MONOGRAPHIC ISSUE: FOCAL THERAPY IN PROSTATE CANCER
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FOCALYX DX, BX, TX ET APPS: A NOVEL CONTEMPORARY FUSION PARADIGM FOR THE MANAGEMENT OF PROSTATE CANCER

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Summary.- *FocalyxTM conceived as a response to emerging evidence data across numerous cancer lesions that questions current standard treatment approaches that too often lead to detrimental quality of life yet delivering limited survival benefit, especially in-lieu of advances in imaging technology applicable to cancer patients. The Focalyx paradigm aims to control cancer with improvement in quality of life. We initially devised 5 milestones: 1- Consistently optimize Prostate MRI imaging using the novel published protocols adopted as guidelines by societies such as the European Society of Urology and Radiology; 2- Evaluate fusion platform software solutions that existed; 3- Determine best fusion platform for Focalyx on practicality, precision, and workflow premises; 4- Evaluate commercially available FDA approved ablative technologies to implement our treatment vision; 5- Design a treatment option that can be performed in the office setting under local anesthesia, which would not impact negatively QOL outcomes of Prostate Cancer patients and seamless constant non-intrusive practical patient-physician interaction by the Focalyx app that facilitates follow up and provides early warning signals shall any change in the disease dynamics emerge. Prostate cancer was identified as the pilot disease for Focalyx to deliver a "GPS" like solution for the prostate gland that destroys identifiable disease without adverse effects such as: cancer anxiety, urinary incontinence, loss of erections and ejaculation. Since September of 2013, over 300 men have been accrued in NCT02381990- clintrials.gov evaluating the feasibility of our solutions for imaging (FocalyxDx), Biopsy (FocalyxBx) and Treatment (FocalyxTx). In this review we detail the tools available to achieve the Focalyx paradigm for men with Prostate Cancer.*

Keywords: *MRI. Fusion. Prostate Cancer. Focalyx.*

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Resumen.- *FocalyxTM ha sido concebido como una respuesta a los múltiples datos del manejo de cáncer de próstata que cuestionan el tratamiento estándar. La evidencia actual cuestiona un beneficio en la supervivencia, especialmente tras los avances tecnológicos basados en la de imagen aplicable a pacientes con CaP. El paradigma Focalyx tiene como objetivo controlar el cáncer con una mejoría en la calidad de vida. Hemos ideado inicialmente 5 etapas: 1- optimizar imágenes de RM de próstata utilizando los protocolos aprobados como directrices por las sociedades internacionales,*

como la Asociación Europea de Urología y de Radiología; 2- Evaluar opciones de software de la plataforma de fusión existentes; 3- Determinar una plataforma de fusión para Focalyx basada en la practicidad y la precisión; 4- Evaluar dentro del mercado aprobado por la FDA las modalidades disponibles para implementar tratamientos de ablación; 5- Diseñar una opción de tratamiento que puede realizarse en régimen ambulatorio bajo anestesia local, que no impacte negativamente en los resultados de calidad de vida de los pacientes. El CaP ha sido identificado como la enfermedad piloto para Focalyx, para entregar un "GPS" como solución para el tratamiento dirigido de la glándula prostática destruyendo la enfermedad identificable sin efectos adversos, tales como: ansiedad por cáncer, incontinencia urinaria, pérdida de la erección y la eyaculación. Desde septiembre de 2013, más de 300 hombres han sido reclutados en NCT02381990- clintrials.gov para evaluar la viabilidad de nuestro protocolo por imagen (FocalyxDx), biopsia (FocalyxBx) y tratamiento (FocalyxTx). En esta revisión se detallan las herramientas disponibles para lograr el paradigma Focalyx para los hombres con CaP localizado.

Palabras clave: *Resonancia magnética. Fusión. Cáncer de próstata. Focalyx.*

Prostate Cancer: What are the issues?

The identification and subsequent characterization of the Prostatic Specific Antigen (PSA) levels in serum as a biomarker lead to approval in 1986 by the FDA in the United States for monitoring treatment success after radical prostatectomy (1). The success of the biomarker in such monitoring prompted critical studies in prostate cancer screening and by 1992 the FDA approved PSA testing as a screening tool (2). The effect of this latter measure triggered four critical events: 1- Increase in number of men identified with prostate cancer; 2- Significant cancer stage migration at the time of diagnosis; 3- A decrease in prostate cancer mortality rates - not completely understood; and 4- The recognition that current standard diagnostic and management practices in prostate cancer may lead to more harm than gain for men harboring this disease (2-5).

A conundrum of questions has surrounded Prostate Cancer management where just in the United States over 200,000 men have received such diagnosis yearly in the last 2 decades alone (6). An unquantifiable research effort has been conducted by thousands of health care providers, investigators, epidemiologists seeking to elucidate the trails from molecular origins of prostate cancer to its clinical virulent variants that pose a real mortality risk. In this process millions of patients across the globe have been treated by several means and all kinds of results have been reported. The pervasive word "may" has been the highlight of most reports, thus there is an ever growing speculation of critical aspects of prostate cancer. However, this millennium has witnessed the results from fine clinical trials generating level I evidence evaluating screening, the role of surgery and radiation as standard bears of treatment, its pros on survival and its cons in quality of life measured outcomes.

