Breast CT – Technical, Market and Strategic Analysis of an Emerging Technology

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Executive Summary

Cancer of the breast is the form of the disease with probably the highest public awareness. In the U.S. alone 40,000 women die of the disease, and 200,000 are diagnosed with it each year. Over the last two decades survival rates have improved markedly owing to a combination of better treatment and early detection through screening.

X-ray mammography is the existing standard for screening of breast cancer, but misses some cancers while frequently signaling trouble where there is none. Breast CT is an alternative approach to breast imaging that generates clearer images and thus is promising in terms of improving accuracy. Importantly, it does not require the painful breast compression of mammography. Currently in the exploratory development stage in academic environments, breast CT is at a point where commercialization is conceivable within a few years.

Patient appeal of breast CT relative to mammography will likely be strong, providing a significant differentiator to hospitals and clinics offering this option. Because of a modest reimbursement situation, cost of the device will need to be in line with the current generation of digital mammography machines.

FDA approval will be crucial, and will be easier to achieve for use as a diagnostic tool, following identification of a suspicious item in a screening mammogram. However replacing mammography as a screening tool should be the ultimate goal, as the market of 40 million exams per year is many times larger, and the competitive landscape less crowded than the diagnostic market.

Overview

Approximately 200,000 new breast cancer cases are diagnosed, with 40,000 women dying from the disease from each year. Every year in the U.S., some 40 million women are screened using x-ray mammography, representing 60% to 70% of the eligible population of women over 40 years of age. One published estimate posits that the number screened will grow by an additional 1 million women per year. With an average reimbursement rate in the vicinity of $100, this represents a $4 billion market.

However mammography is far from perfect. “False negatives” (missed cancers) are problematic, with a rate estimated at 10% to over 25%. “False positive” (abnormal features requiring follow-up) estimates
range from 10% to 30%, causing anxiety, inconvenience and substantial additional cost to the health care system. Undergoing a mammogram is also considered a minor form of torture by many patients.

Mammography has been prominent in the news lately (November, 2009) since the US Preventive Services Task Force (USPSTF) changed their guidelines for mammography based breast cancer screening from a starting age of 40 to 50 years, and lowered the recommended frequency from once per year to every other year. There has been a strong response in opposition from numerous groups (American Cancer Society, women’s advocacy groups) and independent health care providers. Medicare and many private insurers have stated that they were “unlikely to change coverage in the wake of the new guidelines”. According to a November 24th USA Today/Gallup poll, 84 percent of women ages 35 to 49 say they plan to get the screenings anyway.

![Figure 1: Probability of developing breast cancer at different ages within the next 10 years of life](source)

Stated reasons for the new USPSTF guidelines involve the high rate at which false positives are indicated by the current standard of care, that there is some evidence for cancerous lesions which go away on their own over time, that the number of lives saved in the 40 to 50 age group is very small, and offset by the additional risk imposed by the
radiation dose delivered in the exam. Others have argued against each of these points, and the debate is continuing, in professional circles and in the public eye. Figure 1 shows the probability of a woman developing breast cancer as a function of her age.

Existing standards of care

Caught early, breast cancer has a high 5 year (and longer) survival rate. Hence the emphasis in medicine and in our culture on regular screening. A cross section of a breast, identifying skin, fat and glandular tissue, is shown in Figure 2. Glandular tissue, where cancers develop, represents between 30% and 50% of the breast volume. Dense breasts are those at or near 50% glandular.

Breast cancer detection falls into two categories, screening and diagnosis. “Screening” is the term used for what is done proactively on a scheduled basis, without any symptom or other sign of trouble. “Diagnosis” is the term used when following up on something abnormal or suspicious that has shown up in a screening exam.

Mammography was introduced as a routine screening tool using purpose-built equipment in the mid-1960’s and has become a norm in our society. A fraction estimated between 5% and 30% of screenings (estimates vary widely) reveal something suspicious or questionable, and thus lead to diagnostic exams. Diagnostic techniques include further mammograms focused on the area of interest, biopsy, MRI, PET/CT, and additional technological approaches. The majority of these preliminary positive results turn out negative. Biopsy is the most certain diagnostic, but is also the most invasive. The number of biopsies that are found to be negative is between 70% and 90%.

