TITLE: 3D Complete Body Screening (3D-CBS) for Early Cancer Detection Targeted to Reduce Premature Cancer Death at a Lower Cost per Life Saved Compared to Current Cost

ABSTRACT: (Example of a question asked by other competitions: Clearly explain the question or problem to be addressed and the approach to its answer or solution).

Although cancer costs $856 per person per year[1], during the last 50 years the reduction in cancer death was only 5%, yet, with fewer investments, heart disease was reduced by 64%, stroke 74%, while pneumonia and flu were reduced by 58% as reported in 2009 by The New York Times. Experimental data show early diagnosis of cancer saves lives in 90% to 98% of cases. Changes in metabolism associated with cancer cells (up to 70 times greater) is the most reliable information for early detection of most cancer types. To reduce premature cancer death, early detection must be improved. Current diagnostic instrumentation detecting metabolism (Positron Emission Tomography –PET-) is inefficient, requires high radiation to the patient, and expensive examinations. Safe affordable medical instrumentation for detecting such metabolic changes and other biological process changes at the molecular level at a very early stage is possible. Breakthrough 3D-CBS technology as proposed is 400 times more efficient than the current 7,000 PET. It is based on an invention in particle detection approved officially 18 years ago at a major international scientific review held at FERMIlab followed by other inventions by the P.I. in medical imaging applications starting from the year 2000. These innovations maximize signal capture showing minimum abnormal metabolism (or other biological processes), achievable by capturing simultaneously and accurately as many signals as possible from tumor markers at the lowest cost per signal captured. Complex algorithms with the possibility to correlate data received from neighboring detector elements are executed for longer than the time interval between consecutive input data sets, providing maximum utilization of radiation, reducing dosage to a level safe for annual full body screening of asymptomatic patients at high risk as well as enabling early detection and detecting the restart of activity at an early stage in cancer survivors.

SIGNIFICANCE: (Example of a question asked by other competitions: Clearly address how the proposed project, if successful, will have a major impact on the field of cancer research or on the care of patients with cancer. Summarize how the proposed research creates new paradigms or challenges existing ones).

This project challenges existing ones by creating a big impact in oncology with a significant reduction in premature cancer death estimated at 33% reduction achievable within 6 years from when funding is made available. Tests to measure results will be made on a sample of 10,000 people aged 50-75 referring to a location with a constant history of 50 deaths/year in the past 20 years. The cost of this project is $15 million for the construction of three 3D-CBS devices [1] and is estimated to reduce by 40 times the cost for each life saved from premature cancer death. The rationale supporting this claim is detailed in Section 5. This great cost reduction for health care for each life saved and the increased number of lives saved from premature cancer death will create new paradigms to focus more on early cancer detection as supported by experimental data showing that a tumor diagnosed at an early stage has 90% to 98% probability to save the life of the patient, rather than focusing almost exclusively (as done in the past and now) in the development of drugs and therapies attempting to cure cancer diagnosed at a late stage. The proposed 3D-CBS innovative technology is over 400 times more efficient than the current 7,000 PET used in health care facilities. It can capture more accurately more signals from the tumor markers at a lower cost per signal captured, allowing a lower radiation dose for a safe screening on asymptomatic patients and cancer survivors thus enabling early detection.

Anticipated results:

This project is expected to be successful since no one has been able to invalidate the inventor's claims with scientific arguments during ten years of various scientific reviews, plus the innovative sections of the project have been built in hardware proving its feasibility and functioning. While the following estimates used in saving life, cost, etc., are considered by several experts as too conservative (see page 5 of [2] the questionnaire filled out by ABO Project inspectors after four days, and 17 hours of video recorded on site evaluation of the 3D-CBS project), it still shows a significant reduction in premature cancer death at a lower cost per life saved. Following are the estimates used:

[1] The cancer cost of $856/per person per year is calculated by dividing U.S. cost of cancer for 2010 of $263.8 billion by the U.S. population of 308 million.

- It is estimated that the increased percentage of lives saved annually from premature cancer death is 33% and is reachable in 6 years from when the funding of this project is made available,
- The rationale supporting this claim is described in detail in Section 5. However, briefly, here it can be said that if early detection saves lives in 90% to 98% of cases, then a 400 times efficiency improvement in capturing and processing data from radioisotope tumor markers emitted from the patient's body enabling safe screening and early detection, can quite conservatively, claims a 33% reduction in cancer deaths.
- It is estimated that the cost per life saved will be reduced by 40 times compared to current costs,
- It is estimated that the overall project cost for the construction of three 3D-CBS devices will be $15 million over three years,
- It is estimated that the first results will be measurable within three years.

This approach challenges existing approaches that until now have not provided a substantial reduction in cancer death and will create new paradigms in the following areas:

1) The possibility to obtain clear and direct quantitative results relative to the reduction of premature cancer death, rather than being limited to an approach of generic research not quantified. The applicant should be requested to indicate the estimated results, together with their cost and time to accomplish them. Tests of verification will establish the validity of the research (for example, annual tests on a sample of 10,000 asymptomatic people a group aged 50-75 referring to a location with a constant history of 50 deaths/year in the last 20 years. Validity of the research will be proven when the number of deaths -50- is lower in the future),
2) Shift from current research that continues to focus on pharmacological cures and radiotherapies (that frequently do not cure radical cancer) to research on early cancer detection.
3) Use of Positron Emission Technology to detect markers due to metabolic changes which provide precise measurements of nutrient consumption in a unit of time in different areas of the body (or detects other abnormal biological processes) for early detection instead of just measuring the tumor dimensions of late stage cancer.
4) Reduction of the radiation dose to the patient. Before the advent of this discovery it was not possible to use all information from the radiation, and it was necessary to administer to the patient a high radiation dose in order to obtain a small amount of information. The basic innovation by the P.I. of 1992 makes possible an improvement to positron emission technology, enabling a great increase in efficiency, thus reducing the radiation dose and offering a new screening opportunity.
5) Improvement of the quality of the information (data displayed in images) provided to the physician offers more accurate information relative to minimum abnormal metabolism (or other abnormal biological processes) which is quantified accurately for each part of the body (hot spot) together with its location in the organs
6) Increase in sensitivity and specificity as well as reduction of "false positives" and "false negatives",
7) The increase in sensitivity will make it easier check that all cancerous cells have been removed with surgery or killed by a chemotherapy and/or radiation therapy treatment,
8) Reduction of costs and time necessary for the examination without lowering quality,
9) Improvement of other sections of PET device, instead of attempting to improve crystals that have already an efficiency of 95%, allowing the possibility to use economical crystals which are no longer required to have the characteristics of ideal crystals,
10) Replacement of several current, less efficient examinations thanks to full body coverage with a long detector. Also allows simultaneous capture of data from dynamic biological processes within the entire body,
11) Reduction of health care costs per life saved instead of increasing costs,
12) Monitoring in the case of a known cancer to detect the restart of activity in a tumor, offering cancer survivors the advantage of undergoing affordable repetitive examinations that are safe, targeted to early detection without the risk of making their condition worse by administering high doses of radiation,
13) Possibility to open doors to research in other fields such as DNA, blood flow, perfusion, etc. that only a more accurate device with higher sensitivity can provide.

RESEARCH PLAN:

1. *Background:* (Example of a question asked by other competitions: **Present the rationale behind the proposed project, emphasizing the pressing problem in cancer research that will be addressed).**

WHAT IS CANCER? - Cancer is a disease characterized by the **mutation of normal body cells** into cancerous cells whose main characteristic is reproducing themselves out of control, increasing in volume to the detriment of neighboring tissues, also invading other distant tissues, transported through the blood vessels (metastasis). Cells become cancer cells because of damage to DNA. Instead of dying (apoptosis), cancer cells outlive normal cells and keep forming new abnormal cells with the same DNA damage as the first cells. Their shape is different due to a different ratio between nucleus and cytoplasm and their structure is irregular. Because they grow faster, **cancer cells need more nutrient** (up to 70 times more than normal) thus showing an abnormal metabolism.

WHAT CAUSES CANCER? - We know many causes of cancer. The main ones are: heritage, chemical products (smoke), virus, bacteria, radiation, etc. However, we do not know all of them and most importantly **we cannot know when cancer starts developing**.

