

Independent Expert Evaluates CVP Diagnostics & VeriCor Monitor

Prof. Richard Cohen, the Whitaker Professor in Biomedical Engineering at the Harvard-MIT Division of Health Sciences and Technology, evaluated the potential benefits and likely revenue potential of the first and only noninvasive FDA-cleared ICU-caliber monitor, the VeriCor monitor, and his detailed 11 page report follows.

In addition to a detailed technical analysis of the VeriCor monitor, it is worth noting Prof. Cohen's projections of likely revenues to CVP Diagnostics from VeriCor monitoring of heart failure patients.

Prof. Cohen's Revenue Projections. Prof. Cohen projected that, in 5-years at full market penetration, "Potential U.S. Office Market (fully penetrated): \$2.6 billion per year." Prof. Cohen also projected "Total Potential U.S. Home Market (fully penetrated): \$30 billion per year." (See page 7 of Cohen Report).

CVP Diagnostics Revenue Projections Bracket Prof. Cohen's Revenue Projections. As noted in the previous section, entitled "CVP Diagnostics Revenues", annual revenues from Hospital & Community-Based Markets at full market penetration are projected at \$13.5 billion per year, while annual revenues from the VeriCor Hybrid Technologies are projected to be \$43.5 billion a year at full market penetration.

CVP Diagnostics

Summary of Issues and Recommendations
To be Discussed with CVP Diagnostics

by

Richard J. Cohen, M.D., Ph.D.*
Whitaker Professor in Biomedical Engineering
Harvard-MIT Division of Health Sciences and Technology
Room E25-335
Massachusetts Institute of Technology
45 Carleton Street
Cambridge, Massachusetts 02142
Email: rjcohen@mit.edu

With the assistance of Jean Kim, MBA

April 5, 2006

*Richard J. Cohen is responsible for the content of this report and the report should not be construed to represent the views of any other individual or organization including Harvard or MIT. The views presented here represent Dr. Cohen's personal opinion with which other knowledgeable individuals might reasonably disagree. This report represents private confidential advice to Tully Capital Partners, LLC. Preparation of this report was by contract limited to take no more than 30 hours of Dr. Cohen's time and the report is thereby necessarily limited to the extent to which many issues could be investigated.

Dr. Cohen notes, as he has previously disclosed, that he is a consultant and has a financial interest in Cambridge Heart, Inc; he is a consultant to Medtronic Inc; and he is developing in his laboratory a technology for continuous cardiac output monitoring and other medical technologies. He also is a consultant/advisor to other entities.

CVP Diagnostics (the “Company”) is a development stage medical technology company. This report evaluates the technical and commercial aspects of this company.

Technology

The Company’s core technology is a noninvasive means of estimating of left ventricular end-diastolic pressure (LVEDP). LVEDP represents the filling pressure of the left ventricle of the heart and is characteristically elevated in patients with left heart failure. A dysfunctioning left ventricle requires a higher LVEDP in order to generate adequate cardiac output (total blood flow out of the heart). However, if LVEDP is elevated excessively the pulmonary veins communicate this elevated pressure to the lung microvasculature resulting in transudation of fluid into the lung tissue resulting in pulmonary congestion. Very high levels of LVEDP may result in fluid actually entering the alveoli (air sacs) of the lung – a serious acute condition known as pulmonary edema. Pulmonary congestion is responsible for many of the symptoms of left heart failure such as shortness of breath.

LVEDP at present can only be measured directly during cardiac catheterization of the left heart, a procedure generally done only in the cardiac catheterization laboratory. A right heart catheterization procedure may be used to measure pulmonary capillary wedge pressure which is used as a surrogate for LVEDP. A right heart catheter can be placed and left in place in the intensive care unit. However, because of the risk associated with this procedure and lack of demonstrated benefit, the popularity of right catheterization has diminished in intensive care unit patients.