Detection of breast cancer depends on the ability to see masses or lesions in the soft tissue, and so-called micro-calcifications. Micro-calcifications are sub-millimeter points of calcified tissue which have strong x-ray absorption, but being very small can be hard to detect, requiring fine detector resolution. Groups or clusters of five or more of them are a stronger indication of cancerous growth than single ones. Lesions that are spiculated (with points or spikes on the surface) are more likely to be cancerous, so again high resolution in the image is important, to be able to identify the spiculations.
Figure 2 Makeup of the female breast, showing skin, fat and glandular tissue, the chest wall and ribs

Screening

Film/screen mammography, sometimes referred to as “analog” mammography, has been the standard of care for screening since its introduction over forty years ago. This technique uses an x-ray source and high resolution photographic film to create an image of a breast, compressed first along a horizontal plane and then along a near vertical plane. A screen is placed in front of the film to cause interactions with the x-rays, as the film itself is not adequately sensitive. Low excitation voltages are used (~30 kVp) to optimize image contrast, with high beam current to create low noise, high resolution images. Mammographic x-rays deliver 10x to 20x the dose of a chest x-ray, but still considerably less than full-bore CT exams.

Film images are viewed as-is, or increasingly are scanned into a computer for viewing and archiving. When images are scanned it allows for the use of image enhancement tools as well as computer aided detection (CAD) programs. Compression of the breast is required to enable better detection, to a thickness of approx 2 inches (5 cm) and is at best uncomfortable, in some cases painful. Figure 3 shows a view of the actual configuration for a woman undergoing a mammogram.
Digital mammography, in which the image is created not by film but by a large flat panel x-ray detector, was introduced around the year 2000, and is now supplanting analog. Most new machines being installed are digital, despite much higher prices (several hundred thousand versus ~fifty thousand dollars). Of 12,800 mammography units in use in 2009, around 7,500 are digital. These machines offer improved convenience in image handling, as well as a wider dynamic range (difference between light and dark portions of the image).

Figure 3 Preparation for a mammogram, vertical view

Extensive studies have shown that digital mammography is equivalent to analog in most cases, with advantages over analog in cases where the patient is under 50 and/or has dense breasts. For older and less dense breasts, digital has not been shown superior, although there are real advantages in image storage and manipulation.

Other than palpation, as in a breast self-exam or doctor equivalent, no other technologies are commonly used for breast cancer screening. Any new candidate modality would have to demonstrate at least equivalent performance to mammography to be accepted (and FDA approved). While the high rate of false positives and of false negatives provide ample opportunity for a new entrant to the field, the burden of proof required does imply a fairly large clinical study. This is explained by
the fact that many patients must be screened in order to detect a statistically significant number of true positive results, which the new technology must be capable of detecting reliably.

**Diagnosis**

Once a suspicious lump or visual clue is detected, there is a much wider array of choices available for further diagnostic investigation. An additional mammogram, focused on the region of interest, is one approach that requires no additional equipment. A needle biopsy of the tissue, guided by the image, is relatively definitive and commonly performed, but of course invasive.

Technological alternatives abound. Examples are ultrasound, contrast-enhanced mammography, MRI with gadolinium contrast, chest-CT, combined PET-CT, and single photon emission tomography (SPECT). Ultrasound has the advantage of not delivering radiation dose, and of not requiring contrast agent. While it has excellent contrast resolution, it does not have the fine spatial resolution of other imaging modalities, and also cannot detect micro-calcifications. PET (positron emission tomography) requires injection of a radioactive substance. Chest CT delivers a higher radiation dose to not only the breast but to portions of the lung and heart, and does not have as high spatial resolution as mammography. MRI with contrast is promising but has low turnaround, and there are issues with claustrophobia for many patients. All of these involve very expensive equipment. Nevertheless, academic researchers are actively working on novel applications of these and other more exotic imaging tools.

Since there are already many choices available for diagnostic use, and use of one does not preclude use of another, a new technology will have an easier time gaining acceptance here than in use as a screening tool. However the numbers involved in diagnostics are much smaller than screening, with approximately 3 to 6 million (7% to 15%) callback cases in the U.S. each year.