There are three randomized clinical trials that addressed screening and early detection (7-9). These are the screening and prostate-cancer mortality in a randomized European study (8), the Mortality results from a randomized prostate-cancer screening trial conducted in the United States (9) and the results from the prostate cancer chemoprevention trial (7). Notwithstanding sound criticisms and notable observations in the methodology and implementation of these randomized trials, all three studies failed to show a direct improvement in all cause survival attributable to early detection of prostate cancer (7-9). Furthermore, a diagnosis of prostate cancer with long term follow up in the PCPT trial did not impact survival as reported by Thompson et al (7). In addition, the results from both randomized trials comparing Radical Prostatectomy vs. Observation - Scandinavian Prostate Cancer Group 4 (SPCG) (3) and the Prostate Intervention versus Observation Trial (PIVOT) (4) showed no all cause survival benefit that could be attributable to surgery. Sub-analysis suggested for men in the intermediate risk group of PSA levels between 10 ng/ml to 20 ng/ml surgery provided a survival advantage. However most large Radical Prostatectomy series reported over the last two decades show that roughly 80% of those who had surgery had a PSA under 10 ng/ml (10). Certainly this group had no benefit according to the randomized clinical trials. Both studies showed that perioperative adverse events were not uncommon, in 15-20% of surgery patients (4). Two other studies focused on quality of life outcome measures after radical prostatectomy have provided level I evidence. The Vanguard study as reported by Bianco et al (11), evaluated early patient derived continence outcomes in men randomized to Solifenacin succinate vs placebo shortly after robotic radical prostatectomy. Data collected directly from a smart-phone device showed that 3 months after surgery, 27% of men required two or more pads a day to control urine leak (11). The prostate cancer survivors study reported by Sanda et al (12), covered patient and partners

QOL responses after Surgery, external radiation and brachytherapy (12). This study found that roughly one out of 2 patients treated by any modality had significant detriment in sexual function scores while 1 out of every 6 had voiding dysfunction post treatment. Not surprising, regret defined as "the emotion we experience when realizing or imagining that our current situation may have been better, if only we had decided differently" is observed in about 20% of men managed with surgery and these are not the 20-25% of men whom experience a post-surgical rise in PSA (13, 14). Many of these issues lead to a D recommendation - may benefit a small number of men but will harm many others - for Prostate Cancer Screening by the U.S Preventive services task force (5).

All these powerful observations lead to incremental recognition of the "overs" meaning over diagnosis and over treatment of prostate cancer with a resultant increased attention to active surveillance protocols as a mean to preserve QOL. However, active surveillance has it multiple challenges none of which is greater than the anxiety triggered by the word cancer. Such anxiety has been poorly evaluated by most surveillance studies that have focused on issues such as misclassification or reclassification of disease. Notably a recent report of the 1,298 men in the Johns Hopkins Active Surveillance Study revealed a 49%-64% "misclassification" rate and a 40% immediate loss of follow up (15). Furthermore, only 103 patients remained in the cohort after 5 years of follow up. Clearly, when it comes to surveillance talking the talk is easy yet most do not walk the walk.

On a brighter side prostate imaging has been profoundly impacted by MRI imaging. The evolution of Pelvic/Prostate MRI, specifically the emergence of multi-parametric MRI (mpMRI), of the prostate has created a powerful tool to walk what we call the Focalyx line between surveillance, focal or targeted management and whole organ treatment (16, 17).

The Focalyx Paradigm applied to Prostate Cancer Management

Focalyx came as a response to conceived as a response to the discussed Level 1 evidence data and advances in imaging technology applicable to Prostate Cancer patients. It aims to provide a complete and current perspective on focal targeted therapy, a novel likely transcendent management option for prostate cancer patients. Focalyx management is propelled by this GPS-like knowledge from mpMRI fusion techniques. Focalyx in a way mimics clinical behavior applied to other cancer entities such as bladder cancer, where radical bladder excision is seldom the initial course of management. Rather thorough vigilance with cystoscopy and resection when needed provides for control in a majority of patients. Moreover, radical surgery is performed when the tumor shows progression, pervasive recurrence signaling lack of response to focal management. We strongly believe that our Focalyx management strategy will achieve the primum non nocere intent, if not forever, for a significant time, and moreover, it will differentiate prostate cancers by their phenotype by challenging cancers to prove their aggressiveness. Our duty will be to produce factual research, demoting speculation and educating physicians and their patients regarding who is best suited for focal targeted therapy (Figure 1).

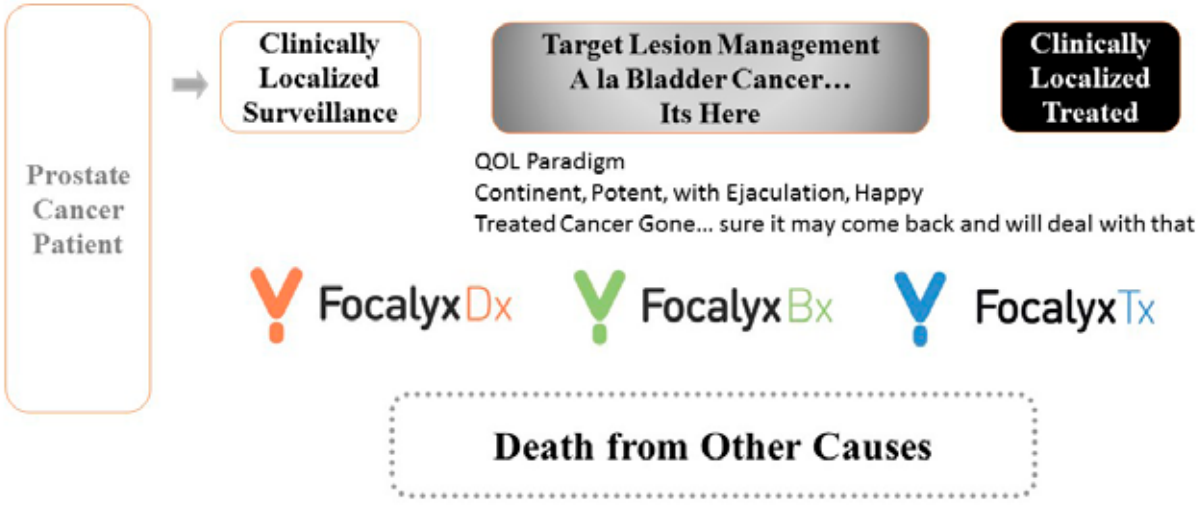


Figure 1. Illustrates the Focalyx paradigm for management of prostate cancer.