HOW HAS THE CANCER CALAMITY BEEN ADDRESSED? Cancer is a serious calamity [3] affecting over 40% of the world population during their lifetime [4], and over 10% will die prematurely (over 7 million/year in the world) due to that disease. In the face of such a calamity that causes more premature deaths annually than any war, and therefore which should be enemy number one, we (the world) are still losing this battle [5] perhaps because a gigantic strategic error is being made. During the past half century, although enormous investments have been made (in the United States alone $8 billion/year for research [6] and cancer costs $263 Billion/year [7]), the cancer calamity has been almost exclusively addressed through the study and development of new drugs and therapies targeted to the cure of cancer diagnosed at a late stage. These investments have yielded meager results [8] in terms of a reduction in cancer deaths of less than 5% during the last 50 years [9] and it even shows an increase by 20% from 1975 to 2007 as reported by the National Cancer Institute –NCI- at [10].

HOW SHOULD THE CANCER CALAMITY BE ADDRESSED? Experimental data [11] confirm that **cancer diagnosed at an early stage has 90% to 98% probability of resulting in a life saved**. (Diagnosis at a late stage for lung cancer, the number one killer, shows a survival rate of less than 10% [12]). It is therefore necessary to address research toward early cancer detection to achieve the capability of capturing the first signals that show the start of a mutation of normal body cells into cancerous cells rather than to focus almost exclusively on the development of drugs and therapies targeted to cure cancer at an advanced stage. In order to understand **which signals are important to be detected**, it is necessary to know how cancer initially manifests itself.

HOW DOES CANCER MANIFEST ITSELF? Cancerous cells differentiate from normal cells through different signals that provide information about their mutation. **These signals are related to CHANGES in: ODOR, TEMPERATURE, TISSUE DENSITY, FLUORESCENCE, METABOLISM, PERFUSION, ETC.**

Among all these signals, **the one most reliable** for early detection and useful for reduction of "false positives" and "false negatives" is the **change in metabolism** because it provides information at the molecular level and because cancerous cells take from 5 to 70 times more nutrient with respect to normal cells.

2. *Hypothesis and Specific Aims:* (Example of a question asked by other competitions: **Concisely state the hypothesis and/or specific aims to be tested or addressed by the research described in the application).**

WHAT IS THE BEST TECHNIQUE TO IDENTIFY CELL MUTATION (EARLY DETECTION)?

Among all techniques to detect signals generated by body cell mutation into cancerous cells (odor, temperature, etc.), **the technique that provides the most reliable signals is the one measuring changes in metabolism and other biological processes** at the molecular level (although in multimodality with others). This technique called '**positron emission technology**' (See Figure 1) captures and counts in a unit of time the signals from the radioactive tracer placed on the molecule of the nutrient to the body cells (or on other compounds

showing biological processes). Because cancerous cells take more nutrient compared to normal cells, positron emission technology allows identification of which cells (or a group of cells) take more nutrient than normal, thus a suspected cancer site. (In comparison, CT, X-ray, mammography and all other devices based on tissue density measurement are much less reliable for early detection because 1 cm^3 of tissue consists of about one billion cells, too many to be considered early stage. In addition, some types of cancer develop without changing density).

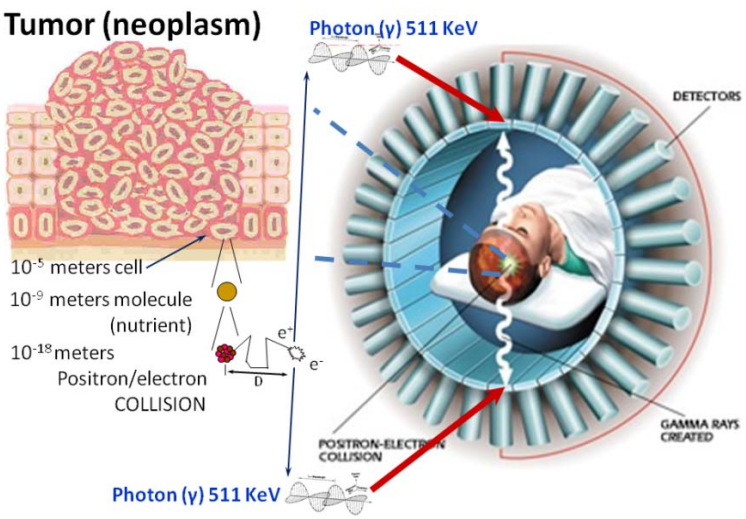


Figure 1 Representation of the principle of operation of Positron Emission Technology. Cancerous tissue (neoplasm) is identified by its natural nutrient uptake (for example: glucose molecules) labeled with a radionuclide. These radionucleides are produced in a cyclotron and are used to label compounds of biological interest. The positron e^+ emitted by the radionuclide, after traveling for a distance D, annihilates (collides with) an electron generating two photons that are emitted in opposite directions. These pairs of photons (or gamma rays) hit two locations on the detector (crystals coupled with sensors converting light into an electrical signal, that surround the body of the patient) almost at the same time (called in-time coincidence). The task is to capture and accurately measure (energy, arrival time and x, y, z coordinates) as many as possible of the emitted 511 KeV photon pairs in-time coincidence that reveal the concentration quantity of the radioisotopes (or nutrient in the body cells). The goal is not just to capture as many as possible of the 511 KeV photons emitted from the patient's body, which provides the benefits of early detection and lowering the amount of radiation needed to be administered to the patient, but also does this at the lowest possible cost per each 511 KeV photon captured.

After having verified that positron emission technology provides the most reliable signals related to cancerous cells mutation, one should also realize that the current over 7,000 Positron Emission Tomography (PET) devices that make use of the principle of operation of positron emission technology, because of their low efficiency, cannot provide early detection because they capture with inaccurate measurements only about one signal out of 10,000 from the tumor markers (and they require administering a radioactive dose to the patient that is over ten times higher than the one recommended for screening asymptomatic people by the International Commission for Radiation Protection -ICRP).

Theoretical efficiency:

Current PET efficiency can be improved theoretically by 100,000% (practically 40,000%). The theoretical number of pairs of photons in-time coincidence generated by the positron-electron annihilation that can be captured by detectors of different length (FOV) has been reported in several scientific articles [13], [14], [15], [16], [17] and is represented by the curve shown in Figure 2.

Where photons are lost in current PET:

Before attempting to improve any system, it is necessary to determine where the inefficiencies are, how great they are, how they can be reduced, and by how much and at what cost. Measuring the efficiency of current PET is straight forward. Simply divide the number of "true" 511 KeV pairs of photons captured by the PET device by the number of 511 KeV pairs of photons emitted, which will depend upon the radiation dose injected into the patient's body. Figure 3 shows in six sections where photons are lost in current PET:

Section (1). Photons lost in the patient's body: Only 15% remain available for being captured because the rest is scattered or absorbed into the body. These data are supported by simulations from scientists at Los Alamos and universities (see [13], [14]).

Section (2): Field-of-view (FOV): Photons from outside the detector area are lost.
Section (3): Solid angle: Some photons from within the detector area are also lost because detector is not covering full solid angle.
Section (4): Detector stopping power: Detector crystals do not have perfect stopping power and do not capture every photon in range.
Section (5-6) Electronics (combined to detector assembly): The efficiency of stages 5 and 6 is equivalent to 8%, calculated by subtracting from the total inefficiency and the sum of the other inefficiencies.