The Company’s Vericor technology involves measuring LVEDP by non-invasively measuring the continuous arterial blood pressure signal while the patient attempts to blow through a tube to maintain an elevated airway pressure (Valsalva maneuver). The response of the arterial blood pressure signal to the Valsalva maneuver is processed by a computer algorithm to obtain a pulse-amplitude ratio (PAR). The PAR has been demonstrated in a number of publications in well respected journals (including the New England Journal of Medicine) to vary linearly with the LVEDP.

Clinical Application of Vericor Technology – Heart Failure

The Vericor technology is intended to be used in the management of heart failure. There are approximately 5 million patients in the United States with heart failure. There are approximately 550,000 new cases of heart failure each year. Mortality associated with heart failure is approximately ten percent per year. The cost of caring for patients with heart failure is high approximately 26 billion dollars in 2004, two-thirds of which is attributable to hospitalization and nursing home care. There are more than one million hospitalizations per year for heart failure.

The clinical management of heart failure is based primarily on a clinical assessment of the patient’s symptoms and findings on physical examination. However, it is believed that physicians in fact cannot accurately assess the severity of heart failure on a clinical basis, and that if LVEDP were able to be measured routinely and non-invasively that heart failure could be better managed using LVEDP level as a target. This approach therefore may be expected to reduce the number of acute episodes of heart failure exacerbation requiring emergency room visits and hospitalizations.

There are some recent data to support this view. Medtronic, Inc has been developing an implantable hemodynamic monitor which monitors right heart pressures. Right heart pressures tend to correlate with left heart pressures such as LVEDP. In a preliminary study of implantable hemodynamic monitors in 32 heart failure patients, implantable hemodynamic monitoring led to a 57% reduction in hospitalizations compared to historical data in the same patients.

The COMPASS-HF trial, was a larger more rigorous prospective randomized study of 274 New York Heart Association Class III and IV heart failure patients, all of whom had hemodynamic monitors implanted. This study found that in patients in whom the implantable hemodynamic monitor data were made available to their physicians that there was a 22% reduction in the primary endpoint - heart failure related events – compared to patients in whom the implantable hemodynamic monitor data were not made available to their physicians. However, this reduction did not reach statistical significance. In a subgroup analysis, the heart failure related events decreased 41% in the New York Heart Association Class III patients; this decrease was statistically significant. Of note, in evaluating clinical trials subgroup analyses carry much less weight than the primary analysis in the entire study population. The COMPASS-HF study has been reported at a national meeting but has not yet been published in the scientific literature.

The Vericor technology might be deployed in the hospital setting, the doctor's office/clinic setting, or be used at home.

Issues with Respect to Current Vericor Technology

Data from Limited Range of Patients

While the published data demonstrated a highly significant correlation between PAR and LVEDP, these data were generated in a limited range of patients. For example, there are almost no data on women. Also, there is a need to determine if specific disease states might alter the relationship between PAR and LVEDP (e.g. chronic lung disease, right heart failure, hypertension, etc).

Availability of Continuous Arterial Blood Pressure Monitor

The technology is dependent on a non-invasive device for continuous recording of arterial blood pressure (generates a continuous signal and not just systolic and diastolic blood pressure). The present system uses a radial artery tonometer device, however the Japanese manufacturer (Colin Medical Instruments, Corp), has reportedly discontinued making this product. Another technology for continuous recording of arterial blood pressure involves finger tip plethysmography. A Dutch company (FMS Finapres Medical Systems BV) manufactures a product to do this but reportedly charges a high unit price (>~\$30,000). Either the Company will have to work out a supply arrangement with the Dutch company at a reasonable unit price, find an alternative supplier or produce its own device for continuous recording of arterial blood pressure. Fortunately, the finger tip plethysmography technology is quite old so that one might expect that there would not be insurmountable patent barriers for the Company developing a product based on this technology (although I have not explored the intellectual property issues). If a new continuous arterial blood pressure device were incorporated into the Vericor system an amended regulatory filing would need to be made with the FDA and proof would need to be furnished that the modified system was equivalent to the currently approved system.