**Breast CT technology**

**How it works**

CT (Computerized Tomography) has been in use for several decades for both medical and industrial applications. Just as a normal x-ray image provides an attenuation shadowgram of the structures inside an object, a CT is made up of a set of such shadowgrams taken from all angles around the object. The x-ray beam is “fan-shaped” and the
detector is one or more parallel linear arrays; the two face one another and spiral around the patient, moving longitudinally to cover the specified region of interest as they circle.

Using the set of acquired “slice” images, mathematical transformations provide 3D volumetric data through the imaged volume, where the value of each “voxel” represents the attenuation of that point within the object. Today’s CT machines are capable of high scan speeds, optimized to deliver the lowest possible dose while delivering low noise, high resolution images. Modern algorithms are effective in rejecting image artifacts that arise from highly attenuating materials inside the object, such as bone and even items such as steel implants.

A dedicated breast CT differs from the commonly used full size CT machines in two key ways. The most obvious one is size; the breast CT is only large enough to allow the pendant breast of a prone (lying face down) patient. The other difference is the use of the cone-beam technique, in which the x-ray beam is cone shaped rather than fan shaped, and the detector is a 2D flat panel detector rather than a linear array. Cone beam geometry, now being used commonly in conjunction with radiation therapy machines, simplifies the design substantially. It eliminates the need for multiple rotations of the source and detector and thus the need for slip-rings for power and signal transmission. The Feldkamp algorithm, a form of filtered back-projection, has been developed to work near-optimally with cone beam geometry, and applications of it are widely published. Figure 4 illustrates how the patient interfaces with the breast CT machine.

Otherwise the concept is the same as in full CT. By providing projection views through the anatomy over a full rotation a complete 3D volumetric data set can be computed. Some of the challenges in full CT disappear in breast CT. For example artifacts due to shadowing of bone or metal implants are not a factor. Without the need to go through as much anatomy or through bone, the x-ray energy (kVp) can be lower, which improves soft tissue contrast. However this has to be optimized against the issues of noise and patient dose; at low excitation voltages the noise is higher since fewer x-rays are created, and the dose is higher since softer x-rays interact within the breast more frequently. Experimental breast CT machines operate at higher voltages than mammography, 60 to 100 kV versus ~25 to 35 kV, but still much lower than whole body CT machines.

Most breast CT work so far has imposed dose limits that are at or near what a patient receives from a two-view mammogram, which is appropriate for screening. At higher doses the image quality improves,
providing advantages for use as a diagnostic tool, where the risk versus benefit curve associated with radiation dose versus improved imaging shifts.

![Figure 4 Arrangement of patient in breast CT](image)

Commercially available “Micro-CT” devices prove the concept and give insight into cost. These are used to image biological and industrial specimens up to a few inches. They can provide extremely high resolution, with voxels (3D pixels) only a few μm across. One such device, the SkyScan 1174, retails for $92k. There are also small CT devices used in ENT and dental applications based on cone beam technology. Resolution is in the range of 0.2 to 0.4 mm voxel size. One company (MCTI) in the Bay Area offers a mobile dental CT service, which increases utilization of the equipment. This is important since few dental offices have the volume needed to support a private unit.

A commercial breast CT device must accommodate the largest of breasts, with therefore a much larger flat panel detector than use in micro-CT’s. It also must complete its scan in a fraction of the time that the micro-CT’s have to work with, e.g. fifteen seconds versus several minutes. Both of these requirements will increase the cost. On the other hand, the breast CT does not need to have anywhere near the same spatial resolution as a micro-CT.

A large body of work has been published by the academic teams, which lays out the issues associated with building a breast CT device, and provides answers to many design questions. The fact that so much has been published, along with the fact that full size CT has been around for decades, should allay much of the concern about intellectual property issues. Some examples include the following:

- Optimization for various operating parameters, such as kVp and beam current set-points, rotation step size, beam cone angle, detector pixel size, and readout frame rate
• Performance of various reconstruction algorithms and filters (Feldkamp, filtered back-projection, etc.)
• Calibration of precise apparatus geometry
• Measurement of coefficients, DgN(ct) for calculating dose to glandular tissue
• Scatter correction algorithms
• Characterization of anatomic noise
• Blood vessel reconstruction algorithms
• Investigations into automatic segmentation of tissue types

With this impressive body of published work the task of developing a viable commercial unit is considerably eased.