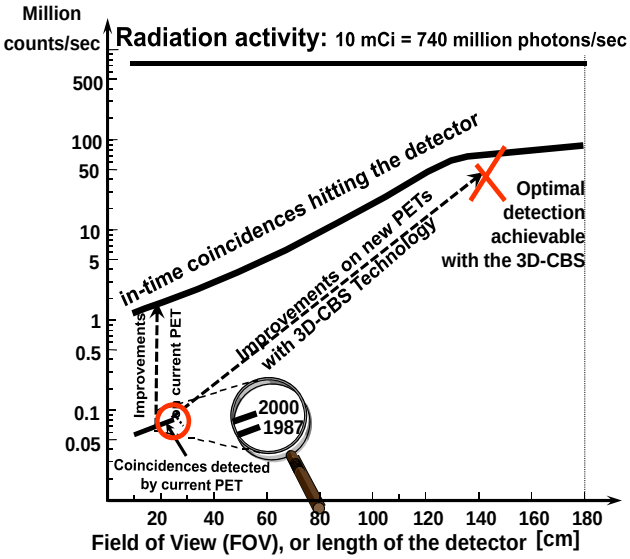
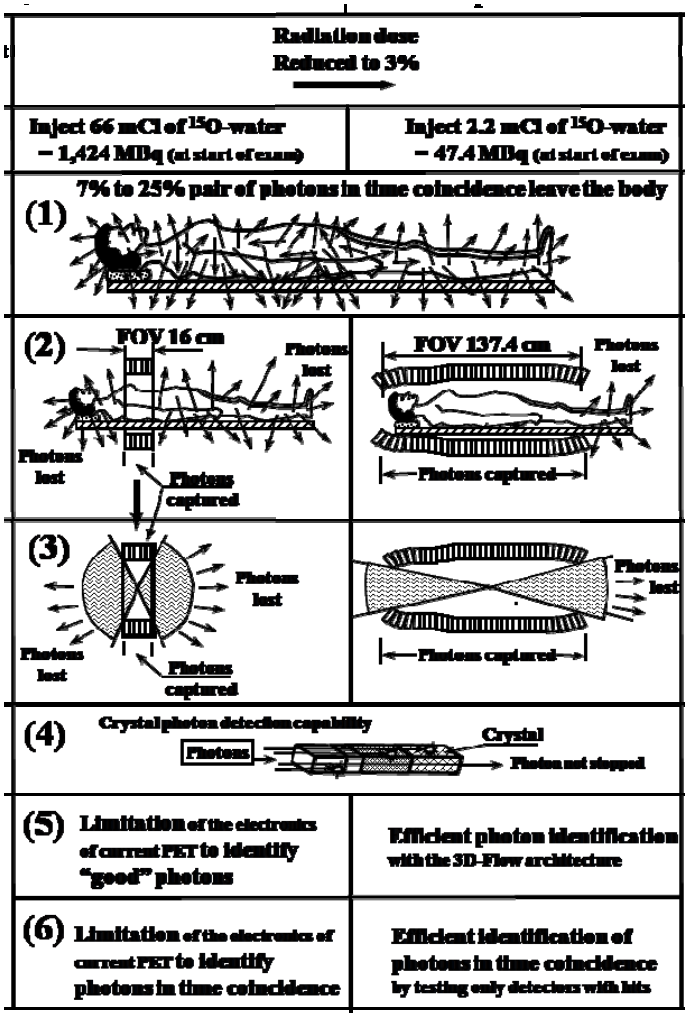


Figure 2. The graph shows that theoretically the number of counts per second can be increased from about 50,000 per second (bottom left) to about 50 million per second (top right). The example shows, for an activity of 10 mCi, e.g., the approximate calculation of the number of pairs of photons in-time coincidence that hit detectors with different FOVs, assuming a patient weigh about 170 pounds. Fewer photons will hit the detector for heavier patients, while more photons will reach the detector for a smaller patient.



Current PET **3D-CBS**

Figure 3. shows the difference in efficiency between the current PET (left) and the 3D-CBS PET with the 3D-Flow™ (right). Areas of inefficiencies are detailed in Sections 2 through 6. Only the innovation of the electronics in sections 5 and 6 allows for the improvement in efficiency, in a cost-effective manner, in sections 2 and 3.

It is clear from this analysis that the section that needs serious study and improvement is the last one which provides only 8% efficiency. Section 1 has efficiency related to a natural phenomenon that cannot be changed. The losses of Sections 2 and 3 can be addressed by increases in length and solid angle only if the electronics of sections 5 and 6 are not overwhelmed by the increased amount of data to be analyzed. Although Section 4 denotes the area in which much effort and money has been invested during the past decades, crystal efficiency has been at 95% for the past half century, some (such as LSO) have nearly ideal characteristics and there is not much room for further improvement.

IN ORDER TO ACHIEVE TRUE SAFE EARLY DETECTION, IT IS THEREFORE NECESSARY TO FOCUS ON GREATLY INCREASING THE EFFICIENCY OF THE TECHNOLOGY USED IN CURRENT PET.

The fundamental problem to be solved in order to obtain such improvements is the same as the one already faced in High Energy Physics (HEP) experiments, specifically about the **impossibility of making accurate measurements on ALL data related to radiation (called events) that arrive at very high data rates from the detector** as the result of millions of collisions between particles generated by accelerators such as the CERN [18] collider LHC [18]. Accurate measurements are necessary in order to be able to distinguish "good events" from those carrying no useful information that are considered background noise. For example, LHC detectors can have something like 600 billion events per second. If all that data were saved for study at a later time, it would fill up every hard drive on the planet in only one day. Hence, because of the need to analyze all of them in real-

time, a sophisticated trigger [18] system was created to analyze, select, and save in real-time about one hundred of the highest quality collision events per second (this number of events to be saved is related in HEP [18] to a parameter called "occupancy" for a specific experiment that is estimated by theoretical physicists, where as in Medical Imaging it is determined by the maximum radiation dose that one can give to a patient).

A similar problem also exists in Medical Imaging. The two aspects are related to the efficiency of the system in particle detection. **The solution is much more important for Medical Imaging than for Particle Physics.** In Particle Physics, inefficiency only causes a delay and a higher cost in discovering new particles. **Much more serious and damaging is inefficiency in Medical Imaging** devices because not only is there a **higher cost to health care** (ultimately to the patient), but it also **requires administering a higher radiation dose, dangerous to the patient, does not provide the necessary sensitivity to diagnose cancer at an early stage, and is not accurate enough to be able to reduce "false positives" and "false negatives."** (See [19])

THE SOLUTION OF THE FUNDAMENTAL PROBLEM: THE P.I.'S INVENTION RELATIVE TO THE TRIGGER

The P.I.'s work on a high-performance 3D-Flow (see Figure 4) programmable, technology independent parallel-processing system was presented to the scientific community in Sept.-Oct. 1992 at three international conferences in Europe at Annecy, France [20], in United States at Corpus Christi, Texas [21] and IEEE-NSS-MIC in Orlando, Florida [22] where different ideas [23], [24], [25], and approaches to the implementation of fast, efficient trigger systems were discussed. The 3D-Flow (see Figure 4) is a parallel-processing system capable of neighboring data correlation with no boundary and of real-time execution of complex algorithms for a duration longer than the interval between two consecutive input data. In addition to solving the problem for different HEP experiments, this innovation can detect very accurately all characteristics of 511 KeV pairs of photons in PET.

In 2000, the P.I. published scientific articles and books describing the advantages of his innovations [29],[26] in Medical Imaging and provided the solution for capturing over 400 times the number of photons more accurately and more cost-efficiently**.**

The new concepts are proven by logical arguments in articles, [27], [28], [29], [30], **by simulation** (see Sections 11, 12 of [27], Appendix of [28], Chapter 13 of [29])**, by construction in hardware of the innovative parts** (see Figure 9 and [31]) **and by experimental results from third parties** (i.e. Siemens [32]) **that confirm the P.I.'s claims**.

The P.I. received many letters of recognition from emeritus scientists in the field [33], from peer reviewed articles, from public scientific reviews, for example at Fermi National laboratory in 1993 at the request of the SCC Director who was also the Director of Fermi Lab. He received $150,000 during the SSC closeout to bring his valuable work to a stage where it could be reopened with more government funding. However, funding to complete the project has not been provided, despite the invention being officially approved and recognized 18 years ago as benefitting mankind.