Possible Incorporation of Cardiac Output Monitoring Technology

It would be desirable to combine LVEDP measurement with measurement of cardiac output (total blood flow out of the heart) from two perspectives. From the physiologic perspective, one wishes to detect heart failure patients with excessively elevated LVEDP. LVEDP may be reduced pharmacologically. However, if LVEDP is reduced too much, then the ability of the heart to pump blood will be compromised and cardiac output will fall to undesirable levels. However, if one simultaneously measures LVEDP and cardiac output, then one can titrate the management of heart failure by reducing LVEDP when needed but not beyond the point where cardiac output is excessively reduced. LVEDP and cardiac output measures could also be used to adjust the programming of biventricular pacing devices that are used in the treatment of heart failure. From the commercial perspective, as discussed below, the foundation patent for the Vericor patent was issued on March 8, 1994 and has limited remaining lifetime (by my calculation expiring in 2011 or 2012 – see below). It would be useful to add an additional patented technology to the Vericor system that adds real clinical value in order to maintain an intellectual property barrier to competition.

Currently, there is limited availability of fully non-invasive systems for measuring of cardiac output. Cardiodynamics International Corp. produces a cardiac output measurement device which is based on electrical measurements of thoracic impedance. This device has not gained acceptance in the hospital market, but the company has been able to place a substantial number of devices in doctor's offices. One might expect that on a physiological basis that this system might not be able to accurately estimate cardiac output in heart failure patients where the fluid content of the thorax (particularly in the lungs, heart and great vessels) may vary significantly between measurements. However, the literature on this subject could be investigated (not done within the context of this report) and a possible relationship with Cardiodynamics explored.

Dr. Richard Cohen's laboratory at MIT has developed a new technology for continuous monitoring of cardiac output from analysis of a continuous arterial blood pressure signal. There are several publications on this technology verifying the validity of the method in animal studies. Two patents have been applied for. These studies used an intra-arterial recording of arterial blood pressure. The accuracy of the technique needs to be verified in humans using a non-invasive continuous arterial blood pressure recording. This technology would be convenient to merge with the Vericor technology because both would use continuous arterial blood pressure recordings as input. There is a potential of licensing this technology from MIT.

Intellectual Property

A detailed analysis of the company's patent portfolio is beyond the scope of this report. Also, legal aspects of patent issues need to be reviewed by patent counsel. The following observations are subject to such a review.

The foundation Vericor patent, US Patent 5,291,895, was issued March 8, 1994. US patents issued prior to June 8, 1995 expire the later of 17 years from date of issue or 20 years from date of filing. The patent is listed as having been filed December 29, 1992 – however material in this patent may have been included in earlier filings which were subsequently abandoned or foreign filings. In any case, it appears to me that the claims in this patent would expire either in 2011 or 2012. It is expected that some time will be required to develop a marketable product, perform clinical trials, obtain additional regulatory approval, obtain a Class I CPT code, and gain reimbursement coverage. Thus this patent will provide a limited period of protection once a product is successfully marketed.

The company has a second US Patent 6,610,018 and has a third patent in preparation. The company also has a number of foreign filings. These additional patents might not preclude a competitor from producing a product similar to the current Vericor product once the foundation patent 5,291,895 has expired.

Team

Dr. Kevin McIntyre has been responsible for the development of every aspect of the Vericor product and commercial development to date. Patricia Woods is an employee of CVP diagnostics – she is an RN and appears very knowledgeable and capable regarding clinical aspects of the technology. Dr. G.V.R.K. Sharma, a practicing well established cardiologist, is Vice President of Research and Development. Engineers have been hired as needed to perform the technical development. If the Vericor technology is to develop into a successful business a dedicated management team should be brought in for commercial development on an accelerated basis. Dr. McIntyre has indicated that he would like to see this happen.

Dr. McIntyre has assembled a group of well established physicians as advisors and collaborators including Dr. Joseph Localzo who is Chief of Medicine at the Brigham and Women's Hospital. Dr. Localzo is a strong believer in the technology and is willing to lend his name and some personal effort to guiding the company. Dr. Localzo's involvement is a strong positive for the company.