**Breast CT results**

At the academic centers involved in breast CT research, images have been taken of phantoms of various designs, to characterize various aspects of performance in a systematic way. Such images have helped establish optimal design and operating parameters. There have also been studies with patient volunteers, some of which are ongoing.

![Breast CT image of phantom with various inserts representing glandular tissue, carcinomas, and calcifications (from Chen and Ning)](image)

**Figure 5** Breast CT image of phantom with various inserts representing glandular tissue, carcinomas, and calcifications (from Chen and Ning)
Figure 5 shows an example of a breast phantom scanned with a prototype breast CT. The phantom was constructed with inserts representing glandular tissue, carcinomas, and micro-calcifications. Except for the smallest of the micro-calcifications, all show up clearly.

Micro-calcifications are the biggest challenge for breast CT, as they require the finest resolution due to their very small extent. In general, mammography uses the very highest resolution detectors available, higher than the breast CT prototypes. In fact this need is why mammography lagged behind other forms of radiography in transitioning to digital detection. To use the same detectors for breast CT would require either higher dose and/or more exposure time to generate similarly high signal to noise values in each pixel. The fact that CT acquires many views not only allows for 3D reconstruction but also makes up for the “information deficit” of using lower resolution detectors.

Figure 6  Comparison of images; mammogram (center) and slices from a breast CT volumetric data set

Another challenge for breast CT relative to mammography is that micro-calcifications are better differentiated at the very low kVp settings of mammography, which do not work well for breast CT. Once again this is for reasons connected to patient dose and signal to noise.
ratio rather than intrinsic limitations of the technology. In spite of these obstacles, researchers believe they can at least equal the microcalcification performance of mammography with breast CT. For example, one technique might be to “tune” the spectral shape of the x-rays to enhance sensitivity to calcium.

On the other hand, tissue masses are very well resolved by breast CT without the “anatomical screening” problems of mammography. By rotating around the breast and taking images from all angles, the raw information to reconstruct unobstructed 3D volumetric data is obtained. The value of this can be appreciated by comparison of images generated by mammography and breast CT of the same patient. Figure 6 shows such images, where the mammogram is shown in the center and various parallel slices of the breast CT volume surround it. The breast CT images are markedly sharper and clearer than the mammogram.

Note also that the breast CT data can be “sliced” along either of the two axes perpendicular to that shown (or along oblique planes as well), allowing the radiologist tremendous flexibility in viewing suspicious areas. The fact that many cancerous tumors are spiculated (have spikes) suggests that this viewing ability can be leveraged toward improved cancer detectability, and perhaps specificity. Figure 7 is another set of images comparing a mammogram and a CT slice from the same breast that shows how the detailed morphology of a lesion is more easily seen with CT.

Figure 7 Mammogram and a breast CT image slice from the same breast
One other test for breast CT is imaging of the axillary region in the upper, outer quadrant of the breast. In mammography, the operator uses the compression paddles to pull the axilla into the field of view. With breast CT’s pendant geometry the axilla does not naturally or easily enter the field of view. However researchers again feel this is a problem that can be solved. Proposed methods include mechanical means of pulling the axilla into the imaged volume; using non-planar source trajectory during rotation; or using patient rotation on the table.

It is important to state that at this time the clearly evident image quality improvements have not yet been proven to result in improvements in cancer screening or diagnosis. Although it may seem intuitively obvious, it is essential to objectively prove that the detection and specificity results are as good as (or better than) mammography, for FDA approval to be granted for screening.

Efforts along this line have been undertaken by academic researchers via volunteer clinical studies. The UC Davis group has imaged at least 200 women. Koning Corp, headed by Ruola Ning of the University of Rochester, is supplying clinical prototypes of their commercially oriented device to academic sites, presumably for similar studies. Koning has submitted an application to the FDA for approval, most likely as a diagnostic rather than screening device for now. A response could come at any time.