The P.I. made the first demonstration of the proof of concept at the IEEE-NSS-MIC Industrial Exhibition in 2001, in San Diego (CA). At the Industrial Exhibition booth, the P.I. set up the hardware demonstration of the 3D-Flow architecture implemented in electronic circuits and input/output test boards to show the execution of real-time photon detection algorithms, centered on each electronic channel of the processor array (3x3 "local maxima" with no boundary, Depth Of Interaction –DOI-, etc.). This system was built using two prototype boards from Altera (each accommodating a Field Programmable Gate Array circuit FPGA EP20K1000), interfaced with two other prototype boards, one to input data from switches and another to display results on LED. The user could select two sets of input patterns of data (configuration of the input switches) that would simulate two subsequent events received from the detector. The results were displayed on LED showing if a "local maxima" was detected, while signal waveform on the oscilloscope proved the algorithm execution in a given number of steps and at the expected speed. The proof of concept allowed extraction of the parameters (power consumption, number of processors per board, etc.) to build an industrialized modular system based on IBM PC boards as described in [34].

Further reviews not only of the innovative electronics but of the entire Three-Dimensional Complete Body Screening (3D-CBS) system took place on several occasions. One of those was in 2003, in Dallas, Texas (see video at www.3d-computing.com), and the final report by the review panel is available at [35] www.crosettofoundation.org/uploads/100.pdf. In 2008 an International review was conducted in Rome, Italy.

Description of one of Crosetto's innovative concepts that enables acquiring data at a very high input rate while simultaneously allowing necessary time to accurately analyze the information

The figure on the right shows the flow of data during twelve clock cycles in an electronic channel of the 3D-Flow parallel-processing system, that, at each clock, acquires a data set as input and provides a result as output, allowing a processing time for each data set, in each layer, for a time longer than the time interval between two consecutive input data sets.

Each layer of the 3D-Flow parallel-processing system consists of an array of processor with fast bidirectional data exchange capabilities between adjacent processors within the array (North, East, West, South –NEWS-).

The entire algorithm must be executed from start to finish in each 3D-Flow processor in order to exchange data with adjacent processors and keep consistency with the same set of input data.

Processors at the same x-y location in arrays at different layers are connected via Top-Bottom ports (as shown in the figure) to form an electronic channel.

In the example, a 3D-Flow processor is replicated five times in the 3D-Flow parallel-processing system.(The number of times the 3D-Flow processor is copied is equal to the ratio between the maximum algorithm execution time and the time interval between two consecutive sets of input data).

The figure shows an example where the maximum algorithm execution time is 500 nanoseconds and the time interval between two consecutive sets of input data is 100 nanoseconds. (Thus it is: 500/100 = 5).

A 3D-Flow processor is represented in the figure with three functions: a) a "bypass switch" to bypass data, represented as a long arrow in a rectagular box, b) a "bypass register" that is an output register, represented as a rectangular to the right of the arrow and c) a CPU or Central Processing Unit, represented as a rectangul below the arrow.

A "bypass switch" sends a set of data to its CPU and transfers ("bypasses") four sets of data to the next layers to the right in the figure.

Time	Proc (1d)	Reg (1d)	Proc (2d)	Reg (2d)	Proc (3d)	Reg (3d)	Proc (4d)	Reg (4d)	Proc (5d)	Reg (5d)
1t	1									
2t	1	i2								
3t	1	i3	2							
4t	1	i4	2	i3						
5t	1	i5	2	i4	3					
6t	6	r1	2	i5	3	i4				
7t	6	i7	2	r1	3	i5	4			
8t	6	i8	7	r2	3	r1	4	i5		
9t	6	i9	7	i8	3	r2	4	r1	5	
10t	6	i10	7	i9	8	r3	4	r2	5	r1
11t	11	r6	7	i10	8	i9	4	r3	5	r2
12t	11	i12	7	r6	8	i10	9	r4	5	r3

Table 1 shows the sequence of the sets of data in different times in one 3D-Flow electronic channel. A set of data contains information received at a given time from a "detector channel" of the 3D-CBS detector.

In the first column (on the left of the table) is shown the time "t". Values below the columns labeled with Proc (1d), Proc (2d), Proc (3d), Proc (4d), Proc (5d) represent the sets of data that are processed by the 3D-Flow processor in the specific "t" time.

Values labeled with ix and rx below columns Reg (1d), Reg (2d), Reg (3d), Reg (4d), Reg (5d) are input data and output results respectively, that flow from register to register in the electronic channel chain toward the exit point.

One should note that data-package No. 1 stays in the first processor of the first layer for five cycles, while four data sets (i2, i3, i4 and i5) are passed forward (via the "bypass switch") to the next layer.

For example at clock 6t, while processor 1d receives data set No. 6, at the same time it outputs results r1 relative to the data processed previously. This result "r1" is then transferred to the output of the 3D-Flow system without being processed by other layers.

One should note that input data and output results in the 3D-Flow system are intercalated in such a way that on the left there are only input data, on the right only results and in the center are intercalated, increasing the number of results toward the exit of the system.

www.crosettofoundation.org/uploads/291.pdf

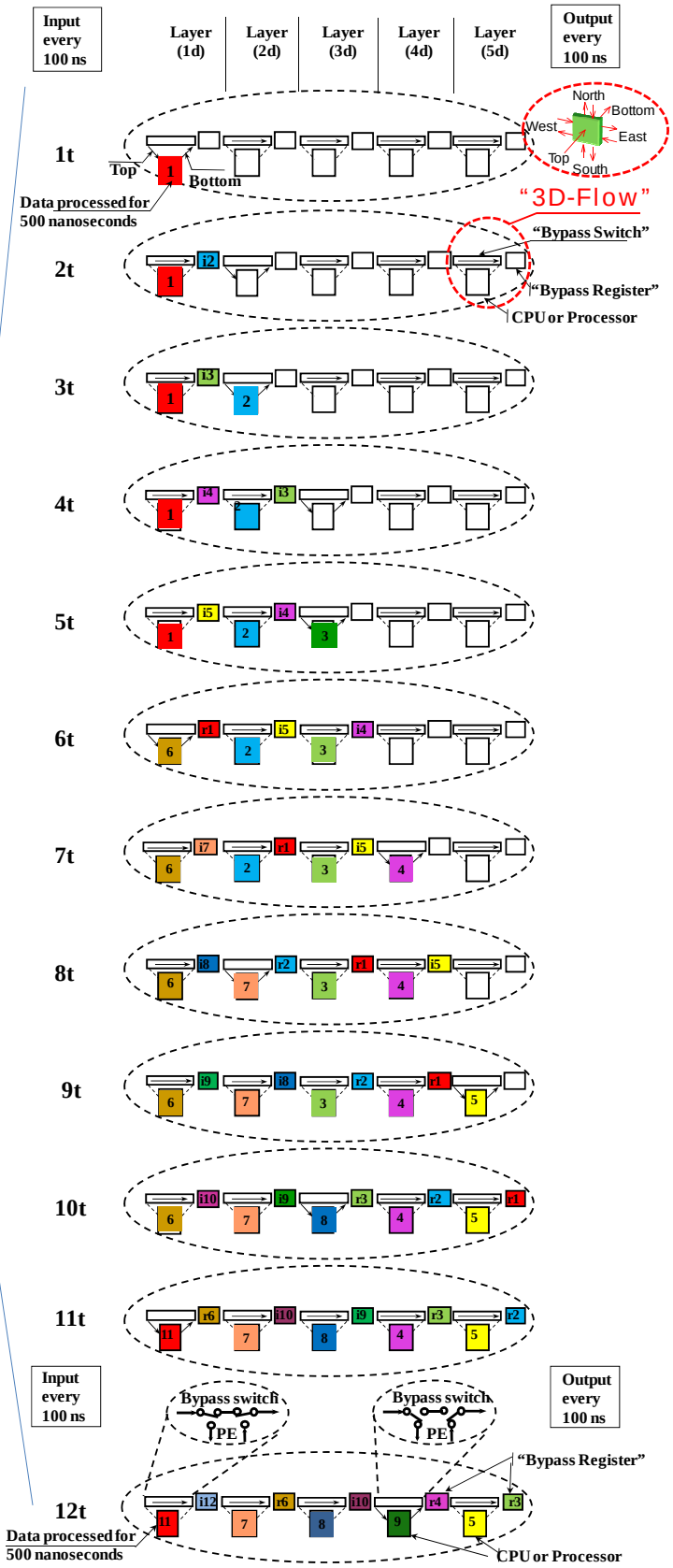


Figure 4. 3D-Flow architecture. The system architecture consists of several processors arranged in two orthogonal axes: One layer is an array of 3D-Flow processors, where each processor is interconnected to its four neighbors through North, East, West and South ports. Several layers, assembled one adjacent to another interconnected through bottom-top ports (as shown in figure) to make a system, is called a "stack." The first layer is connected to the input sensors, while the last layer produces the results processed by all layers in the stack. Data and results flow through the stack from the sensors to the last layer. An electronic channel consists of one set of 3D-Flow processors connected from the bottom port of one chip to the top port of an adjacent chip

KEY INNOVATIONS OF THE 3D-CBS TECHNOLOGY

A solution for safe screening targeted to early cancer detection has been in existence for over a decade, documented in several publications [27], [28], [29], [36], [30], [31], [37], [38], [39], [40], [41]. It is an innovative technology that allows building a device over 400 times more efficient than current PET. Figure 5 summarizes the P.I.'s innovations described in more detail in the references.