FocalyxDx™

Is directed at imaging information. One of the backbones of the paradigm related to the quality of imaging, this starts on how, from what source are they obtained. Not all mpMRI are equal. However, Focalyx seeks to evaluate and standardize imaging acquisition. Much progress in this area has been generated by our radiology colleagues answering the question of what is a well performed MRI, in other words what equipment is used at what tesla level, sequence of imaging, diffusion settings, b-values cuts, contrast injection rate per second and picture acquisition intervals. Focalyx provides solution for imaging departments and centers for quality assurance and optimization of MRI imaging.

The patient is prepared with enemas so the rectal vault is empty when the MRI is conducted. We routinely have a blood test to confirm their renal function. Creatinine and eGFR should be recorded on the request form. Contrast will be held in anyone with eGFR <45. The recommended protocol follows recommendations from the European association for Radiology and Urology (16-18). The critical steps include: no angulation, T2 Haste 3 plane localizer, Diffusion (b-values at 0, 100, 300, 800, 1000, 1400-T1.5 or 2000-T3) that will provide for ADC maps and values, Cor T2 SFOV High Res, Ax T2 SFOV High Res, T2 Spacing, followed by diffusion contrast enhancement (DCE) with dynamic Vibe measurements 16 runs every 17 seconds. Injection of contrast starts at the second DCE measurement at a rate of 3cc/s.

As mentioned, great image acquisition allows for pristine planning, such can be done by most DICOM processing software. There are a couple of things we ought to keep in mind. Most fusions platforms will allow for planning, however, few provide for multi-physician planning while making such plan readily available for the Urologist to execute. Thus Focalyx uses computer clients' solution that serves in the standardization process. Using our preferred fusion software, we follow these steps: 1-images and planning are easily transferable over our cloud; 2-We have implemented our Dx proprietary workflow that accomplishes a systematic multiplane review of coordinated MR sequences; 3-Prostate and prostate lesions contouring are performed seemly as the radiologist navigates the workflow, 4-A report is generated at the end of workflow. The report is quite illustrative and can be part of the medical record. Importantly, the findings from the workflow are saved into a session that serves as the basis for our FocalyxBx technique. Figure 2 shows a classic multi-panel view of a FocalyxDx processed MRI.

FocalyxBx™

For decades, the standard diagnosis of Prostate Cancer has been by a random transrectal ultrasound biopsy of the prostate gland (TRUSBx). This procedure is generally reserved for men at risk: elevated PSA levels or elevated PSA velocity, an abnormal digital rectal exam or a combination of those. Usually about 8-14 cores are taken from "zones" of the prostate. However, this approach

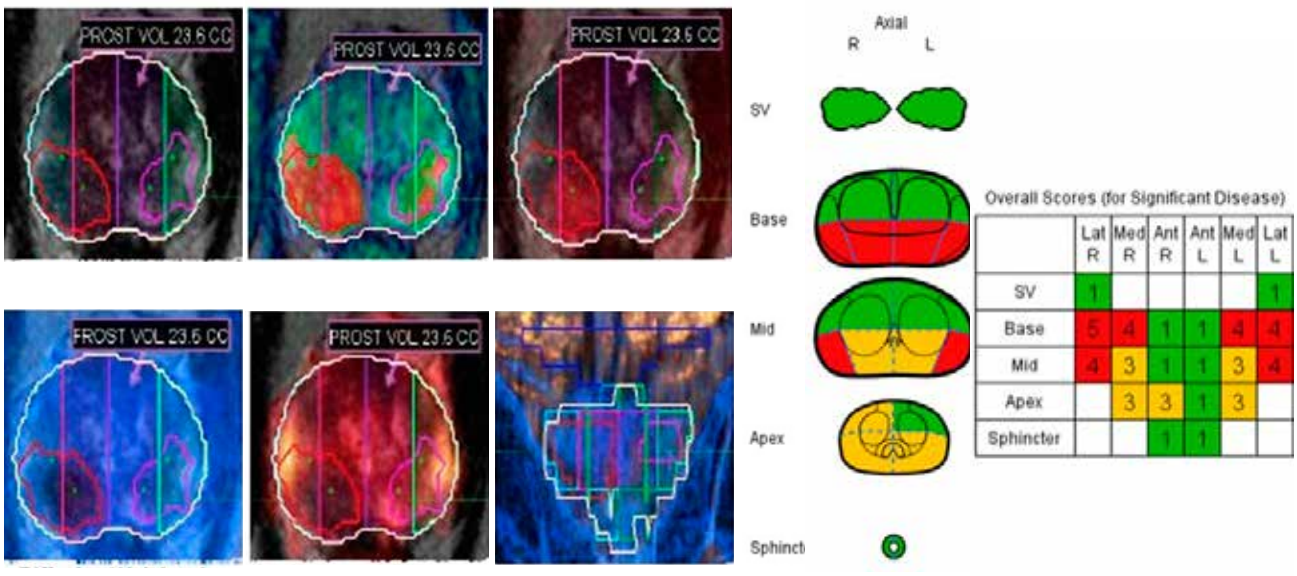


Figure 2. FocalyxDx. mpMRI processing in multiple views and shows plans for either Transperineal biopsy (preferred method) or a Transrectal biopsy. The color shows the areas that in the Transrectal case will be oversampled.

carries several limitations, such as: 1. A TRUSBx is performed "blindly", no distinct lesions are seen, it aims towards an area or zone of the prostate -i.e. right lateral base. As a result, areas that are in difficult location are seldom sampled; 2. They are more likely to detect low risk tumors or those of low to no clinical significance - tumors that are very unlikely to produce any significant harm to the patient, yet may trigger treatments that are likely to produce long term side effects; 3. When Prostate Cancer is identified using this techniques, there is no precise information regarding location and dimension of these tumors. Think "there is no GPS"; 4. The risk for infection is not marginal. Recent studies suggest that up to 2-3% of patients may require post TRUSBx admission because of post biopsy fever and chills triggered by bacteria.