**The Opportunity for Breast CT**

**Motivation**

Rather than seeing the market for breast diagnostics shrinking as a result of the recent change in mammography screening recommendations for women under age 50, one can take the new guidelines as a call to arms to provide a superior solution. Breast CT can be such a solution since it solves the problem of anatomical noise, particularly important in younger and denser breasts. In general the improved ability to see structures clearly using a true three dimensional dataset promises to lower the false positive rate as well as reducing the false negatives.

To health care providers and those providing the funding, better images and improvements in the specificity (lack of false positives) are huge incentives in the context of an annual rate of 40 million screenings per year. Even a modest improvement in specificity would
generate significant savings through avoidance of follow-on diagnostic procedures.

To the women undergoing the procedures, improved images will surely be welcomed by those who understand the medical advantage, but realistically may not play a significant role in the decision process of most patients. But what will surely be front and center in their minds is the clear reality of a painless procedure. In addition, while almost all mammographers in the U.S. are female, there is still some degree of discomfiture in having someone else manipulate a part of one’s anatomy that is so much an aspect of one’s image in our society. In an informal poll undertaken for this report, women were enthusiastic about the prospect of replacing the mammography paddles with breast CT’s technique of laying facedown on a table with their breast suspended into the apparatus through a shaped cutout. More scientific published data indicates 50% of women undergoing a mammography scan experience either moderate or greater discomfort.

**Proposed approach**

**Strategy**

Given the technological, reimbursement, political and societal situation, it is argued here that an effective approach would involve developing a device targeted at a price point of $400k to $500k (manufacturing cost at or under $200k), and focused on the screening market. This can be done if the “bells and whistles” of the academic groups are left out of the design, and components are chosen that provide good but not ultimate performance.

For example the flat panel detector commonly used in academic prototypes lists for $90k, but has four times the resolution capability currently used. While having that capability is nice for the future and for research, it drives the cost up substantially. It should be possible to partner with a manufacturer to provide the needed resolution at less than half that cost.

Similar if less dramatic savings exist in other areas relative to prototypes built in labs, which have been reported to cost roughly $400k as one-off prototypes. Production volumes approaching 100 units per year, associated with providing screening capability at the almost 9000 breast centers, will impact not only the cost of purchased items but will even more dramatically lower the cost of components such as machined or molded parts, sheet metal or plastic skins, etc.
Breast screening centers currently paying at the stated price point for digital mammography machines should find it easy to justify paying similarly or even somewhat more for a breast CT unit.

**Development plan**

A product development plan has been created that delivers a first simple prototype in 7 months, a second, more sophisticated prototype at 16 months, and a pre-production unit suitable for field trials after approximately 36 months (see Appendix B). Costs at each of these milestones are estimated at $800k, $2,900k and $8,300k respectively. These costs are solely for development, burdened to account for space and utilities but otherwise do not take into account the overhead of indirectly related groups such as marketing, sales, etc.

The plan assumes a small team, growing slowly with time. The first prototype is delivered as early as possible to provide a test bench for the algorithm and physics team members to work with and acquire data from. Simultaneously it allows the mechanical engineering team to get started with something simple, then quickly move on to the more sophisticated second prototype. This follows the learn-as-you-go approach, which applies well here. The concepts are well known and recorded in the literature, it is the reduction to practice that remains, and that is best accomplished by actual practice.

A small team structure would be maintained as long as it takes to receive FDA clearance. Initially the organization would be primarily R&D/Engineering staff supplemented by a clinical consultant, later followed by Quality and Regulatory to establish proper procedures and begin FDA submission. Full time clinical staff would then join in order to set up and execute the in-field data taking that the FDA will require.

Once it became evident that FDA clearance was certain, the team would build up the finance, marketing and sales organizations, and flesh out the manufacturing department from its roots in Engineering. This approach keeps the burn rate low for as long as it takes to surmount what is probably the biggest hurdle.

**Business and financial considerations**

**Reimbursement**

Compelling reimbursement is a challenge for any new medical technology. Medicare rates were $86 for film and $135 for digital mammography in 2005. As always, geographic variations are
substantial. This is not considered generous, with clinics often operating at or near break-even for the service, but providing it as a medical necessity for their patients. Patient retention for other profitable services is the operative strategy.