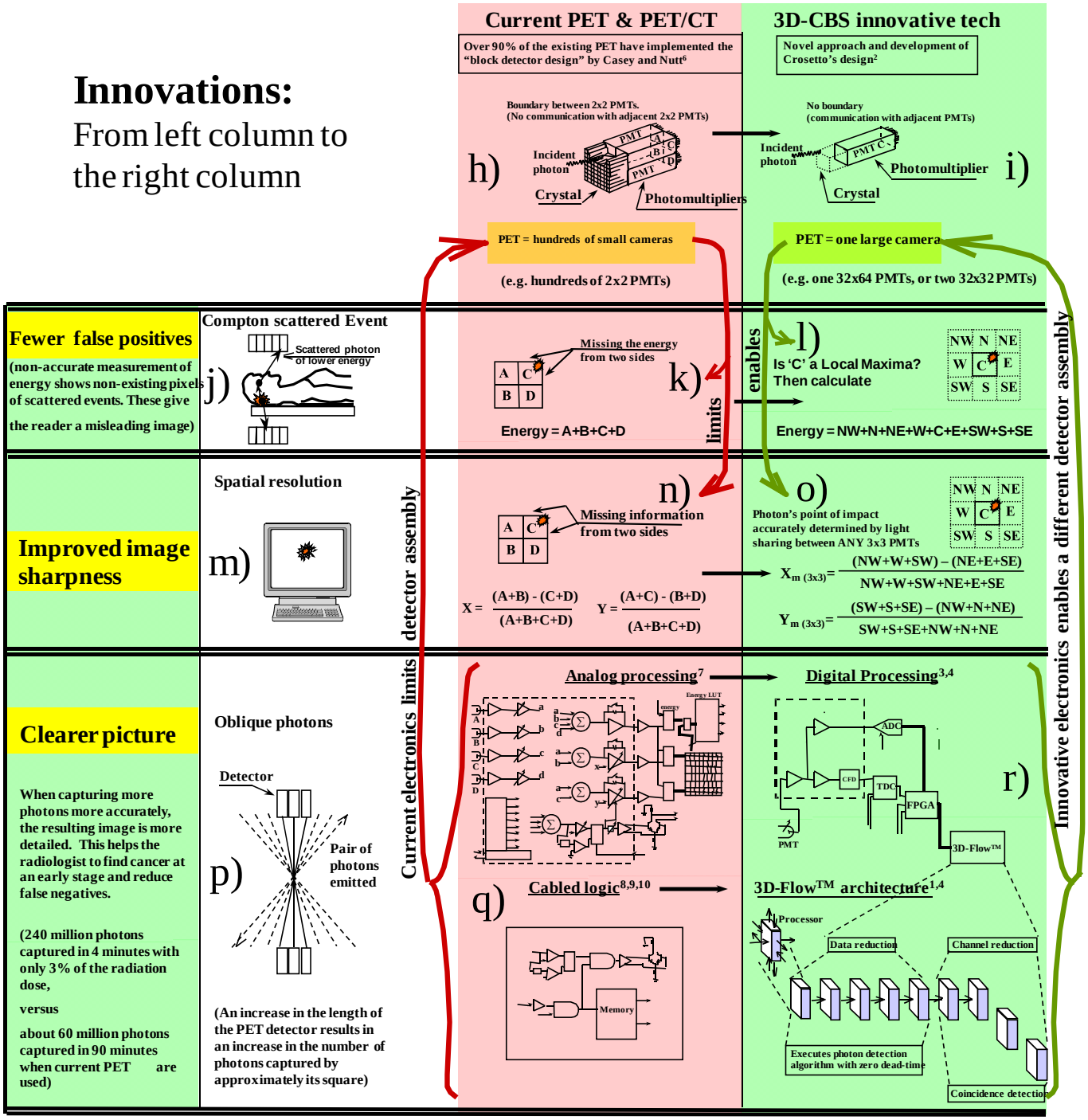


Figure 5. The three titles in the left column summarize the advantages of the 3D-CBS with respect to current PET in a language addressed to the doctor/radiologist. In the second column, supporting the statement to the doctor/radiologist is illustrated the corresponding physical phenomenon that make it possible to obtain such advantages. The third column shows the limits of current PET and the last column to the right how such limits are overcome with the 3D-CBS technology. Boxes j, k, and i concern the energy resolution; m, n, and o the spatial resolution; and p, q, and r the sensitivity. The key innovations start from the feature in box "r," which enables the innovation in box "i," which in turn enables the innovations in box "l" and "o." Additional innovations are achieved as a result of synergy of all three, allowing huge and cost effective improvements to the five parameters listed in Section xxx which ultimately provides accurate measurements at a lower cost for each photon captured.

How claimed objectives are achieved with the P.I.'s innovations

The key elements of the P,I,'s innovative technology that allow building a device of the type 3D-CBS can be divided into five main areas: electronics, an improved and simplified detector assembly, the capability of executing complex real-time algorithms, increased detector length (FOV), innovation in the visualization of the information obtained.

These five parameters are:

1. Accurate measurement of the total photon energy [42], using the signals received from 9 electronic channels (rather than 4 as used in current PET), that allows discrimination of "good events" from "scatter events" [43].
2. Accurate measurement of the photon arrival time, the Time-of-Flight , (TOF) that allows discrimination of "good events" from "randoms" and "multiple" [44] events.
3. Accurate measurement of the spatial resolution referring to the 'x' an 'y' coordinates [45] (distance in the axial direction and distance at a 90° angle to the axial direction of the impact of the photon onto the surface of the crystal. Centroid is calculated based on a 3x3 array rather than the 2x2 array used in current PET)
4. Accurate measurement of the photon Depth Of Interaction (DOI) [46] which eliminates the parallax error.
5. The improved signal-to-noise ratio makes it possible because of the capability of the 3D-Flow system to execute complex algorithms in real-time, while sustaining at the same time a high input data rate.

The constant question the P.I. had while conceiving all his inventions was "how will it be possible to extract all the particle's characteristics, make very accurate measurements, reject noise, and achieve maximum efficiency while building an economical hardware?"

As an example a figure extracted from one of P.I. patents reported herein (Figure 6) illustrates how accurate measurements and low cost can be superior to other approaches.

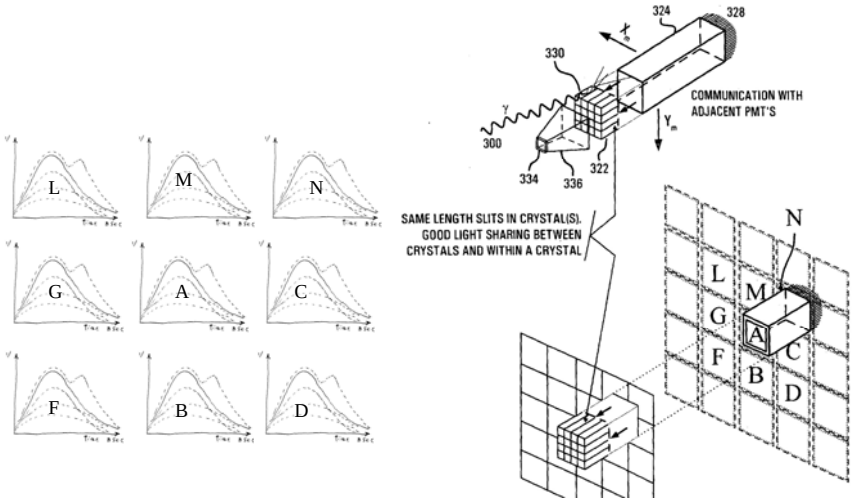


Figure 6. Key innovations extracted from one of P.I.'s patents.