Market Size

There is a recognized need for improving physician's ability to assess the severity of heart failure. In fact, this realization is being promoted by Medtronic which is developing an invasive hemodynamic monitor as discussed above.

A key issue in determining potential market is whether the Vericor device will be configured with a suitable disposable. The disposable might, for example, involve the mouthpiece or arterial pressure transducer. It is important to decide whether the system will involve a disposable, and develop a pricing policy early in the commercialization cycle since Medicare will determine the reimbursement for the disposable based on actual charged price.

For the sake of the analysis below I will assume a disposable price of \$100 – this is somewhat arbitrary since the nature of a possible disposable has not yet been determined. Of note, by comparison Cambridge Heart, Inc which I helped found has disposable electrode sensors priced in the \$75 - \$85 range. A crude estimate of potential market size (assuming 100% penetration which in fact of course would not be expected to be achieved) is given below:

Doctor's Office/ Hospital Device

Assuming that there are 100,000 such sites (offices of cardiologists, internists and general practitioners) likely to adopt this technology and capital equipment has a life time of 5 years, in steady state there would be 20,000 pieces of capital equipment sold per year at an estimated \$30,000 per piece of equipment which would yield an annual capital equipment market of 600 million dollars per year. Assuming that the 5 million patients with heart failure on average have a test done on a quarterly basis that would represent a 20 million tests per year (200 per site per year) and assuming a \$100 disposable that would yield a disposable market of 2 billion dollars per year.

Total Potential U.S. Office Market (fully penetrated): 2.6 billion dollars per year.

Home Market

If a home use version of the Vericor could be developed that patients could use on their own or with the help of relative or caretaker, then this device could be used frequently to monitor the severity of heart failure. Vericor could become to heart failure what a glucometer is to diabetes.

If there are 5 million patients with heart failure and each one buys a home unit every 5 years then in steady state there would be one million units sold per year and assuming a unit price of \$5,000 this would represent a capital equipment market of 5 billion dollars per year. If each patient performed one test per week assuming a unit disposable cost of \$100 then this would represent a total disposable market of \$25 billion dollars per year.

Total Potential U.S. Home Market (fully penetrated): \$30 billion dollars per year.

These potential market sizes are obviously extremely large, and market sizes would still be substantial even if pricings assumed above cannot be achieved and even if market can be only slightly penetrated. Even if a suitable disposable is not developed, or favorable pricing for a disposable cannot be attained, the capital equipment market alone would be very large in the home use market and less so but still quite large in the physician's office/hospital market. There are of course other variant strategies for marketing not considered here such as stand alone testing centers, etc.

Of note, Dr. Loscalzo suggested that general practitioners and internists care for more heart failure patients than cardiologists do, and they are currently limited in terms of reimbursable doctor's office procedures that they can do and therefore the Vericor test may be attractive to them. However, I believe that cardiologists would have to endorse the technology before it is likely to be adopted by internists or general practitioners.

It is likely that one would need to gain acceptance in the doctor's office before one could hope to establish a home care market.

Regulatory

The Company has obtained from the FDA 510K clearance of the technology limited to male patients. Additional filings based on data will be needed to include women in the claim. Additional filings based on data will be needed if a different noninvasive monitoring device other than the Colin Medical Instruments, Corp radial artery tonometer is used to measure arterial blood pressure, and if a cardiac output technology is incorporated into the device.

Reimbursement

Reimbursement for medical services and procedures involves coding and coverage. The following discussion would be applicable to the Vericor test done in the physician's office.

Coding

Coding involves obtaining an electronic billing code – CPT code. The CPT code is issued by the American Medical Association. The Company has obtained a Class III which is an emerging technology code. Class I codes lead to Medicare performing an analysis to determine the reimbursement level. Class I codes are difficult to obtain and require both demonstration of efficacy (based on publications of clinical trials in peer reviewed journals) and widespread clinical use (which is difficult to achieve without reimbursement!).