How breast CT would fit into this situation is uncertain, but can be broken down into two main possibilities.

In the first, worst-case scenario, reimbursement would stay substantially the same as currently paid for digital mammography. As long as the device cost is similar to that of current digital mammography units, clinics will do equally as well financially as currently. But their strategy of providing this service in order to get patients in the door would receive a large boost from the breast CT comfort factor. So given a choice between upgrading their old analog mammography units either to digital units or to breast CT, the advantage would go to breast CT.

The second possibility anticipates higher rates. To encourage innovation, CMS often provides significantly higher reimbursements in the early years of a new technology. For example, Xoft’s x-ray system was reimbursed at twice the later rate in its first few years of availability. This admittedly temporary effect still makes early adoption more attractive to purchasers. More significant in the longer run is the potential that CMS will see breast CT as good for the healthcare system, in that there is the promise of fewer missed cancers/earlier diagnoses and fewer unnecessary follow-up procedures. This could lead to substantially higher reimbursement guidance.

Note that digital mammography is already reimbursed higher than analog, even though it has not proved superior in most cases. Thus CMS has shown a willingness to reimburse on a cost-based paradigm. A presumably superior technology such as breast CT should do better. The needed data could emerge as early as from the clinical studies needed for FDA approval.

**Market potential**

There are now 12% fewer sites offering mammography, about 8700, than in 2000. Yet demand is high - wait times for an exam can be several months - and while some centers have shut their doors for financial reasons this only increases the demand pressure.

As stated earlier, there are about 12,800 mammography units in service, roughly half analog and half digital, with the digital fraction growing as older machines are retired. Even in the absence of any
hard sales numbers, one can estimate that there must therefore be multiple hundreds of new units installed every year. For every hundred unit sales captured by a breast CT unit at, say $500k sales plus installation, there will be $50M revenue for the company. Service contracts will add to the total, particularly as the installed base grows.

From the clinic’s point of view, the attractiveness of breast CT over mammography to women will bring more patients into their sphere of influence and provide a competitive edge even at current break-even reimbursement rates. If CMS increases the rates, clinics should be able to quickly show a profit. As an example, breast MRI, covered for certain high-risk cases, is paid $1200. While the health care system is not likely to pay this much for each of 40 million annual screenings, it provides a data point of how high things can go.

Outside the U.S. is potentially a large additional market opportunity, as is the boutique market, individuals who can afford to pay out of pocket for the comfort and improved imaging capability.

**Screening vs. diagnostics**

Although it will presumably be easier and quicker to obtain FDA approval as a diagnostic device, screening should be the ultimate goal. Even at current digital rates, the 40 million mammograms per year represent a $5.4 billion market. At an average of 4600 mammograms per site, clinics will generate over $600k per year, more than covering the cost of the unit.

On the other hand, diagnostic use, in a field of many worthy alternatives, would make the number of cases too low to justify the capital cost at many locations, unless reimbursement is markedly higher. Diagnostic use of mammography is more complicated as it can involve additional codes, but the core technical rate is quite similar to that for screening at this time.

Diagnostic codes for other modalities, such as MRI, needle biopsy, PET, etc. are also complicated by multiple codes covering different options, and by the existence of add-on procedures such as needle guidance and image interpretation. As an example, using bilateral MRI in combination with and without contrast is covered at $525. If breast CT for diagnosis were to be reimbursed at this rate, the economics then might be favorable.
**Challenges**

Several challenges exist, some of which are eminently controllable and others which are only partly so. As has been argued here, cost will be a critical success parameter to reach the huge screening market. But this is straightforward to deal with. On the other hand, items like FDA approval will be only partially controllable. Understanding at the outset what the issues are, and setting out a plan to acquire and present the appropriate study data will be key.

Competition is always an unknown variable, but one might expect that the large companies will be handicapped by inertia, their unfamiliarity with controlling costs, and commitment to evolution of their own product line (see Tomosynthesis section in Appendix A).