Over the last 2-3 years several scientific studies have evaluated the impact in diagnostic precision that is provided by MRI/US Fusion Biopsies. However, none has been as thorough and telling as the recently reported investigation from the national Institutes of Health in the United States. The investigators in this study lead by Dr. Peter Pinto - published on JAMA in 2015 (18) - evaluated 1,003 men referred for a prostate biopsy. Using a crossover model all patients underwent both a "traditional" TRUSBx and a MRI/US Fusion Prostate Biopsy. The results were clear, an increased yield of 30% in detecting clinically significant and aggressive prostate cancer tumors associated to the MRI/US Fusion Technique (18).

Consequently, fusion imaging is at the core of FocalyxBx. However, several elements are required for the execution of our FocalyxBx protocol. It starts with the Focalyx client hosted in the Focalyx (MAC/PC), it's where all happens, is the trunk where the pillars plug. It can be monitored and "coached" live from our Focalyx headquarters fulfilling the fundamental premise of the Focalyx experience: to deliver high and quality, reproducible and safe Dx, Bx and Tx processes. Currently the MIM Software platform is one that best fits the Focalyx paradigms. The client and fusion software carries apps of all sorts and drivers preprogrammed that Communicate with Focalyx cloud systems leading to ease in the processing of patient information, system plain fixation and report generation. Since the client can be accessed from Focalyx HQ and or any Focalyx Coach, at any given time the Focalyx experience can be monitored with direct "live" feedback. This is a critical safe measure in successful reproducible quality assurance. As physicians gather experience this "live coaching" is less required.

HighDef Ultrasound machine with bi-planar probe: This hardware is tailored and optimized by Focalyx in order to deliver pristine fusion imaging. The high definition of the ultrasound system allows for incremental safety at procedure execution time. The visual interphase requires a multichannel video digital conversion that optimizes the ultrasound output imaging into the fusion software making real-time fusion possible.

Stepper: Digitalizes milimetric information acquired by the ultrasound transverse and sagital movements into the fusion software. After auto-capturing the ultrasound information and integrating it with the MRI diagnostic or treatment plans. The physician movement of the stepper produces real time fusion enabling unparalleled precision. Artifact movements from the operator hand are avoided as is any plausible image distortion. Such precision is sustained for the entire procedure.

With all these elements in place FocalyxBx (Figure 3) takes on where FocalyxDx left off. Our

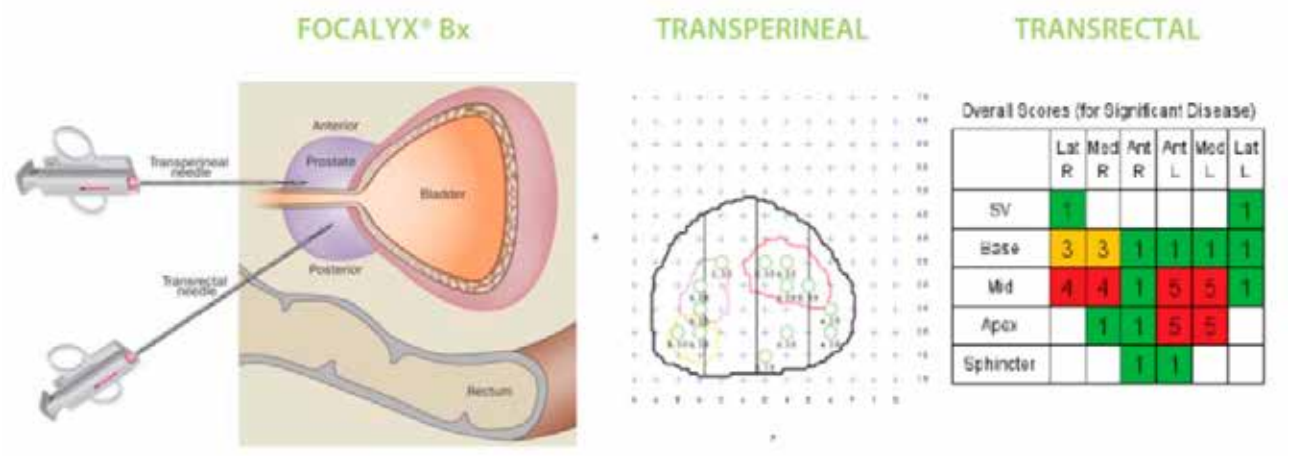


Figure 3. FocalyxBx- shows graphic views on how the samples would be taken depending of the technique.

team reviews the multi-parametric MRI and identifies any areas of interest - FocalyxDx - this process requires of specific software and using proprietary algorithms anatomic landmarks such as prostate, seminal vesicles and the urethra are identified along with any significant lesion(s) that has a >50% risk of harboring cancer cells. The fusion software allows the planning of the MRI/ Ultrasound Fusion Prostate Biopsy. The silhouettes of the prostate, its lesions and the planned sampling will be fused with the ultrasound prostate imaging, proving a GPS of the lesions and samples areas.

Either using our local anesthesia technique or under sedation or regional anesthesia the biopsy can be performed employing a transperineal technique "real-time" fusion or under a transrectal approach either under real-time or cognitive fusion (Figure 2). The advantages of the transperineal approach include a negligible risk for infections or bleeding and superior precision in focal target treatment (FocalyxTx) for those eligible.

FocalyxTx™

Builds on the premises of FocalyxDx and FocalyxBx. It aims at targeted the in-situ destruction of tumors guided by the most sophisticated imaging available: currently for prostate cancer, a multi-parametric Prostate MRI. Focalyx Tx moves away from the paradigm that the entire gland must be treated into a more direct and distinct one that aims to treat and destroy the targeted area(s) of the gland that harbors cancer, thus multifocality is addressed.

Thus our paradigm is a holistic approach that emphasizes quality of life. The premise is to destroy the tissue with cancer while preserving tissue without disease and therefore, prostate and adjacent organs function is preserved. We believe that patients must have all the information available for thorough decision making. Ask our physicians for the pros and cons of each approach and specifically ask yourself and your doctor the question: why this approach fits me best? what are the risks? and most importantly what are my options if the cancer recurs or comes back?

Whilst FocalyxTx is not for every patient with prostate cancer, however, most prostate cancer patients are eligible to a FocalyxTx protocol. Hardware solutions are required for implementation of a FocalyxTx solution - being Cryotherapy or hi-frequency ultrasound machines (HIFU) or generator for electroporation. Currently, there is one therapeutic technology where real time fusion has been tested and reproduced. Cryotherapy delivery mimics the introduction of needles sampling used for biopsy. It can also be performed in office, ambulatory and hospital settings. The very fact that a fusion diagnostic plan - that has provided the "GPS" coordinates to know with precision where the cancer is - can be employed for treatment delivery using cryoablation needles, has made this the option of choice. Electroporation of tissue, so called "Nanoknife" also involves placement of transperineal needles and allows for transperineal fusion using MIM Software, Bioject or Eigen. Real time fusion for HIFU has proven more complex and most focal HIFU treatments have been performed by cognitive approaches. However, software fusion companies such as In-Vivo, Eigen and MIM Software have developed packaged planning that is exported and imported by some HIFU machines so real-time targeted fusion HIFU can be conducted. Likewise, we envision in the coming future: fusion targeted brachytherapy.

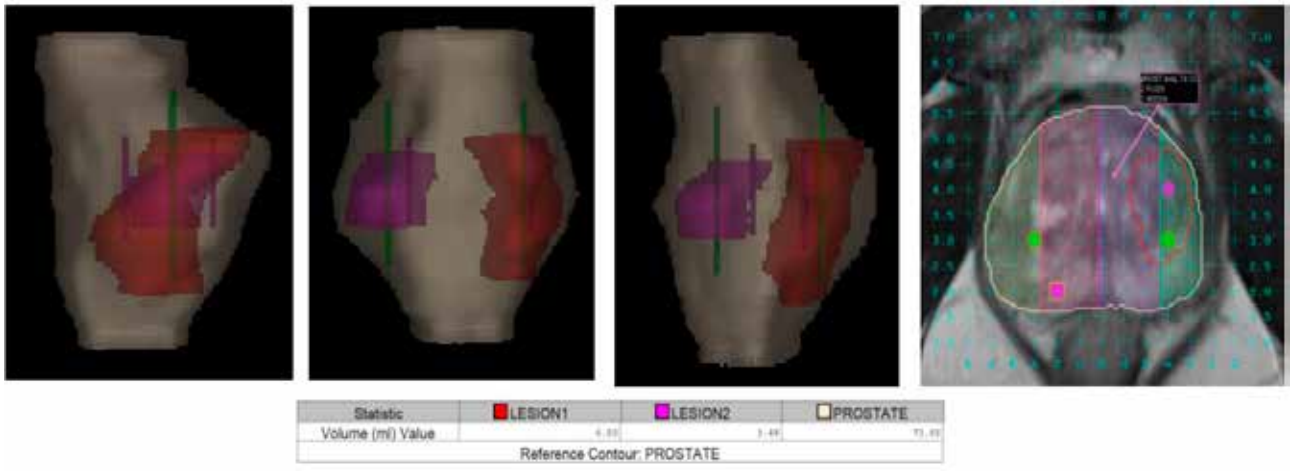
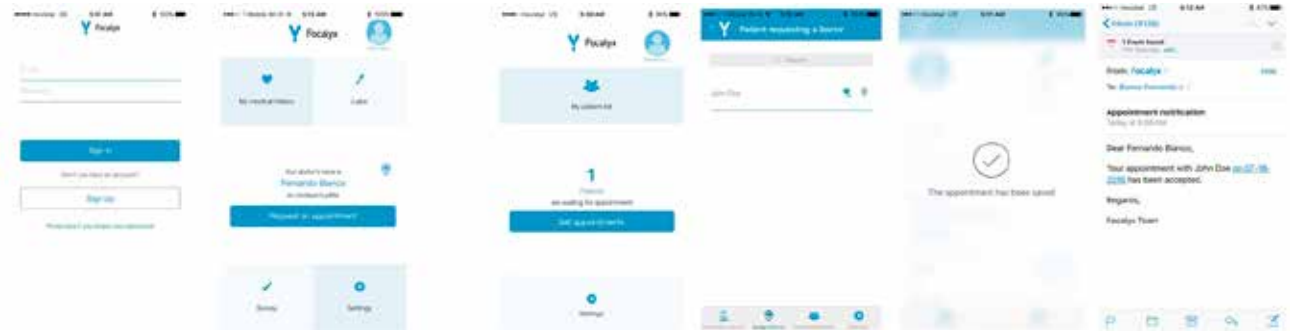
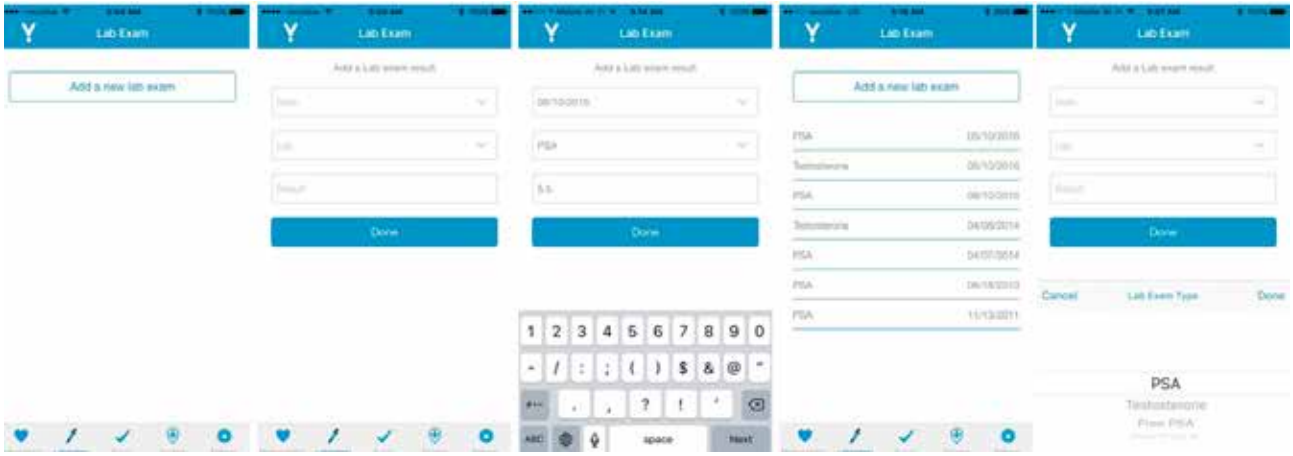