Coverage

Medicare

Once a Class I CPT code is obtained, Medicare will perform an analysis to determine reimbursement level. However, coverage – meaning approved medical indications for use – are normally determined by local carriers who cover one or more states. The Center for Medicare and Medicaid Services (CMS) issues National Coverage Decisions on 5-10% of procedures covered by CPT codes – those in which CMS perceives a need for uniform national coverage. Such procedures are generally those which CMS views as being most significant for Medicare beneficiaries.

Private Payers

Private payers are reluctant to reimburse for new noninvasive diagnostics and may not cover a procedure which Medicare covers. The private payers for example often rely on the issuance of guidelines by national medical societies (or perhaps by the issuance of an NCD by CMS) or technology assessment bodies such as the Blue Cross Blue Shield Association TEC assessment group.

Blue Cross Blue Shield TEC assessment criteria for approving coverage of a new technology are as follows:

1. The technology must have final approval from the appropriate governmental regulatory bodies.
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
3. The technology must improve the net health outcome.
4. The technology must be as beneficial as any established alternatives.
5. The improvement must be attainable outside the investigational settings.

Dr. Localzo mentioned that a number of private payers are setting up “pay for performance” contracts with health care organizations. The health care organizations might be convinced to adopt Vericor technology if it could be clearly demonstrated to reduce costs of caring for heart failure patients – this would require convincing clinical trial data including an economic impact analysis. To demonstrate reduction in cost, the pricing of Vericor might need to be reduced.

Medical Products and Supplies Used Outside of a Physician’s Office

Medicare reimbursement for home use of a Vericor system would require attaining a CMS level II HCPCS code which are issued directly by CMS. I do not have experience with the procedures for acquiring these codes. I suspect that as a practical matter one would first need to obtain the CPT code for doctor’s office use. Similarly, the Company would need to pursue private insurance coverage for home use.

Clinical Trials

Health Outcome Trial

Coding and coverage will tend to be driven most strongly by clinical trials that demonstrate an improvement in health outcomes, as opposed to natural history studies. In the case of the Vericor technology a natural history study, for example, might be designed to determine whether elevated LVEDP measured by Vericor predicts increased hospitalization rates, other heart failure events, or increased mortality. A health outcome study would be designed to determine whether use of LVEDP measurements made using the Vericor technology actually reduces hospitalization rates, other heart failure events, or mortality.

A Health Outcome Trial for Vericor might be modeled after the COMPASS-HF study referred to above which was designed to evaluate the effectiveness of an implantable hemodynamic monitor in reducing a composite measure of heart failure events comprising heart failure related hospitalizations, emergency room visits or urgent clinic visits requiring intravenous therapy. This study involved 274 home-based patients. Of note, this study did not achieve its primary objective in the entire patient population (the composite event rate measure was reduced 22% in the entire patient population but this reduction did not achieve statistical significance) but only in a subgroup of patients – patients with New York Heart Association class III heart failure (subgroup analyses carry much less weight from a clinical trials perspective).

A Vericor study should be designed to optimize likelihood of its meeting its primary objective which COMPASS-HF did not. Of note, Vericor by measuring LVEDP may provide more relevant data than an implantable hemodynamic monitor which measures only right heart parameters. On the other hand, the Vericor data is more intermittent than the continuous data obtained from an implantable hemodynamic monitor.

Study design factors that could be considered to improve likelihood of the study meeting its primary objective:

- 1) Instead of just informing physicians of the LVEDP (and possibly cardiac output data) the study protocol could direct physicians how patient's treatment should be adjusted in response. From the information I have available it appears that this was not done in COMPASS-HF and it was left up to the physician to decide how to modify therapy. Since the full COMPASS-HF study has not yet been published I cannot at the moment confirm however that this was in fact the case. Without this provision, physicians may have wide variability in the extent to which they use or not use the LVEDP data in managing their patients.
- 2) Study a larger number of patients.
- 3) Have longer follow-up (COMPASS-HF had a mean follow-up period of 6 months).
- 4) Limiting the patient population to the subgroup (patients with New York Heart Association Class III heart failure) in which COMPASS-HF reported a significant decrease in heart failure event rates.