In fact, each 3D-Flow processor can perform accurate measurements by analyzing nine data (8 neighboring channels), obtaining an accurate photon's energy by summing the area of those signals, can improve photon's arrival time by balancing arrival time of nine signals, can measure accurately x, y spatial resolution by interpolating the area of signals north-south and east-west. Can measure Depth of Interaction of techniques described by other authors during the past decades as reported in P.I.'s book [29] at page 109, but most importantly it can eliminate the parallax error with P.I. technique illustrated in the figure xx where a signal from APD 334 received through guideline 336 is interpolated with a signal from PMT (or APD) 324.

What is important in the P.I.'s concept is not the use of the finest crystals, the best sensors and the fastest electronics, but rather the system architecture of the 3D-Flow electronics, detectors, sensors and geometry allow the latest and cheapest technology to be used while obtaining the best over all measurements. In the P.I.'s approach the surface to be covered with sensors is minimal because of the use of the light guides, but more importantly because of the processing power of the 3D-Flow system array that provides the very important feature of good noise rejection. APD and MPP technologies are advancing and the programmability of the 3D-Flow system can use the one that becomes the most cost-effective any time. This means it can always compete for superiority with other systems that do not focus on such a small surface to cover with sensors and that do not foresee the use of economical crystals.

The P.I's inventions provide a simple system although the detector length has been increased and more information is extracted using more economical crystals. The result is a much more powerful system not previously envisioned at a reasonable cost. The optimized improvements are the right balance between the extension of the Field Of View (FOV), the reduced cost of the crystals, a simplified detector assembly, and novel electronics at lower speed that are more cost-effective. The improvements can process digitally each electronic channel of the detector with signal correlation between neighboring electronic channels and have the capability to execute programmable complex real-time algorithms to accurately measure energy, spatial resolution, and depth of interaction, while determining the arrival time of a photon and improving greatly the signal to noise ratio. There are several unusual, innovative ideas underlying this system that require thorough, careful study of the system as a whole and of each of its parts separately. One cannot just skim over any one part and hope to provide a knowledgeable criticism of that part, let alone an assessment of the entire system. The result will be lower costs, reduced radiation to the patient, and the capture of more data that will allow early cancer detection. Before this innovative 3D-CBS technology, this result would not have been possible because the solution had not been found to process the complex data acquired and the increase in length of the detector was not feasible due to its high cost. The 3D-CBS technology knocks down the high cost thanks to the new architecture of the system and the electronics that allow the use of cheaper crystals and solve the problem of complexity needed to analyze the data.

The synergy of coupling several innovations allows capturing more accurately all possible signals from tumor markers providing the physician more accurate measurements of the five parameters that will reduce "false positives", "false negatives" [19], the examination cost and will enable early diagnosis.

SUMMARY OF THE ADVANTAGES OF THE INNOVATIVE 3D-CBS TECHNOLOGY COMPARED TO THE OVER 7,000 PET IN USE CURRENTLY

The specific aim to improve efficiency and lower the cost for each valid ("true") signal captured from the tumor markers described above provides the following advantages (Figure 7) and therefore benefits to the patient.

$$\text{Efficiency} = \frac{\text{Pairs of photons in time coincidence detected by the instrument}}{\text{Radiation activity in the patient during the scanning time}}$$

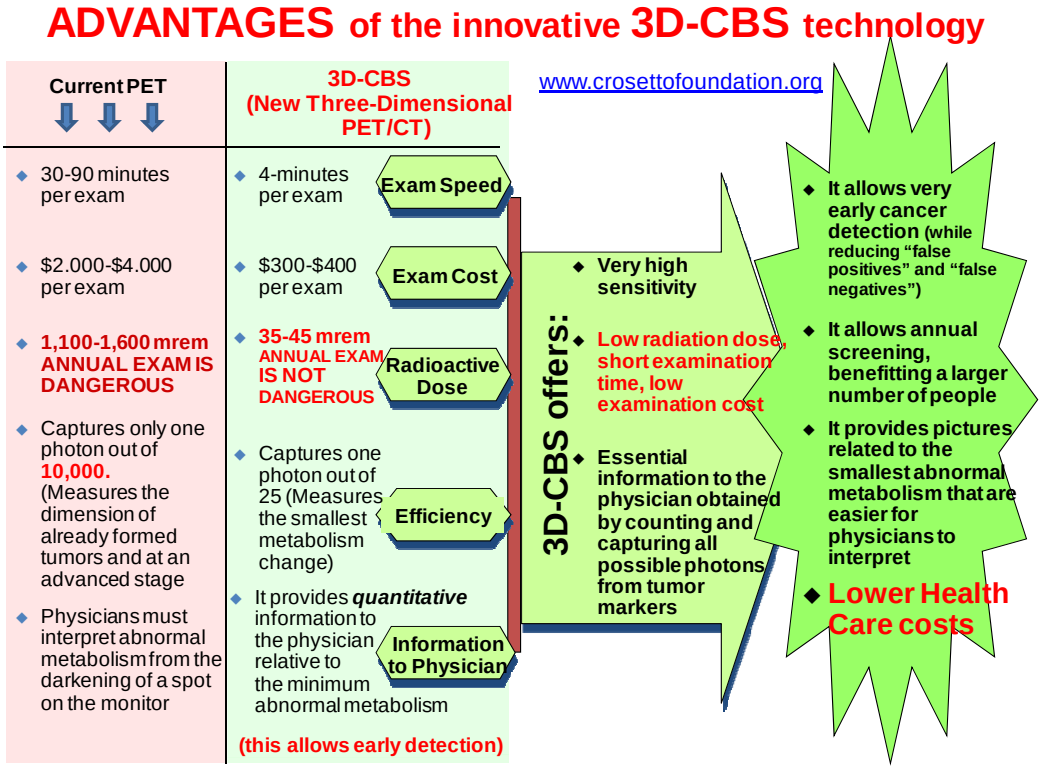


Figure 7. The way the information is displayed must change. A fine-grained photo of pixels, one on top of another as shown on the left does not provide accurate information about abnormal metabolism (nutrient consumption). The physician, radiologist, oncologist, should have coded colors for a quick overview of alarming spots and more detailed quantitative information showing the abnormal metabolism on a background profile of organs as shown on the right

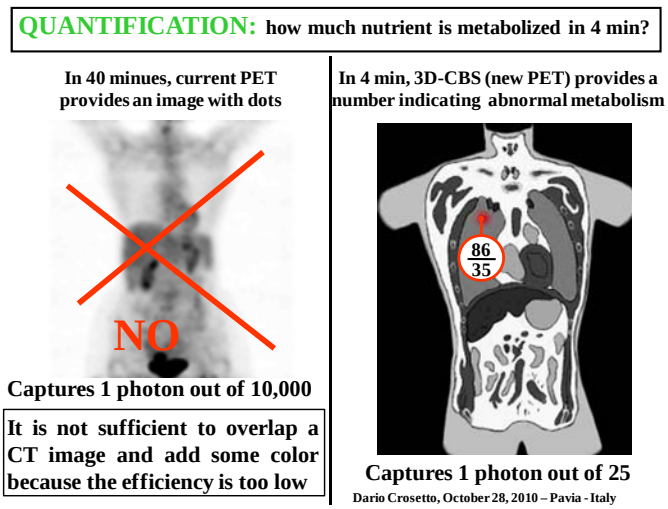


Figure 8. Comparison between the approach used in current PET (left on The figure) to measure tumor dimensions at an advanced stage and the new 3D-CBS approach to measure the minimum abnormality in biological processes targeted to early cancer detection.