Market acceptance is impossible to accurately quantify in advance. In this case it involves both prospective patient response and that of the facility providing the care. It is reasonable to assume that patients will be at the very least positive, and more likely enthusiastic, about a procedure that does not cause pain or discomfort while providing better images. On the other hand one can only speculate on how this will affect the decision maker of the purchasing process. Keeping the cost in line with that of digital mammography, which clinics are already used to purchasing as their analog equipment reaches end-of-life, should prove advantageous.

**Summary**

Breast CT as a technology is ripe for commercial development. It has the enormous advantage from a patient’s perspective of avoiding the pain and discomfort of traditional and even newer mammography based screening modalities. It also has significant promise to be a more accurate screening tool via true 3-D images, unencumbered by the anatomical interference common in mammography. Increase in diagnostic accuracy will translate directly into lower patient anxiety, lower health care system costs and hopefully an increase in survivability.

The academic world, building on four decades of work on computerized tomography in medicine, has published a large body of work that lays out the parameters and approach required to build a high quality dedicated breast CT device. What remains is to productize the concept, using a combination of good science, cost conscious engineering, and an understanding of the true clinical performance and ergonomic requirements.
Such a commercial device can be constructed to the clinical prototype phase for $8M in a period of 3 years by a relatively small team. The proposed approach emphasizes maintaining a small engineering-centric team for an extended period to keep costs down through the possibly lengthy process of generating enough clinical data to gain FDA approval as a screening tool. Interim approaches involve use of the device outside the U.S., and inside the U.S. as a diagnostic tool.

Once clarity has been achieved on performance, market enthusiasm, and likely FDA response, the envisioned positioning would allow for either moving toward full commercialization, or acquisition by a larger entity.
Appendix A - Competition

Competition for a breast CT product comes from a number of directions. At least one of the academic breast CT researchers has started a company to develop a commercial breast CT. Mammography manufacturers have not done much more in breast CT than provide seed money to some of the academics, ostensibly to keep an eye on developments. Most work by mammography companies has been on evolving their current technology toward “tomosynthesis”. Other technologies are also being actively developed either by large established firms, as in breast MRI, or by academic researchers working on new concepts or novel combinations of existing concepts. The latter are of course far from commercialization and will not be dealt with in detail here.

Breast CT

Koning corp. (Rochester, NY) was founded by Prof. Ruola Ning of the University of Rochester. They have developed what they refer to as a commercial prototype, using U.R. staff on the scientific side and an outside contract manufacturer to design and build the device. Interestingly, Ning's publication count dried up a number of years ago, probably coinciding with starting Koning Corp. Partly as a result of relying on the outside firm, the cost to produce is $400k, implying a sales price of $800k to $1M. They are seeding it to some academic sites to gather additional clinical data to supplement what they have gotten at U.R. The work has been funded largely by NIH and other public grants. There is evidence the work has stalled, with funding questionable and as they await a response from the FDA.

The academic leader in the field is Dr. John Boone's group at U.C. Davis. They have published extensively on their designs and optimization approaches. Boone is in the process of formalizing an agreement with a firm based in Germany to commercialize the work. They plan to begin commercialization in Europe while seeding U.S. academic sites to build up the clinical data for FDA submission. Like Ning, their focus seems to be heavily weighted toward extracting the highest possible performance from the technology, without cost consideration. This is quite consistent with their background as academic researchers, where each paper tries to push the boundaries further than the last. Their most recent prototype cost them $400k to build.

Boone has received funding from Hologic and Varian. Varian is interested in selling their high-end flat panel detectors at $90k each.
Hologic is keeping their options open as they pursue a strategy based on their own tomosynthesis product.

**Mammography machine manufacturers**

One might wonder about the low level of interest displayed by major mammography manufacturers in breast CT. Speculation suggests that they have a vested interest in keeping to the path from analog to digital mammography, followed by the upgrade to tomosynthesis (see below). Breast CT at this time would be disruptive to that path and to the work already invested in creating tomosynthesis-capable versions of their equipment. Any perception in the market that they were working seriously on BCT could potentially hurt sales, and a product introduced by them too soon would only cannibalize sales of their tomosynthesis lines.