In my opinion, a multi-center health outcomes study should be central to the Company's development strategy. The study should be done with the version of the product that is to be marketed.

Technology Validation Study

The Company should also collect data on a wider range of patients, in particular women and patients with a range of underlying diseases) to validate the Vericor measurement of LVEDP with a direct catheter measurement of LVEDP. This study can be conducted in patients undergoing cardiac catheterization.

Natural History Study

This study (already planned/underway by the company) can be conducted in hospitalized patients to demonstrate that elevated LVEDP is predictive of duration of hospitalization and heart failure exacerbations. This study would involve performing periodic Vericor measurements and following the patients for varying periods of time.

Competition

The potential competition for the Vericor technology includes:

- 1) Implantable hemodynamic monitors. Medtronic is planning to combine their implantable hemodynamic monitor with implantable defibrillators and/or biventricular pacing devices (both of which are used in the treatment of heart failure patients and themselves may be combined into a single device) and may convince physicians and payers that heart failure patients should routinely receive an implantable device with hemodynamic monitoring capability. If a patient already has an implantable hemodynamic monitor it would seem unlikely that physicians would also recommend a noninvasive test such as Vericor – even if it measures a more directly relevant parameter – LVEDP. On the other hand, Medtronic and other manufacturers might penetrate only a fraction of this market leaving the remaining patients available for non-invasive monitoring.

- 2) Measurement of serum factors such as Brain Naturetic Peptide (BNP) as measures of heart failure. It seems unlikely to me that measurement of such factors would be equivalent to a direct hemodynamic measurement. However, I would recommend (as Dr. Loscalzo suggested) that BNP measurements be included in the clinical studies so that a side by side comparison can be made.
- 3) Competition from products similar to Vericor produced by other manufacturers especially once the foundation patent expires.

My Recommendation of Principal Tasks to Be Accomplished

- Assemble team and develop technology incorporating new blood pressure monitor, possibly cardiac output technology, and new disposable. Clinical testing to verify accuracy of LVEDP and cardiac output measurements in wide range of patients. Obtaining additional needed regulatory approvals. Also, during this time clinical trials are designed, protocols developed, clinical performance sites recruited, human studies approvals obtained.
- Run clinical trials with product developed above: enroll patients, gather follow-up data, data analysis and presentation at national meeting.
- Reimbursement approval after completion of clinical trials. Involves publishing of manuscripts describing studies and obtaining approvals. Most payers will only consider reimbursement after publication of trials in peer reviewed journals.

Summary of Opportunity and Risks

The area of hemodynamic monitoring for heart failure is an important one and there is growing recognition that clinical assessment of heart failure is inadequate to guide optimal therapy. The potential market for a noninvasive technology that monitors LVEDP (and perhaps also cardiac output) is extremely large and therefore commercially extremely attractive. The Vericor technology has generated published data in premier clinical journals which do establish that it is capable of non-invasively estimating LVEDP.

However, there is risk associated with investment in this (or for that matter any) development stage company. Any of the development objectives described above may not be met or could require more time or financial resources to achieve, and other risks and issues (including but not limited to those described above) could possibly prevent the company from being successful.

Information Sources

Information sources used to generate this report include:

Interview with Dr. Kevin McIntyre, Patricia Woods, Dr. G.V.R.K. Sharma

Interview with Dr. Joseph Loscalzo

Biographies of principals

Published journal articles and abstracts

Two issued US patents and one patent application

FDA application for Vericor technology and approval letter

Physician survey conducted by Company

Internal company documents including draft executive summary of business plan dated February

2006 and executive summary of business plan dated October 2005.

CPT coding approval letter and committee review.

Blue Cross and Blue Shield Association TEC Technology Assessment Criteria

Press reports of outcome of COMPASS-HF study

Other public documents describing reimbursement and regulatory procedures

Specific reference citations can be provided upon request.