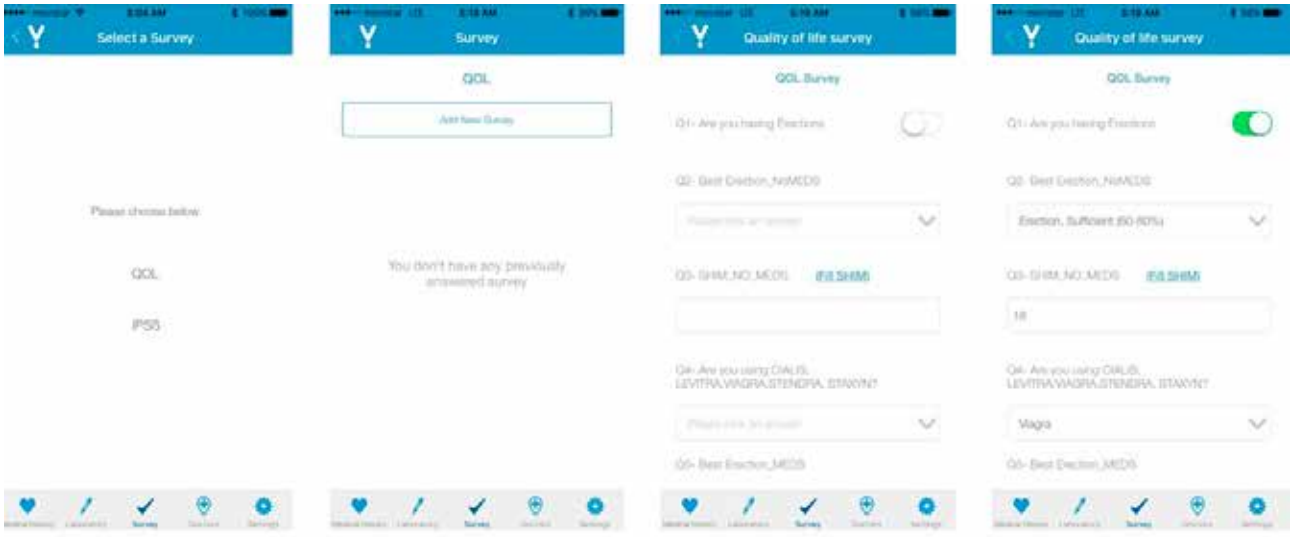
Figure 4. FocalyxTx – The figure shows #D views of treatment planning. In this particular case 2 lesions are targeted and would be hit with ice seeds(pink) and rods(green).