3. *Research Strategy:* (Example of a question asked by other competitions: Describe the experimental design, including methods, anticipated results, potential problems or pitfalls, and alternative approaches. Preliminary data that support the proposed hypothesis are encouraged but not required).

The research strategy is to build three very efficient, cost-effective 3D-CBS devices with 1.4 meters in length, according to the basic specification reported in Section 17.1.2, page 174 in the book [29] published in 2000: "400+ times improved PET efficiency for lower-dose radiation, lower-cost cancer screening", ISBN 0-9702897-0-7, available at www.amazon.com, just for the PET/CT application (no SPECT section will be considered) modified according to the updates in successive publications [28], [30], [41], for maximum optimization of low cost and high performance.

In order to avoid delay of FDA (or EU Regulatory Agency) approval of the CT section that transmits radiation to the patient, a commercial 16-slice CT will be leased to acquire, with a very low dose radiation, the attenuation coefficient for the correction of the PET data and also to provide the tissue density information that will help to localize the tumor (shown by the PET section of the 3D-CBS device as a hot spot for any abnormal biological activity) within the organs and/or body tissues.

With this initial strategy, there will be no need for FDA approval (ethical approval with consent of the patient should be sufficient) because the 3D-CBS device will be just like an eye observing the radiation activity emitted by the radioisotope from the patient's body that for the initial tests uses the residual radiation from immediately previous tests requested and approved for examinations on other traditional PET/CT commercially installed devices in hospitals. Subsequent tests for a screening study will require administering a dose of FDG (or any new radioisotope considered more suitable to signal to the physician the start of the development of a tumor) that is 1/30 of the 10 mCi used in the current PET examinations, bringing the radiation dose to a level lower than the 1 mSv recommended by the ICRP for screening examinations.

The sequence of the tests on the new 3D-CBS device will be

- first on phantoms to measure its efficiency, sensitivity, spatial resolution, etc.;
- second on patients (who went through the examination on traditional PET/CT) using the residual radiation of the radioisotope administered for that exam and comparing quantitatively results relative to the minimum abnormal metabolism - or other abnormal biological processes - in any area of the body acquired from the 3D-CBS with those acquired from the traditional PET/CT;
- third, a study will be organized and conducted on a sample of asymptomatic high-risk patients following the procedure that has been used in the past for CT screening study, however, in this case the total amount of radiation that the patient will receive from CT and the PET tracer should be lower than 1 mSv in order to comply with ICRP regulations.

Because the efficiency of the 3D-CBS is over 400 times that of the 7,000 plus PET and PET/CT installed in the hospitals around the world, it is expected that, besides lowering the costs and providing more accurate

information to the physician and patient, the role of PET will change from the current role of confirming the presence of an existing tumor (however detected, in most of the cases with other procedures when it is at more advanced stage) to that of a diagnostic role of asymptomatic patients and cancer survivors who need to be monitored closely for signs of recurrence. An early detection of minimum abnormal metabolism (or other abnormal biological processes), will offer both a much higher chance for curing with efficacy their cancer and for them to be statistically among those with a 90% to 98% survival rate.

Preliminary verification of the innovations have been built in hardware, and have been demonstrated to function according to expectations. This greatly reduces the risk of not achieving the overall expected results of increased efficiency from the scientific standpoint.. Figure 9 shows the board with sixty-eight 3D-Flow processors arranged in stacks of four layers of 4x4 processors with one 3D-Flow chip at the last layer to funnel results to a single electronic channel. The board is modular in design and therefore supports building a 3D-Flow system of any dimension. Two boards have been built and tested to demonstrate the feasibility and functionality in hardware of the interconnections in six directions of the 3D-Flows processors across chips in a board and also across boards. This proves the feasibility of the entire 3D-Flow system.

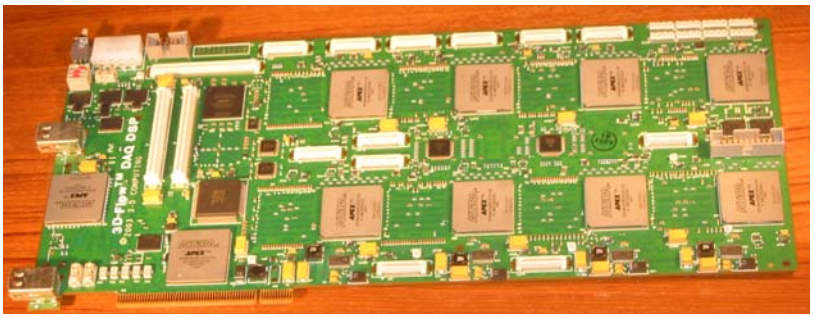


Figure 9. 3D-Flow DAQ-DSP IBM PC board for photon detection

In order to reduce the risk of not achieving results for lack of funding to complete the project or for problems connected to people or the environment, the following method is recommended:

The project should aim to secure funding of $15 million for the construction of three 3D-CBS devices.

The reason for planning to build three units and not one is because:

1. As is the case of other experiments involving physics detector apparatus at research centers (the 3D-CBS is a detector apparatus) , more than one detector apparatus is always planned. (For example at the CERN LHC accelerator four detector projects have been built, and at the Supercollider two were planned, each costing over half a billion dollars. In this case three is the choice)
2. To best amortize the Non-Recurring-Engineering (NRE) costs that will drive the cost of the first unit very high, ordering a large volume of 3D-Flow chips for three units will lower the cost of each component and thereby lower the average cost per unit.
3. It would be difficult to find qualified professionals to be on the team who would accept a job lasting for only for one year (the time it would take to build only one machine with shorter field of view with no funding guaranteed to continue). Instead offering professionals a secure job lasting for three years with the possibility to continue if milestones are met, has a greater potential to attract young bright post-graduate and senior professionals with experience in the field, and therefore security for success.
4. Building three units and placing them in three different locations (even countries) will lower the risk of poor results due to improper operation of tests. It would be sufficient for one of the three to obtain good results to help the others correct their errors in operating the machine and to obtain similar results.

The strategy is to outsource most of the work (detector, electronics, etc.) while a team of eight professionals assemble the parts with input from some consultants. This team should consist of a Director of operation, a professional for detector assembly and test, a mechanical engineer, an electronics engineer, an

electronics/firmware/software engineer, two software engineers and one person to handle administration. In order to keep overhead costs down, consultants will be hired as necessary for specific jobs.

A business plan has already been prepared which details the cost of each component and service, down to the cost of the electronic boards, crystal detector, rent of facilities, utility expenses etc. The estimated cost is $7,000,000 for the first 3D-CBS unit and $4,000,000 for the subsequent two units.

It is in everyone's interest that this business plan is not under or over-budgeted; therefore, estimated costs will be further checked and whenever there is doubt, a Request For Quote (RFQ) will be made to verify the estimate with an updated commercial cost.
The existing business plan consists of several pages of spreadsheets of a relational database. If for instance the price of the crystal currently estimated at $20/cm3 changes, then just by changing that value, all other estimates of the cash-flow detailed by month for the first year and quarterly for successive years, including the break even point and all other parameters will change to reflect that new value.

Having passed this phase of not finding any other project in the world that can claim superiority in efficiency, lower cost per life saved and higher percentage of lives saved, in an open transparent discussion when compared to other projects, this project (or the one that shows superiority) needs to be supported for funding by everyone who wants to reduce cancer death and costs.

After the total $15 million fund for the entire project is assured and all the milestones, for example achieving the functioning of stage one of a 3D-CBS with a FOV ring of 20 cm long, then 40 cm, 80 cm, 140 cm, have been set and agreed upon, a contract will guarantee all parties (employees, and all people involved with the success of this project) that unless someone breaks the rules (for instance in not achieving the milestones because of low performance) that the project will continue regardless if one of the parties defaults (some form of penalty should be established in the contract to discourage defaulting).

4. *Human Studies:*

The plan for recruiting of subjects will follow what has been used in the past in several studies of screening with a low-dose CT (however, in this study, the sum of the radiation from CT section and the radioisotope for the PET section should be less than 1 mSv recommended by ICRP for screening) and will comply with all regulations for screening.