**Breast tomosynthesis**

**Description**

Breast tomosynthesis is a technique in which several mammogram-like images are taken over a narrow range of angles, then synthesized into a 3D-like data set. It uses a modified version of digital mammography machines, with the ability to move the x-ray source and in some cases the detector over a restricted angular range. In one of the leading examples, 11 images are acquired over ±15 degrees of travel. Each image delivers a reduced radiation dose, so that the total dose of all images is the same as a standard mammogram. This means each individual image has poorer signal to noise ratio than a mammogram. So while the proponents may claim the image set has all the information in a standard mammogram and more, there is an important caveat involved; the mammogram-equivalent image is notably noisier.

Tomosynthesis images reveal better depth information than regular mammograms and suffer less from “anatomic noise”, or the obscuration of interesting features by others in their path. However the images are not truly 3D and so not nearly as clean in separation of anatomic features as that of breast CT, particularly along the dimension parallel to the x-ray beam.

Perhaps most notably, since the devices are based on mammography equipment they still require clamping the breast between plates, so there is no advantage to the patient in terms of comfort. To a patient
deciding where to go for her yearly screening, indeed whether to go at all in many cases, this technology will have little if any draw.

**Players in breast tomosynthesis**

Hologic is in the lead, with currently shipping digital mammography machines ("Selenia") already having tomosynthesis capabilities built in. Since tomosynthesis is not yet FDA approved in the U.S., the function is not turned on. If and when FDA approval is secured, it can be software enabled for an incremental price of $200k. The base mammography system lists for $380k, with the screen and workstation another $100k. Clinical trials began in 2004, but the FDA has twice turned down Hologic’s submissions.

Siemens also has a “tomosynthesis ready” machine, the Mammmomat Inspiration, which is labeled as an investigational device in the U.S. GE has supported tomosynthesis studies with equipment it has supplied to researchers, but does not advertise availability of the equipment on its website.

**Other screening technologies**

Breast MRI has adherents and there is at least one company that has developed a commercially available MRI machine (Aurora 1.5T) with dedicated breast magnet coils. This device sells for $1.2M, with a mobile version priced near $1.5M. The mobile version includes a truck that is set up to be very patient friendly. GE, Siemens and Philips Medical are also working on dedicated breast MRI products. This approach improves the image resolution by concentrating the RF signal and modulated magnetic field in the breast region rather than spreading it out over the entire torso.

Breast MRI provides functional images rather than pure anatomic images, and can be effective in identifying tumors by their profusion of blood vessels. As a diagnostic tool, and for high risk patients in screening, MRI is reimbursed at $1200.

A typical breast MRI takes between 30 and 60 minutes, and requires the injection of a gadolinium based contrast agent. For patients with claustrophobic tendencies, additional medication is often prescribed. The high cost of MRI and the need for an injected contrast agent is a strong disincentive for its use as a routine screening tool.

Recently concerns have emerged about the use of gadolinium based contrast agents in patients with kidney disease. Nephrogenic systemic fibrosis (NSF) has been tied to the use of such agents provided by GE.
in their Omniscan contrast product, and by Bayer Healthcare (Magnevist) and two other manufacturers. NSF can be fatal, and over five hundred lawsuits have been filed in US courts, three quarters involving GE. In this context, the expansion of breast MRI into the screening realm seems ever more unlikely.
Appendix B – Development plan highlights

This section provides a view of the first 12 months of a sample research and development plan, plus a spreadsheet model of the costs and personnel needed to build preliminary through clinically ready prototypes.

Figure 8 Timeline for development of breast CT prototypes. Upper plot, weeks 1 through 26; lower plot, weeks 27 through 52
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**Figures 9** Spreadsheet model of personnel and costs associated with building preliminary and clinical prototype breast CT units
Appendix C – Selected References

The following is a sample of references that provided direct and indirect information for this report.

Personal communications and site visit with J. Boone, UC Davis


Andrew P. Smith, PhD, Patricia A. Hall, Donna M. Marcello, RT “Emerging Technologies in Breast Cancer Detection” Hologic, Inc. White Paper 2006


J. Gerth, “The Spectre Haunting GE” Business Week, October 15, 2009

J. Gerth, “The FDA May Tighten Rules on Omniscan, a GE MRI Drug” Business Week, December 2, 2009


Peer-reviewed papers:


