FMN:NAD(P)H oxidoreductase and luciferase, has been used as an analytical tool for quantitating the substrates of NAD(P)H-dependent enzymes. The development of inexpensive and sensitive biosensors based on bacterial bioluminescence would benefit from a method to immobilize the oxidoreductase and luciferase with high specific activity. Toward this end, oxidoreductase and luciferase were fused with a segment of biotin carboxy carrier protein and produced in *Escherichia coli*. The *in vivo* biotinylated luciferase and oxidoreductase were immobilized on avidin-conjugated agarose beads with little loss of activity. Coimmobilized enzymes had eight times higher bioluminescence activity than the free enzymes at low enzyme concentration and high NADH concentration. In addition, the immobilized enzymes were more stable than the free enzymes. This immobilization method is also useful to control enzyme orientation, which could increase the efficiency of sequentially operating enzymes like the oxidoreductase–luciferase system.

Bacterial luciferase (luciferase), a heterodimeric enzyme composed of α (40 kDa) and β (37 kDa) subunits, catalyzes the reaction between reduced flavin mononucleotide ($FMNH_2$), a long chain aldehyde, and molecular oxygen to yield a long-chain carboxylic acid, flavin mononucleotide (FMN), and blue–green light (1). In bioluminescent bacteria, $FMNH_2$ is generated by FMN:NAD(P)H oxidoreductase (oxidoreductase, 24.5 kDa), which catalyzes the reduction of FMN at the expense of reduced pyridine nucleotides (NAD(P)H) (2). $FMNH_2$ is also generated by NADH- and NADPH-specific oxidoreductases (30). In a coupled reaction of the oxidoreductase and luciferase, production of light by the luciferase is directly proportional to the NAD(P)H concentration at limiting concentrations of NAD(P)H (10). When the oxidoreductase–luciferase system is coupled to NAD(P)H-dependent enzymatic reactions, light production can be proportional to the concentration of substrate of the enzyme reaction, and thereby used as a sensitive method to quantify medically important metabolites (3). Coupled enzyme systems have been developed to measure glucose, lactate, malate, alanine, and phenylalanine (4, 5, 11). In practice, detection limit and linear range in the assays depended on assay conditions including enzyme and reagent purity and reaction efficiency (3).

To develop inexpensive and sensitive biosensors based on enzyme reactions coupled to bacterial bioluminescence, it is advantageous to immobilize the luciferase and oxidoreductase. Enzyme immobilization in biosensors generally offers the advantages of repeated use, increased stability, easier handling, and decreased cost (3, 9). In addition, coimmobilization of sequentially operating enzymes, including the oxidoreductase–luciferase system, has been shown to improve reaction efficiency leading to higher specific activities (3, 8–11, 15, 24–26, 28). For example, Wienhausen and DeLuca (11) showed that the coimmobilized enzymes produced 10–20 times more light than the individually immobilized enzymes. In these previous reports, luciferase and/or oxidoreductase was chemically conjugated on the solid materials, including glass, nylon, and Sepharose (3, 9, 10, 15). These traditional immobilization methods resulted in substantial loss of activity as a result of the immobilization procedure, resulting in inconsistent enzyme activity (3, 9–11). For example, Nabi and Worsfold (10) showed the activity recovery of oxidoreductase and luciferase chemically coupled to Sepharose beads was 33 and 14%, respectively. Wien-

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DEVELOPING A BIOSENSOR FOR L-PHENYLALANINE BASED ON BACTERIAL BIOLUMINESCENCE

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Introduction

The determination of L-phenylalanine (Phe), an essential amino acid for mammals, is of great interest in several fields, including medicine, food science, and biotechnology (1). The measurement of Phe levels is important in screening for phenylketonuria (PKU), an inborn error of metabolism, and for monitoring the dietary management of PKU patients (2). Most Phe measurements, including microbial, fluorimetric, enzymatic, and chromatographic assays, are performed in centralized laboratories, often resulting in delays, inconvenience, and significant costs (2)

There is growing interest in self-monitoring and self-treatment of PKU in the home environment. Self-monitoring of the blood Phe concentration is important so patients can manage their diets and maintain appropriate Phe levels. There have been efforts at developing easy-to use assays for Phe (3).

Bacterial bioluminescence is a powerful and sensitive analytical tool. A flow sensor for Phe using immobilized phenylalanine dehydrogenase (PheDH), FMN:NAD(P)H oxidoreductase (OR), and bacterial luciferase (LF) was developed based on the following reactions (4);

$$\text{Phe} + \text{NAD}^+ + \text{H}_2\text{O} \xrightarrow{\text{PheDH}} \text{phenylpyruvate} + \text{NH}_3 + \text{NADH} + \text{H}^+ \quad 1)$$

$$\text{NADH} + \text{FMN} + \text{H}^+ \xrightarrow{\text{OR}} \text{NAD}^+ + \text{FMNH}_2 \quad 2)$$

$$\text{FMNH}_2 + \text{RCHO} + \text{O}_2 \xrightarrow{\text{LF}} \text{FMN} + \text{RCOOH} + \text{H}_2\text{O} + \text{light} \quad 3)$$

where NAD is nicotinamide adenine dinucleotide, NADH is the reduced form of NAD, FMN is flavin mononucleotide, $FMNH_2$ is the reduced form of FMN, and RCHO is long chain aldehyde. However, this method is not suited for self-monitoring of Phe, because it involves a peristaltic pump, preparation of solution, and a sample injection system.

A dip-stick type sensor is needed for self-monitoring of Phe in the home environment. Dip-stick devices are, in principle, easy to design and manufacture, resulting in reduced cost. In addition, they are easy to handle and use by people without special techniques or training.

We are developing an inexpensive dip-stick type-Phe sensor based on bacterial bioluminescence for self-monitoring in the home environment. This study evaluated the feasibility of a high performance Phe sensor based on the PheDH, OR, and LF reactions, and its optimal reaction conditions in homogeneous solution.

Materials and Methods

OR and LF were produced from E. coli by using recombinant techeniques. Their purity were over 90 % and their specific activity were close to the enzymes from Boehringer. PheDH (Cat. No. P-4798) was purchased from Sigma (St. Lousis, MO, USA) and used without further purification.

NADH (Cat. No. 128023) and FMN (Cat. No. 476501)were purchased from Boehringer (Indianapolis, IN, USA). Dodecanal (Cat. No. D-3042), Phe (Cat. No. P-8324), and phenylpyruvic acid (Cat. No. P-8126) were purchased from Sigma. NAD (Cat. No. 481911) was obtained from CalBiochem (La Jolla, CA, USA). All other reagents for buffer solutions were obtained from Sigma. All reagents were used without further purification.

In order to investigate the effect of those reagents on the PheDH reaction, all measurements were started by adding the PheDH solution to the cuvette containing all other necessary reagents (see Results). The conversion to NADH at 5 min was monitored by a spectrophotometer (Lambda 2, Perkin Elmer, Norwalk, CT, USA) at 340 nm (ε=6.22 x 10^3 M^{-1} cm^{-1}) (5) and at room temperature.

For investigation of the effect of the reactants and products of the PheDH reaction on the bioluminescence system, bioluminescencent assays were started by adding the NADH solution into the tube containing all necessary reagents (see Results). In the assay for study of the pH effect and the buffer concentration effect, and for calibration curves, all assays were started by adding the Phe solution to the tube containing all other necessary reagents (see Results). The total integrated light emission at 5 min was measured by a luminometer (TD-20/20, Turner Designs, Sunnyvale, CA, USA) at room temperature and reported in relative light units (RLU).

All solutions were in phosphate or tris buffer of different pH or concentration (see Results). All reagent stock solutions were made freshly before assay and kept at 4 °C until use. Dodecanal was dissolved in methanol and used within 5 h. FMN and NADH solutions were also protected from the light.

Results and Discussion

A homogeneous-type biosensor, wherein all enzyme reactions are in progress at the same time and in the same volume, has fewer assay preparation steps. However, each enzyme competes for the substrates and products; the overall optimal reaction rate depends on the specific conditions.

The effects of the substrates and the products of each reaction on the other reactions must be determined and an optimal set of conditions for all reactions deduced in order to design a high performance homogeneous-type biosensor (6). The precise values of the substrates and the products in this system are not critical to the overall outcome (Figs 1 and 2); OR influenced the PheDH reaction, decreasing the output by about 20% (Fig. 1), and Phe, NAD, and PheDH influenced the bioluminescence reactions, decreasing the output by about 20% (Fig. 2). This ensures that the substrates and the products of each reaction do not significantly affect the other reaction when all substrates, except analytical one, are present in excess.

The effect of pH on the response in the homogeneous-type assay comes from two effects (7). Firstly, enzymatic activity is a function of pH and each enzyme has an unique optimal pH. Secondly, pH may affect the dissociation equilibrium of the product. Optimal pH of the bioluminescence reactions is pH 7.0 (8). However, PheDH from *Sporosarcina ureae* shows a pH optimum at pH 10.5 (9). The optimal pH of the overall assay system was pH 8.0 (Fig. 3). This pH value is closer to that of the bioluminescence reactions, suggesting that the PheDH reaction is driven by the NADH consumption of the bioluminescence reaction. In addition, the bioluminescence reaction is probably more sensitive to pH than is PheDH.

An optimal molarity of the buffer in the assay is also important. This effect was studied in phosphate and tris buffer (pH 8.0) with concentrations ranging from 10 mmol/L to 400 mmol/L. The highest light emission was showed in 50 mmol/L phosphate buffer (Fig. 4).

Optimal buffer concentration for the bioluminescence system is 100 mmol/L phosphate buffer (8). However, many different buffers can be used in the PheDH reaction. The bioluminescence reactions are probably more sensitive to the buffer condition than the Phe reaction.

The enzyme amounts needed for optimal assay are important in designing an economical and sensitive sensor. In the bioluminescent assay, 0.1 nmol of OR and LF were suitable for an assay volume of 250 µL. (data not shown). For our system, the optimal enzyme amount of PheDH was 0.4 U (Fig. 5). However, the enzyme amounts needed for

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Homogeneous Bioluminescence Assay for Galactosuria: Interference and Kinetic Analysis

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CHEMICAL SENSORS IN THE HOME: Discussion Paper

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Home Health Workshop, April, 1999 FDA/NSF

Many medical conditions require the measurement of one or more biochemicals in order to facilitate diagnosis, manage a disease or condition, or monitor a treatment. Physicians and other health care providers regularly order a range of chemical tests, generally performed on blood or urine. The samples are generally obtained by the health care provider and are sent to centralized analytical laboratories, which perform the analyses and report the results. Historically, the techniques and procedures involved require skilled personnel and specialized instrumentation.

In the last several decades analytical and clinical chemistry has developed to the point where many useful analytical measurements can be made using relatively simple and inexpensive instrumentation and often by unskilled personnel. Some of these technologies have now become over the counter, readily available, kits and instruments for home use. The most common of these is quantitative glucose measurement, used regularly by millions of Diabetics throughout the world. Using a microlancet to generate a small (50-100 microliter) blood droplet, the patient transfers the blood sample to a dip stick device, which serves to collect the sample, performs needed separation steps, and delivers the sample to one or more analytical zones in which a specific chemical reaction is carried out, resulting in a signal which is read by a small, inexpensive analytical instrument. In the case of diabetes, glucose specific dipsticks are used and small hand held reflectance colorimeters, commonly called Glucometers, are employed with acquisition costs in the range of $30-100 or more.

The individual Dipsticks cost in the range of 50 cents to $2.00, depending on the manufacturer and quantity considerations. In addition to the enzyme based colorimetric assays used for glucose, immunoassays can also be employed, the most common of which is the over the counter pregnancy test. The current over the counter cholesterol test is an enzyme based colorimetric system.

The major Diabetes Control and Complications Trial (DCCT) recently documented the enhanced health benefits of tight glycemic control for diabetes. Regular monitoring of glucose and regulation of insulin intake leads to much more effective management of the disease and the minimization of the chronic complications which are so burdensome to both the patient and to the health care system.

The diabetes community is leading and driving major research and development activities to further improve the measurement and monitoring of glucose and of other metabolites important to diabetes, with an emphasis on sampling methods which do not involve the trauma and discomfort of blood sampling. There is a move towards the use of interstitial fluid as the analytical sample and even to the development of truly non-invasive methods of analysis. Considerable research and development is now being

focused upon minimally invasive approaches for obtaining samples of interstitial fluids for glucose analysis. Such fluid can be collected from the skin epidermal layer, which is devoid of blood vessels or nerves. The process is therefore painless and bloodless.

A problem with minimally invasive approaches to sampling is that the volume collected is often one microliter or less and thus considerably smaller than a typical blood glucose sample, generally 30 microliters or more. This presents a considerable challenge for current analytical methods of detection, which in the case of glucose is primarily electrochemical or reflectance colorimetry. There are many groups developing means for interstitial fluid collection and analysis (www.jdfcure.com and www.diabetes.org). It is likely that these efforts will be successful and that truly, minimally invasive, painless means for acquiring samples for biochemical analysis will become available in the very near future.

The problem of sensitivity is also being addressed by a number of groups, including our own. We use a bioluminescence approach to the analysis of glucose and other metabolites in blood, urine and interstitial fluids. Bioluminescence has an advantage over existing approaches to such measurements in that it is generally at least 100 times more sensitive. Bioluminescence is light produced by biological compounds undergoing specific, enzyme catalyzed chemical reactions. The most well known example of bioluminescence is the firefly, however, other organisms employ similar reactions to produce light, e.g., there are also bioluminescent bacteria, fish, and fungi. All bioluminescent reactions employ an enzyme, called luciferase, that makes the reaction possible, e.g. there is a firefly luciferase, a bacterial luciferase, etc. Practically all of biochemistry is linked to two very unique and ubiquitous molecules - ATP and NADH. ATP and NADH represent the "energy currency" of metabolism and are both linked via other enzymes to firefly luciferase bioluminescence and bacterial luciferase bioluminescence, respectively. In our approach, the bioluminescence is detected with an opto-electronic device, often a CCD camera. The amount of bioluminescence measured can be related to the specific biochemical of interest in the sample.

These technologies permit the development of sensors for a many other diseases. Of particular need are the many inborn errors of metabolism, exemplified by Phenylketonuria (PKU) and Galactosemia. PKU is an inherited enzyme deficiency disease which results in the accumulation of Phenylalanine to toxic levels. The disease can normally be managed by careful dietary control and by regularly measuring phenylalanine concentration in blood. Phenylalanine is an essential amino acid, so the patient and his health care provider must walk a fine line between providing adequate phenylalanine for growth and renewal and yet keep the circulating blood concentrations of this essential amino acid in ranges which are non-toxic and non-damaging. This requires frequent blood monitoring, preferably weekly. Given the relatively low incidence of that disease (one in ten thousand), the fact that the current analytical methods require a large volume of blood for analysis (of the order of 200 to 500 microliter), and that there are no home based sampling or analytical methods available, most PKU patients are not optimally monitored or managed.

The situation with Galactosemics is even more difficult. Although Galactosemia is a more complicated disease and is not as easily managed, it is important for Galactosemics to minimize their Galactose intake. The major source of Galactose is lactose in milk and diary products; Galactose is also common in a wide variety of fruits and vegetables. Galactose and Galactose-1-phosphate should be monitored regularly.. But as Galactosemia is even more of an "orphan disease" (incidence one in 50,000), the technologies and resources for convenient monitoring are simply unavailable.

Although industry has responded to the analytical and instrumentation challenges required for the appropriate monitoring and management of diabetes, that is only because it is a relatively high incidence disease. The numbers are such that it is cost effective to develop and market products for diabetes. When a disease has an incidence of one in ten thousand or significantly lower, it becomes extremely difficult to justify any such development or expenditure by a commercial entity. Hence we call such diseases "orphan diseases", as we are now familiar with the term "orphan drug".

It is clear that new and different incentives will need to be developed in order to meet the health care needs of these small segments of the population. The good news is that Diabetes is basically driving the entire analytical biochemistry field with respect to technologies which can be utilized at home.

A major application of home based over the counter biochemical measurement devices is likely to be in the nutrition and food supplement communities. The ability to monitor amino acids levels, vitamin levels, and a range of other nutrients and food supplements is of interest to these major segments of the population. It would be of interest for sports and physical performance enthusiasts, for example, to learn whether or not creatine supplements do indeed influence the circulating levels of this important bioenergetic chemical. Consumers taking mega doses of Vitamin C would learn that such dosages do not need necessarily lead to an increase in the circulating levels of Vitamin C, thus, perhaps, prompting them to modify their behavior or at least minimize their expenditures and intake.

Those empowered consumers and patients who are interested in their circulating blood or urine levels of various analytes can now, via the worldwide web, order such tests from centralized analytical laboratories and obtain such information privately, if they so choose. As the technology continues to miniaturize, as it continues to become more reliable and inexpensive and easy to apply, and as it becomes possible to make such measurements painlessly, using minimally or non-invasively derived fluids, there is likely to be growing interest in the application of home based analytical sensors. There is even talk of incorporating the analytical unit as a PC card or using existing CD drives directly as measurement devices.

The data derived from such measurements can thus easily be incorporated into PC based personal medical advisor software and thereby facilitate personal diagnosis and disease management. The present generation of instruments for the monitoring of glucose already includes the capability for recording and storing the data and for downloading it on a regular basis to the health care provider. Such capabilities will of course be available in home based analytical chemistry devices for orphan and other metabolic diseases.

The key questions are:
What should be measured?,
How should the data be interpreted and utilized?
How can one develop incentives to facilitate the development of the technologies and instruments required for currently unmet health care needs?
How can these new technologies be incorporated in evolving tele-connected living environments?

General References:

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Topic B: PERSONAL STATUS MONITORING IN THE HOME

By J.D. Andrade and A. Kinsella

Draft Report for Home Health Workshop April, 1999 FDA/NSF

Basic Principles and Assumptions:

1. Focus on the Patient and Home Provider

The home medical care environment must first and foremost be a HOME. Devices, monitors, and other technological facilities must be designed and manufactured with the home or residence in mind. The patient's room must NOT look, feel, or smell like an intensive care unit (ICU) or an emergency room (ER). All devices and facilities must serve to empower the patient and to aid and facilitate self-care and care through the aid of family or live-in providers. Devices and facilities must be customized and tailored to the particular needs and preferences of the patient and family. This means that home care devices will be very different from the present generation of ICU, ER, hospital, or even physicians' office point-of-care devices and equipment.

The biomedical engineering and medical device and hospital products communities have little experience in these areas, and neither does the FDA. The Food and Drug Administration (FDA) has been skeptical of home devices. The FDA must become a close partner with the bioengineering and manufacturer communities in assuring that the next generation of devices and equipment for home care are appropriately designed, tested, manufactured, and implemented.

All devices and equipment must be very easy to use, preferably requiring only a third grade education and reading level. The operation of such devices must be obvious. Their use and application in the home must be "transparent"

2. Nature of Wellness and Illness

Western medicine deals with pathologies -- abnormalities; it doesn't deal well with "normality" -- with wellness. What is "well"? How do we measure "wellness"? There is little understanding and thus no concensus (there is, in fact, little interest in the medical community!). The well state is the baseline; deviations from that baseline, depending on their magnitude and severity, represent non-wellness or pathology -- an illness or condition which must be "repaired", returning the patient to normality -- to wellness.

Consumers are voting with their feet and pocketbook -- they are demanding wellness by buying and eating or taking alternative medicines, "medicinal" herbs, vitamins, metabolites, etc. Alternative Medicine and Wellness is a booming business. We cannot ignore it. Most home health patients participate in alternative medicine and alternative nutrition activities.

We must learn to parameterize and measure wellness. Although we have a set of physical parameters which are generally accepted (Temperature, Blood Pressure, Pulse Rate, ECG), we rarely consider chemical parameters. Except for glucose and cholesterol, biochemical measures are not used for wellness assessment, although specific chemical and enzyme activity assays are regularly ordered to "confirm" the diagnosis of various diseases or pathologies. How can we promote wellness if we lack the means to parameterize and measure it?

3. Sensors and other Measurement Devices

Given a set of wellness parameters, we must be able to measure those wellness parameters. And we must be able to measure them in the home -- easily, simply, and non-invasively. Many Science Centers throughout the nation measure EEG, Pressure, and Temperature of their visitors and participants; so do high school and even junior high classes, with very inexpensive, safe, easy to use equipment. The major constraint is chemistry. We need simple, easy to use, inexpensive, quantitative, and reliable means to measure the key metabolites, nutrients, and other chemicals necessary to the assessment of personal wellness.

The diabetes community is leading and driving major research and development activities to further improve the measurement and monitoring of glucose and of other metabolites important to diabetes, with an emphasis on methods which do not involve the trauma and discomfort of blood sampling. There is a move towards the use of interstitial fluid as the analytical sample and even to the development of truly non-invasive methods of analysis. Considerable research and development is now being focused upon minimally invasive approaches for obtaining samples of interstitial fluids for glucose analysis. Such fluid can be collected from the skin epidermal layer, which is devoid of blood vessels or nerves. The process is therefore painless and bloodless.

A problem with minimally invasive approaches to sampling is that the volume collected is often one microliter or less and thus considerably smaller than a typical blood glucose sample, generally 30 microliters or more. This presents a considerable challenge for current analytical methods of detection, which in the case of glucose are primarily electrochemical or reflectance colorimetry.

There are many groups developing means for interstitial fluid collection and analysis (www.jdfcure.com and www.diabetes.org). It is likely that these efforts will be successful and that truly, minimally invasive, painless means for acquiring samples for biochemical analysis will become available in the very near future. These new methods, together with more specific and sensitive means for chemical analysis, will make home chemical measurement and monitoring practical.

4. System Integration

Home health care must be seamlessly and transparently connected to and a part of the overall health care system. The patient's physician, nurse, dietician, physical therapist, psychiatrist, pharmacist, etc. must be available; the patient's data and medical/health/wellness record must be readily available. Data and images obtained in the home care environment must be easily accessible to the health care system, with appropriate controls on privacy and security issues. There must be algorithms and expert systems to assess the voluminous streams of data from home care patients who are being continuously or regularly monitored. In addition to the integrated system providing for the care of the patient, the system must be a source of data for researchers and others whose aim are to more fully understand wellness and illness, in order to better treat all

patients. Thus every patient "encounter", every measurement, must be a source of information, again with appropriate concern for anonymity and privacy.

5. Patient Education

Personal and private health and wellbeing are very powerful pedagogical tools for education and learning. Patients, and their at home providers and caregivers, must be empowered to learn, understand, criticize, observe, control, and measure their disease. They must be interested and involved in their personal return to wellness and in the treatment of chronic disease. They must be part of the "solution". Clearly, there are many kinds of patients; some are more readily empowered and involved than others, but all must be given the opportunity to become interested, involved, and empowered.

6. Inter-Agency Collaboration

There are many stakeholders in home care -- many agencies, both state and Federal; foundations and other not for profit institutions; patient support groups; industry; insurance firms; and, of course, physicians and other care givers. They must be empowered to work much more closely together. They must facilitate -- FUND -- demonstration projects. They must provide incentives to encourage the community to meet the needs of effective home care. They must minimize myopic, short term economic and cost/benefit analyses in order to consider the long term consequences of effective home health care.

What is Likely to Happen?

1. Consumer Demand for Home Health and Home Health Care.

If patients have a choice, and if they have a reasonably stable and caring home environment, they choose to go home, almost without exception. If they have a severe, chronic, difficult condition it is difficult to permit them to go home, unless the home is fitted with the appropriate technology and care giver.

The modern consumer has grown to accept and expect technological advances -- she expects such advances in medical and health care technologies. Industry is slowly responding, although payers, and the FDA, are not responding efficiently.

It is indeed possible to design, manufacture, install, and implement medical and health care technologies which are simpler, easier to use, and don't require Ph.D. or M.D. degress to operate. Consumers today operate highly sophisticated devices and equipment, assuming such devices are appropriately designed and engineered. That is the challenge. The home must remain a home, and not look like an ICU or ER. The home health care system must be transparent, and it must be integrated -- seamlessly -- with the total health care system.

2. The Communications Infrastructure

Appropriate communication technologies and networks are already in place and rapidly becoming more effective and more affordable. The need and challenge is to seamlessly connect home health care monitors, sensors, and assist devices to these communication systems and thus to the various professional care providers. Challenges include reliability, security, privacy, quality, and related issues, most already well addressed by the existing informatics and telehealth communities.

Knowledge Gaps and Research Needs

1. Patient Perceptions and Motivation

What motivates patients to become educated, empowered, and involved? How do we design, produce, and use education materials to facilitate their education, understanding, and involvment? How do THEY perceive their disease or condition; their health care providers; the instruments and devices in THEIR home? What is the role of patient support groups, now so readily available on the Internet? Can we use physicians or nurses with the same illness or pathologies, who understand and empathize, to help the patients become more involved?

2. What is Wellness?

What parameters most effectively indicate normality and abnormality? How patient specific are these measures?

The drug community is now very involved in pharmacodynamics and pharmacogenomics, meaning the individual or patient-specific response to particular drugs.

What is our personal Biochemical Individuality? What is my personal wellness baseline? Yours? What magnitude of deviation from that personal baseline constitutes an illness or a pathology?

3. Which and What Home Care Technologies, Devices, Methods Really Work?

4. How can Economic and Cost/Benefit Analyses be Performed?

The health care economics and payer communities rarely consider the integrated lifetime costs, from conception to burial, yet that is indeed the most relevant societal health economics metric. Can we develop more long range economic models and analyses? How do we collect data to facilitate such analyses? How do we define and analyze the "cost effectiveness" of a particular technology or device? How do we deal with "orphan diseases" and the "orphan" technologies or devices needed by those patients? How do we incentivize researchers to study, and companies to develop and produce, information and devices for which there is no conventional "market"?

5. How can we Develop High Volume, Adaptable Manufacturing?

How can we assure access to highly reliable, easy to use, nonintrusive (even "transparent"), customized, and even orphan devices? One way is to encourage (FUND) the development of highly adaptable, high volume manufacturing processes. The best current example is the microprocessor or the charge coupled device (CCD) light detection/imaging chip. These are manufactured in such high volumes that they are very inexpensive, even though sophisticated manufacturing proccesses are used. The low costs are a direct result of the high volume, which is due to the flexibility and adaptability of the product. What about physical and chemical sensor "chips" that can measure almost anything of possible interest? They can be wired, programmed, or otherwise implemented in a manner to provide true custom sensors and devices, perhaps disease or condition specific.

6. Effective Education and Training

How do we educate and empower a new generation of design and manufacturing engineers, bioengineers, physicians, other health providers, etc. to study and do what we have enumerated above? How do we encourage academic engineering, and especially bioengineering, programs to deal with the needs of home health? How do we get them to involve patients -- not just after the fact, but before the fact -- in the design, development, and testing of appropriate devices and technologies? How do we educate the academic health policy and health economics community to develop means and methods with which to take a long term, integrated view? How do we educate and incentivize payers, including Medicaid, Medicare, HCFA, etc to do the same?

Summary Recommendations

Items 1 - 6 above (Knowledge Needs) and:

1. Fund the development of a Personal Health Profile. What are the parameters? How should they be measured? How should the data be assessed and analyzed? How should the data be presented to the patient? to the professional providers?

2. Fund the development of Personal Health Education programs and materials.

3. Fund the design and development of adaptable manufacturing processes.

4. Fund the study and development of health economics tools and models which consider chronic, long term, greater societal needs and issues.

5. Fund demonstration projects, preferably interagency, which address the issues and needs discussed above.

Toward Dollar Devices for Measuring Metabolic Biochemistry

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Chapter in
Anti-microbial, Anti-infective Materials,
S.P. Sawan and G. Manivannan, editors
Technomic Publishing Co., ~~1998~~ 1999, in press.

APP F: PAPERS IN PREPARATION (Titles)

Book: We are planning to produce a book based on our Symposia at the Feb. 2000 AAAS meeting, on the three meetings of our National Advisory Board, and on our experience and work during the three years of this grant. Please refer to text of report (Education Section) for the AAAS program, which will provide an indication of the contents of the book.

Theme issue of journal: As noted in the text of the report, we are assessing the feasibility of organizing a theme issue of a major technical journal, wherein the activities of many investigators in the CRHCT program could be represented.

R. Huefner, Simple Rules for Preliminary Assessment of the Cost Effectiveness of Proposed New Technologies and Devices, journal to be selected

N. Waitzman and collaborators, Effects of Testing Frequency on Phenylalanine Levels in PKU, Amer. J. Public Health, to be submitted

N. Waitzman and Collaborators, Effect of a Free Diet on Phenylalanine Levels in PKU, journal to be selected.

R. Huefner, Progressive Precision: An Iterative Model for Cost-Benefit Analyses of very early stage Technologies, journal to be selected

R. Huefner, "Orphan" Devices for Rare Conditions: Incentives and Assessment, journal to be selected.

E. Clark, A Pediatrician's Technology Wish List for Bioengineers, probably Ann. Biomed. Engrg

S. Kern, Healthcare Economics Issues for Medical Technology Developers, journal to be selected

S. Kern, Cost to Whom? Understanding the Impact of Technology on Healthcare Costs, journal to be selected

R. Davies, J. Andrade, et al., A Homogeneous, Bioluminescence Assay for Creatine and Creatinine, Anal Biochem., to be submitted

A set of technical biosensor papers will be presented at the 11th International Symp on Bio- and Chemi-luminescence, Asilomar, Calif. in Sept. 2000; extended abstracts will appear in the Proceedings; full papers will be submitted to the appropriate technical journals