5. *Rationale on how this innovation will reduce health care costs while saving more lives*

The U.S. alone in 2010 spent $102 billion for direct medical costs (see on page 3 of [47] (total of health care expenditures) for treating cancer most of the times at an advanced stage. Even with a much reduced budget for early detection, a better result in number of lives saved from premature death is guaranteed. When early detection is achieved, drug use drops and the cost for post-surgical treatment decreases because it is needed for a shorter period of time, in particular when the problem is solved mainly by the removal of an early stage cancer with surgery.

A higher return in lives saved is supported by the following:

- **Efficacy of early detection:** Experimental data show that when cancer is diagnosed at an early stage it is curable and lives are saved in 90% to 98% of the cases ("Early-stage ovarian cancer is more than 90% curable; late stage is 75% deadly")
- **Approved screening based on the measurement of tissue density which has low efficacy:** Despite the fact that cancer grows without always showing a change in tissue density, there is widespread screening with techniques such as mammogram which are based on measuring differences in tissue density
- **Higher efficacy obtained from measurements of metabolism** (or other abnormal biological processes) **(even using current PET) with respect to measurements of tissue density:** Knowing that there is a better chance to detect cancer by a change in a normal biological process rather than a change in tissue density or other signals, "safe radiation dose" PET should be preferred over mammogram, CT, etc.

- **Validation by third parties (including Siemens) of the P.I.'s discovery made a decade ago - the possibility to increase efficiency of current PET by 400 times by improving the electronics and other sections of the PET.** Having had third parties (such as Siemens who initially denied the possibility that efficiency could be improved by improving electronics, but who then had to take back their claim when different results were revealed by their own experiments) validate the P.I.'s discovery and confirms the claim that current PET efficiency can be increased by 400 times by extending the FOV and improving other sections of the PET.
- **Certainty of obtaining at least 33% efficacy from screening (instead of 90-98%) with highly reliable and enormously more efficient technology.** It is conservative to estimate not 90% to 98% of lives saved as experimental data show relative to early detection, but at least 33% because of other techniques based on the less efficacious measurement of tissue density (e.g. mammography) that claim lives saved through screening. **The new 3D-CBS device**, much superior in technology (based on measurements at the molecular level rather than density) and with an efficiency 400 times superior compared to current PET, **offers far greater advantages compared to the results in lives saved obtained during the past half century.**

The National Cancer Institute (N.C.I.) claims a reduction in cancer death of 2% per year (although this result is more likely due to smoking cessation or diet change, with a very small percentage due to research).

However, SEER data reported by The New York Times [9] on April 24, 2009 show that during the past 50 years cancer death declined only 5% and NCI data show that from 1975 to 2007 there was an increment [48] of cancer death of 20%.

Furthermore, when analyzing data obtained from the U.S. Census and U.S. C.D.C. (Center for Disease Control), National Vital Statistics reported that from 2000 to 2003 the reduction ranged from 0.5% to 1.04% (see page 14 of [19]). Even by granting 6,000 additional lives saved every year, considering the annual expenditures for cancer treatment of $64 billion for the year 2003 as reported by N.H.I. [49], the cost for each additional life saved is approximately $10.5 million ($64 billion/6,000).

Having established that the cost per each additional life saved has been approximately $10.5 million per person, one can compare that with the P.I.'s innovative solution targeted to early cancer detection, making it possible to reduce such expense by approximately 40 times.

The claimed health care cost reduction for cancer is supported by the following:

a) Conservative estimate of the percentage of cancer death reduction through early detection: Although experimental data show that early detection saves life in 90% to 98% of the cases, in order to have good certainty that goals will be reached, only a conservative estimate of 33% reduction in cancer rate is assumed through screening with a technology that is 400 times more efficient than current 7,000 PET devices.

b) Cancer death rate for the age group 50-75: Statistical data show an annual percentage for cancer death rate of 0.5% in the age group 50-75.

c) Number of annual examinations required to save 6,000 people based on the mortality indicated at item b) and the estimate of people saved at item a): In order to save 6,000 people through early detection on a sample of population showing an annual death rate of 0.5% and using a conservative estimate of 33% success, it is necessary to examine about 3,640,000 people annually.

d) Cost to examine 3,640,000 people: Because the cost of the examination performed with the P.I.'s innovative 3D-CBS technology is $400, to examine 3,640,000 people will cost $1.5 billion (plus the cost of surgery and post-surgical procedures)

e) Cost for each additional life saved: Dividing the total cost $1.5 billion for the number of lives saved, the cost per additional life saved is $0.25 million (plus the cost of surgery and post-surgical procedures)

f) Possibility to save over 100,000 people per year at a cost less than half compared to the current annual expense for cancer treatment: With the P.I.'s discovery it is possible to greatly surpass the current limit of saving only 6,000 people per year from premature death. By screening a larger sample of 60,000,000 people, it will be possible to save 100,000 per year at a cost of $24 billion (plus the cost of surgery and post-surgical procedures).

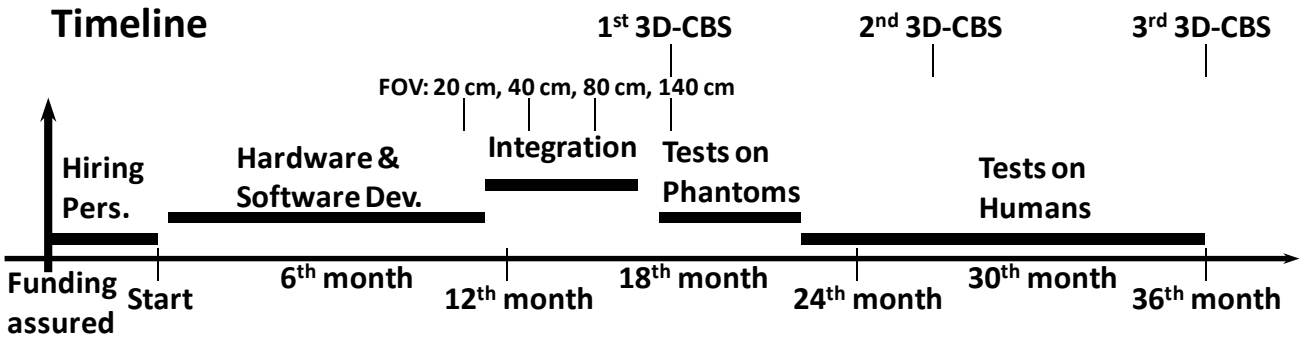
The greatest impact in the fight against cancer started ten years ago by the P.I. will be the **achievement at point e) above** – the cost per additional life saved of **only $0.25 million** (plus the cost of surgery and post-surgical procedures). Because currently **the cost for each additional life saved is approximately $10.5 million, the cost enabled by this new discovery will be only one/fortieth the current cost.**

The achievement at point f) listed above deals with the possibility to save not only 6,000 people annually, but over 100,000 at the cost of $24 billion. That is still ten times less than the current annual cost for cancer to the U.S. of $263 billion (see page 3 of [7]). Furthermore, there is an additional gain to the economy from people aged 50-75 brought back to productivity instead of incurring high expenses for treatments of late stage cancer.

6. *Measuring Results:* (The applicants should describe how they will conduct experimental tests to demonstrate the achievement of the figures estimated in Section 5).

Annual 3D-CBS examination will be performed on a representative sample of 10,000 people aged 50-75, selected from a population in a location with a constant cancer death rate of 50 deaths per year recorded over the previous 20 years. The examination should be safe for the patient requiring administration of a total radiation dose of 1 mSv, it should comply with ICRP regulation and with screening regulation, as for example, has been done in the past for CT screening studies for cancer. Results will be measured in terms of the cost/benefit ratio similar to other reports (for example the study made in Japan when in 2005, 50,000 people underwent PET screening in 46 hospitals [50]). Results should be published. Any reduction from the steady 50 deaths per year recorded during the previous 20 years will show success of the project. If the target of 33% premature cancer death reduction is achieved after 6 years, the project should be strongly supported and expanded with large investment.

7. *Timeline:* (Provide an outline of anticipated major milestones tracked in the proposed project).



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