Panel A

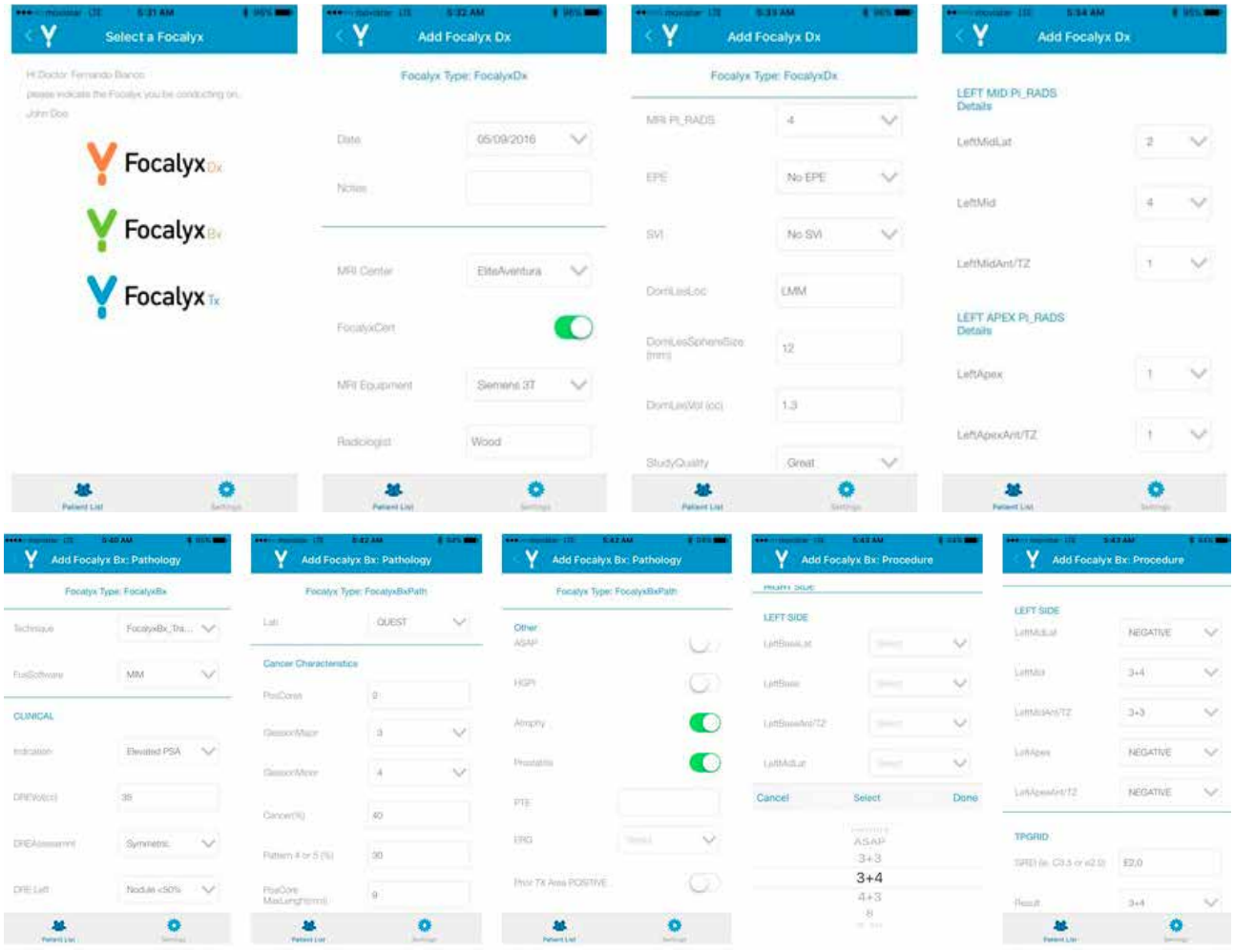


Panel B

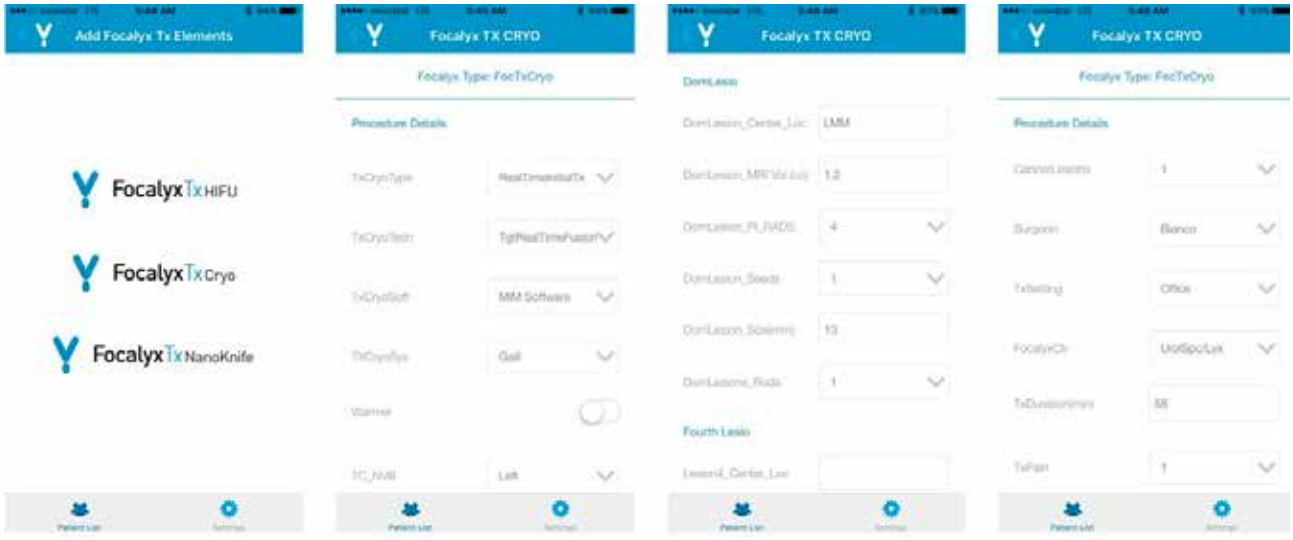


Panel C

Figure 5. Focalyx App. Freely downloadable from the app store. The panels show several transitions across the platform that ensure non-intrusive close monitoring using a smart phone device.
Panel A). Patient and Physician interphases in the appointment request and response flow on the app.
Panel B). The app shows the ease of adding a lab exam, importantly this can be done by patient or physician.
Panel C). Patient interphase for adding QOL information upon request by physicians or Focalyx algorithm triggered by due follow up. Importantly, QOL information can only be added from patients. The information is available to physicians to see but can't edit.

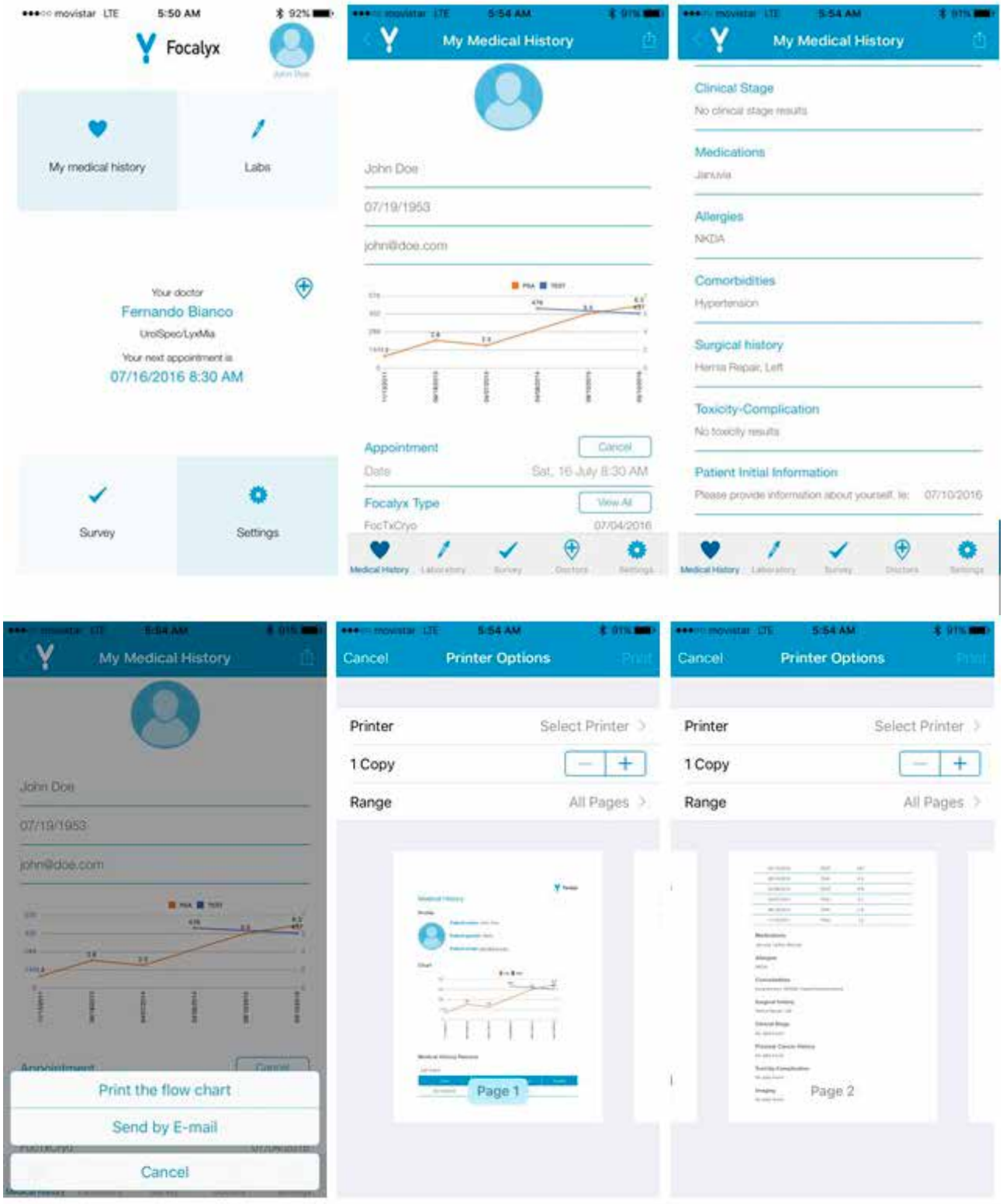


Panel D



Panel E

Figure 5. Focalyx App. Freely downloadable from the app store. The panels show several transitions across the platform that ensure non-intrusive close monitoring using a smart phone device.
Panel D). Focalyx Dx and Bx digital data acquisition at the time of the respective procedure.
Panel E). FocalyxTx Cryo interphase showing data digitalization by Physician at time of procedure.



Panel F

Figure 5. Focalyx App. Freely downloadable from the app store. The panels show several transitions across the platform that ensure non-intrusive close monitoring using a smart phone device.
Panel F). Medical History synopsis along with graph showing PSA and Testosterone.
Powerful tool that patient's controls, and share with any caregiver.

We have observed several advantages in our experience of over 300 patients with FocalyxTxCryo, among them:

• Minimally invasive office based (without incisions) precise curative approach.

• Source of energy is freezing (Cryoablation) has over 10 years of clinical data that supports this energy source security and efficacy destroying tissue, particularly cancer tissue.

• Individual tailored treatment executed in an ambulatory or office center.

• Avoids hospital stay and risk hospital acquired infections, expedited recovery time fast return to regular daily activities.

• Minimal risk of rectal irritation.

• Improvement in urinary function. Unlike most prostate cancer treatments that have strong associations with voiding dysfunction and urinary incontinence. Targeted fusion cryoablation provides opportunity for concomitant destruction of prostate enlargement tissue leading to improved flow rates and efficient voiding.

• No postoperative pain.

• Outstanding choice in rescuing patients whom experience recurrence after management with other approaches such as radiotherapy or seeds.

• It does not burn any bridges. Patients are carefully monitored and those who prove to harbor more aggressive cancers can be managed with robotic surgery or external beam radiation.

FocalyxTxCryo does not escape the old adage of any action generates reaction. However, the precision involved in the treatment delivery ensures a very low probability of any significant side effect. Prostate intervention may trigger urinary tract infections; however, the risk is under 1% because of the transperineal approach.

The most common adverse event is urinary retention after removal of the Foley catheter. This is why we take our time to ensure prostate swelling is greatly diminished at the time of pulling the catheter out. Transient urinary incontinence may happen albeit is rare. Sexual dysfunction may occur, especially if there is preexisting weakness of erections. Otherwise if happens should be transient and limited to weeks' time.

Focalyx Apps

The Focalyx App, currently available in iOS represents the backbone of the Focalyx management paradigm. Widely available and freely downloadable from the iOS app store. It aims to provide a flawless simple non-intrusive interaction among patient, physicians and departments or practices. It incorporates the digital findings of Focalyx Dx, Bx and Tx. It empowers patients and serves them as a tool for a personalized health record where they can add elements of their medical history, laboratory information and importantly fill validated QOL surveys. Importantly, physicians can sole add any Focalyx plan, patients can see them and can share their information at their own will. QOL information can only be added by patients. Under the interphase, physician may request and can see responses but have no ability to add QOL measures. This keep outcomes patient based, therefore more transparent and less biased. Patients can also inquire about appointments with their physicians and its proprietary Focalyx algorithms wars both patients and physicians of missing tests that are required for thorough follow up. For example, the recommended follow up after executing a FocalyxTx treatment requires PSA, testosterone levels testing every 3 months for the first year along with QOL surveys-IPSS and SHIM scores. It also mandates for a compulsory 1-year fusion biopsy of treated areas along with any suspicious areas on mpMRI. When the biopsy is negative, surveillance is performed solely by annual or bi-annual mpMRI. When a patient goes 10 days without recording a follow milestone, the Focalyx App will alert them and their physicians. Such reminder is quite helpful for busy patients and physicians who traditionally don't have such tool for effective monitoring. Figure shows examples of screens with information in the Focalyx App.

CONCLUSION

Focalyx is committed to providing outstanding Imaging processing, 3D Fusion Biopsy planning and Fusion Treatment services to patients suffering from Prostate Cancer managed at physician offices, ambulatory and hospital facilities. It also provides a tool to keep information available at the palm of patient and physicians hands. Over the last few years, our team has been hard at work developing a transformational clinically relevant management model that strides in the quality of life for both: men at risk or those who have a diagnosis of Prostate Cancer. The strong and grateful reactions from our patients towards our management paradigm let us to further work. Evaluating vast implementation with quality

assurance that cements patient confidence as we help them overcome the impression and fear triggered by a Prostate Cancer diagnosis and the consequential unintended effects associated with known standard management. The positive responses and feedback to our novel diagnostic and management systems that provide reproducible outcomes for our patients.

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