Article

A novel modality enables new evidence-based individual risk stratification that can lead to decisive management and treatment decisions in prostate cancer

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Abstract: A key step in providing management/treatment options to men with suspected prostate cancer (PCa) is categorizing the risk for the presence of benign, low risk, intermediate risk, or high-risk disease. Our novel modality brings new evidence, based on the long-known hallmark characteristic of PCa – decreased Zinc (Zn), which is the most direct metabolic sign of malignancy and its aggressiveness. To date, this approach has not been adopted for clinical use for a number of reasons that are described in this article and which have been addressed by our approach: Zn has to be measured on fresh samples, prior to fixating in formalin, therefore samples have to be scanned during the biopsy session; as Zn depletion occurs in the glands, where the tumors develop, estimation of the glands' levels in the scanned tissue along with their compactness, are essential for accurate diagnosis. Combined with the Zn depletion, this facilitates a reliable assessment of the disease aggressiveness. Data gathered in the clinical study described here indicate that in addition to improving the biopsy quality by real-time interactive guidance, a malignancy score can now be established for the entire prostate, allowing higher granularity personalized risk stratification and more decisive treatment decisions for all PCa patients.

Keywords: cell proliferation; epithelial glands; interactive biopsy guidance; malignancy score; risk stratification; individual treatment recommendations.

1. Introduction

1.1 Prostate Cancer Background

Prostate cancer (PCa) is the most common cancer among non-smoking men with an incidence rate of 60% in men over 65. Early detection and accurate risk stratification are essential for providing appropriate management/treatment options leading to reduced morbidity and mortality. Delayed and/or inappropriate treatment can lead to the evolution of more advanced disease such as metastases to the bones or bladder and eventually death.

Current diagnosis consists of screening — PSA blood tests — followed by needle biopsy, where 12-14 cores are typically extracted and sent for histopathology, which has the largest weight in treatment decision making today.

About 2 million biopsies per year are performed in the US and Europe combined [1].

1.2 Zinc Depletion as a PCa Marker

PCa stakeholders agree that *"… New biomarkers are needed to avoid unnecessary biopsies and radical prostatectomies to distinguish benign from malignant lesions and to better discriminate localized from advanced disease..."* [2] (pp. 1355). A known biomarker — depletion of Zn in the epithelial glands of the prostate — is already being used in research for a few decades, but hasn't yet been reduced to the clinical practice.

"… It has been clinically established that markedly decreased zinc concentration in prostate cancer tissue and prostatic fluid, compared to normal and benign prostate, exists in virtually all cases of PCa and, thereby constitutes the most consistent hallmark signature identification of PCa. The decrease in zinc is an early event in the development of malignancy and persists in progressing malignancy. These relationships offer the opportunity for an accurate specific biomarker…" [3] (pp. 11,12). In spite of this powerful citation and other works [4-7], these important findings rest in the domain of researchers and until now haven't been incorporated into the PCa diagnosis routine clinical flow.

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1.3 X-Ray Fluorescence (XRF)

Traditional qualitative microscopy methods of Zn detection are far from being sufficiently accurate for PCa grading, nor have the ability to avoid impacting the clinical workflow.

XRF scanning is used for very accurate non-contact measurement of trace elements. It is in use also for several medical applications such as in-vivo detection of: lead (Pb) in bone; cadmium (Cd) in kidney; mercury (Hg) in brain; and iodine (I) in thyroid. XRF is a proven non-destructive and safe technology, most appropriate for detecting small quantities of elements, including Zn. Since biopsy samples sent to histopathology are fixated in formalin and lose the Zn information, XRF scanning must be done on fresh biopsy samples, during the biopsy session, to achieve accurate quantitative measurements without compromising the workflow or delays in the biopsy session.

Scientists at the Weizmann Institute of Science in Rehovot, Israel (WIS) have conducted an extensive study at Sheba Medical Center in Ramat Gan, Israel [8,9], using XRF for scanning fresh biopsy samples from over 600 patients (over 2,400 biopsy cores), in order to establish for the 1st time that Zinc depletion is proportionate to the severity (grading) of PCa. The results have indeed consolidated the correlation between PCa aggressiveness and Zinc depletion. However, they were short of the required accuracy and resolution needed for assessing individual PCa aggressiveness.

2. Materials and Methods

This article elaborates on a novel modality — ScoRisk, for accurate prostate cancer (PCa) aggressiveness scoring, risk stratification and treatment decision support, based on Zn depletion in the PCa epithelial glands and related proliferation changes in tissue parameters (covered in one granted patent and 2 pending patents).

2.1 X-ray Fluorescence (XRF) for ScoRisk

XRF scanning provides the data described in the graph of Figure 1: Zn = Zinc count; C = Compton count (inelastic scattering), which is mainly indicative of tissue quantity; C_0 = C + (the elastic scattering component), which includes the component of the K-lines of the Rhodium target in the X-Ray tube and is indicative of cell proliferation/density/compactness; The difference ΔC= C0-C is a direct surrogate measure of the amount of epithelial glands in the tissue.

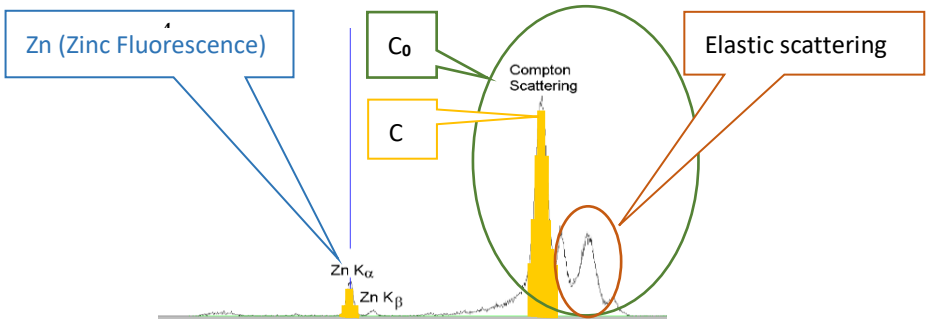

Figure 1. Zn and scattering counts

As there is considerable non-uniformity in the thickness of the biopsy samples while scanning, C_0 is used for normalizing the Zn count, as due to the elastic scattering component, it includes a more representative indication of overall tissue quantity/proliferation/density than C. To facilitate this, we use a $45^0/45^0$ source/detector configuration.

C_0 is also crucial for deriving personal tissue information, indicative of molecular structure, cell proliferation and density/compactness - changes which occur in the epithelial glands when malignancy starts and increase while tumors develop [10].

2.2 The Souraski Clinical Study

The purpose of the study was to gather XRF tissue and Zn data from fresh biopsy samples on parameters indicative of PCa, for the development of Prosight's algorithm, ScoRisk.

2.2.1 Equipment

An off-the-shelf XRF (M4 Tornado from Bruker GmbH), modified and adapted to our specific needs was utilized. The modifications included beam size, intensity and scan time

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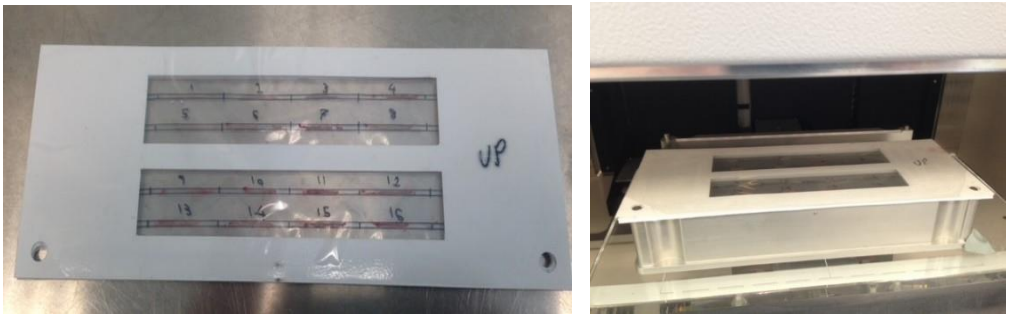
that allow, in due course, routine use of the final product during the biopsy session. For the purpose of this study, real-time was not essential.

The beam diameter was 2 mm, which at 45^0 resulted in a spot size of 2mm by 3mm in the scan direction (the 2mm diameter covered for the typically ~1 mm wide sample that is often distorted while releasing the sample from the biopsy needle). The pitch (pixel) was 1 mm. A dedicated low background plastic tray, with mylar openings was used for placing the samples at predefined, numbered intervals. An X-Y-Z stage was installed, including a dedicated tray holder. It permitted moving the tray holder to the loading station and then realigning and focusing the samples on the tray under the beam prior to start of scan.



(a) **(b)**

Figure 2. Samples tray and tray holder in the Bruker XRF device. (a) Low background plastic tray; (b) Tray holder located on the XYZ stage, with plastic tray on top.

2.2.2 Study Routine

Upon extraction, the biopsy samples were placed by the urologist's assistant in numbered grooves onto the plastic tray. The tray with several samples was then placed onto the XRF tray holder; all samples were scanned in batches and subsequently placed in individual formalin bottles, as routinely done during biopsy, and then sent to histopathology for diagnosis.

2.2.3 Pathology Report

The pathology report was at the level of the sample. The diagnosis for each sample was provided according to the Gleason grading scheme. [1]

For negative (benign) samples, pathology provided the type of tissue (SGH, FMH) and/or metabolic condition (BCH, TCM, AA, MCI and Prostatitis [2]).

For positive (PCa) samples, pathology provided the sample score. For example: g6(33) score, corresponding to two g3 tumor grades in the sample; g7(4,3), corresponding to g4 and g3 tumor grades in the sample, etc.

Positive samples scores encountered in the study included: g6(33), g7(g34); g7(g43), and g8(g44). Since no g5 tumor grade was encountered, g9 and g10 samples scores are not listed. The cancerous portion in the samples varied from 5% to 90%. A total of 320 biopsy samples (cores) from 20 patients with 16 biopsy cores each (about 3200 pixels) were scanned in batches as described above.

2.3 Data Analysis and Results

2.3.1 Background

In prostates, Zn accumulates mainly in the epithelial gland cells. Each sample/pixel contains variable amounts of epithelial gland cells within the stroma and/or fibromuscular supporting tissue. The amount of Zn in benign prostate tissue is typically linearly dependent on the amount of gland cells in that tissue. The linear relationship between tissue and Zn values for normal tissue (i.e., non-cancerous or other metabolic tissue) indicates that the tissue value in each pixel incorporates the relative amount of epithelial gland cells in that pixel.

PCa develops predominantly in epithelial glands when the Zn is depleted and also tissue proliferation is induced. Consequently, the Zn/C_0 ratio for PCa pixels/samples will be smaller than that for benign pixels/samples.

2.3.2 Analysis Observations

[1] For the sample level, histopathology diagnosis was provided according to the then used Gleason grading and scoring scheme for PCa. The newer sample grading scheme by Epstein (GG1 to GG5), is not used here in order to avoid confusion with Epstein's prostate grading scheme (G1 to G5, used by Prosight in this article for scoring the prostate malignancy).

[2] Inflammation, Fibro-Muscular Hypertrophy (FMH) Stroma & Glandular Hyperplasia (SGH),
FMH or SGH + metabolic (Atrophic Acini, Basal Cell Hyperplasia, Transition Cell Metaplasia, Mild Chronic Inflammation)

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During the analysis of the data, the following was observed:

- Zn levels vary substantially among prostates and therefore a population (all prostates, all cores, and all pixels) normalization scheme was introduced.
- Each prostate has a unique malignancy signature/score (akin to Epstein's Prostate Grade [11]), which is dependent not only on the Zn content, but also on tissue characteristics typical of PCa: oncogenic manifestations of neoplasia/hyperplasia in glands and tissue proliferation mechanisms, which are known indicators of the malignancy processes.

It is important to note the distinction between a low level of Zn and an actual cancer-typical Zn depletion in a biopsy sample or pixel.

2.3.3 Analysis Steps — Scanning and Data Generation

During scanning, Zn, C and C_0 for each pixel are acquired. As discussed above, C is used for volume and density normalization of Zn, and C_0 - which includes C - is used as a measure of tissue proliferation.

The following parameters are then generated for each pixel, sample and prostate: $\triangle C = C_0 - C$ - which is a measure of the relative amount of epithelial glands in the tissue; Zn/C; and Zn/C_0, which is the amount of Zn normalized to tissue proliferation.

A population database, comprised of the statistical population levels for each of the parameters is then generated from the data from all the pixels from all the samples, from all the individual prostates scanned by the system, following data cleaning (see below).

Subsequently, the values for each pixel, sample and individual prostate are normalized to the respective population levels.

2.3.4 Data Cleaning - Population and Prostate Levels

- The normalized population level data are cleaned to remove invalid pixels: non-uniform, or certain edge pixels, or pixels that are disconnected from the sample, or very small and/or very thin pixels, typically characterized by very small C and very small Zn/C.
- Pixels with very small $\triangle C$, indicative of low or no glandular tissue.

In addition, for each individual prostate, standard statistical steps are used to remove outliers at the level of the prostate: pixels with very small C and/or $\triangle C$ and/or Zn/C.

2.3.5 Prostates - Population Data

When establishing the PCa aggressiveness of the prostate – the Malignancy Score – the parameters for each prostate are normalized and compared to the corresponding Population parameters. Table 1 below presents the current average values of the population parameters database (not including 2 prostates with prostatitis – that we detected as such).

Table 1 - Population parameters database

Statistics	C_0 (tissue)	C	$\triangle C$ ($C - C_0$)	Zn	Zn/C	Zn/C_0
Mean	1.14	1.00	0.14	1.00	1.41	1.23
STD	0.24	0.23	0.05	0.76	1.01	0.88
Q1	0.96	0.83	0.10	0.47	0.60	0.60
Median	1.13	0.99	0.13	0.78	1.10	0.97
Q3	1.29	1.15	0.17	1.24	1.76	1.54

Q1 - 1st quartile; Q3 - 3rd quartile

2.4 Prostates Aggressiveness – Malignancy Score

In the standard of care prostate grading scheme by Epstein [11], the lowest level is G1 and the highest is G5. Our prostate malignancy scoring scheme differentiates between G0 (not available in Epstein's prostate grading scheme) and G1 in two aspects:

1. G0 corresponds to prostates where no positive samples were identified during the biopsy - due to either the absence of tissue proliferation or Zn depletion or both at the prostate and core levels; while,
2. G1 corresponds to a prostate where tissue proliferation (C_0) and Zn depletion for the prostate were around population average and only a few samples had levels of C_0 and Zn depletion (Zn/C_0) characteristic of low malignancy score PCa.

This prostate aggressiveness scoring distinction has importance in relation to early detection and the type of active surveillance that the Urologist decides for such patients.

2.4.1 Prostate Malignancy Score - Diagnosis Results

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Prostate characterization during a biopsy is possible since Zn, C_0 and Zn/C_0 for negative prostates are significantly different than the same characteristics in positive prostates.

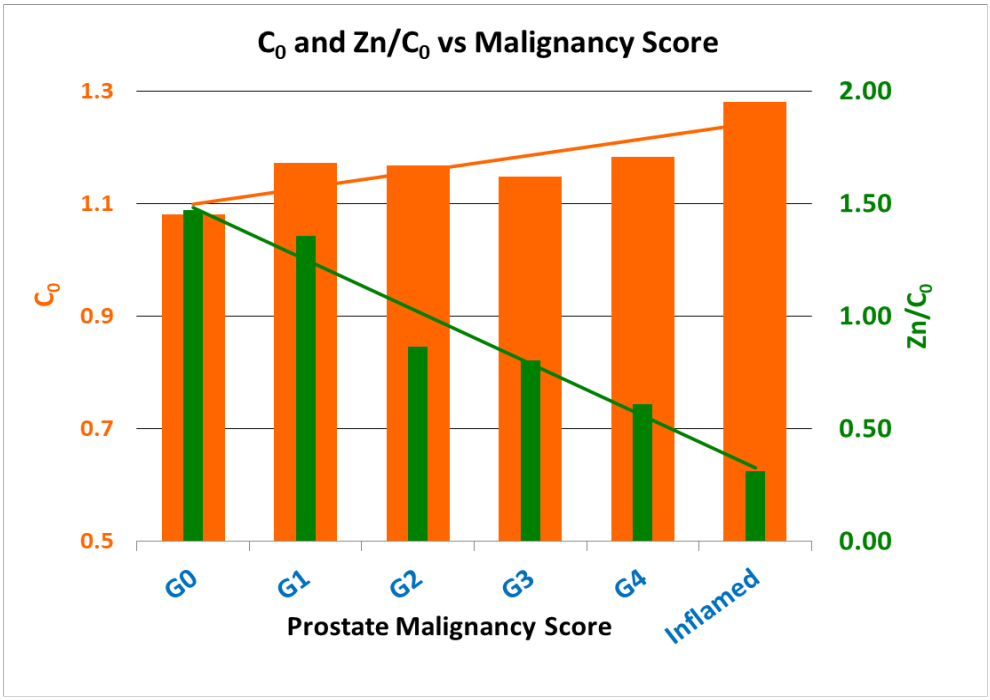

Figure 3. Prostate Malignancy Scores as a function of the prostate levels of C_0 (tissue proliferation) and Zn/C_0 (Zn depletion). No G5 prostates were found in this study.

There is a strong and evident differentiation between the XRF levels of C0, and Zn/C0 characteristics for high PCa malignancy score prostates and those for benign or low malignancy score prostates. The levels of these parameters are also dependent on whether the Zn level in the prostate is low, mid or high. It was found that:

1. For Low/Mid Zn prostates (positive):
   - The mean C_0 for PCa samples classes are significantly higher than those of the benign classes.
   - The mean Zn/C_0 for PCa samples classes is smaller (and for the majority of the classes, much smaller) than the benign sample classes.
2. For High Zn prostates:
   - High Zn PCa Prostates have much higher C_0 (tissue proliferation) values than those for High Zn, benign Prostates.

Additionally:

- High malignancy score in a prostate is also correlated with a high number of positive cores in the prostate.
- Decrease in Zn/C_0 in tandem with high tissue proliferation (C_0) is indicative of higher malignancy score.

2.4.2 Pixels Grading

Once the analysis for the prostate is generated, all population-normalized pixel parameters are classified in relation to the prostate parameters. Pixels with very low C, very low $\triangle C$ and very low Zn/C0 relative to the respective prostate levels are cleaned out of the sample analysis. The Following are some global rules for the pixel level grade:

- High Zn/C_0 → No Zn depletion → non-PCa pixel.
- Very Low C_0 → No tissue proliferation → non-PCa pixel.
- Mid or low Zn/C_0 and Mid/High C_0 → PCa pixel.

Below are two examples, out of the scanned prostates.

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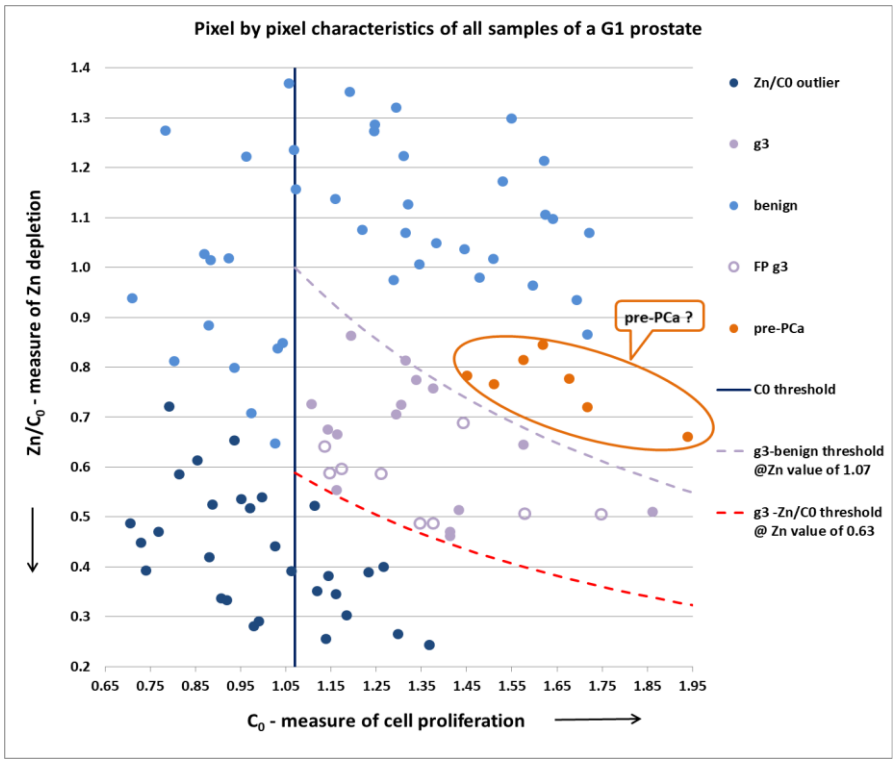

Figure 4. Pixel characteristics and thresholds in a low PCa malignancy score, G1 Prostate (9 samples out of 16 were g33 — only g3 and benign pixels)

The positive pixels — g3 in this case — have a C_0 (x-axis) threshold level = 1.07 (for this specific prostate), and have values of C_0 and Zn/C_0 (y-axis) bound between the two Zn threshold lines for this specific prostate: lower threshold between g3 and outlier low pixels corresponding to a Zn value of 0.63; and upper threshold between g3 and benign pixels corresponding to a Zn value of 1.07.

The same logic applies for the High PCa malignancy score (G4) Prostate below.

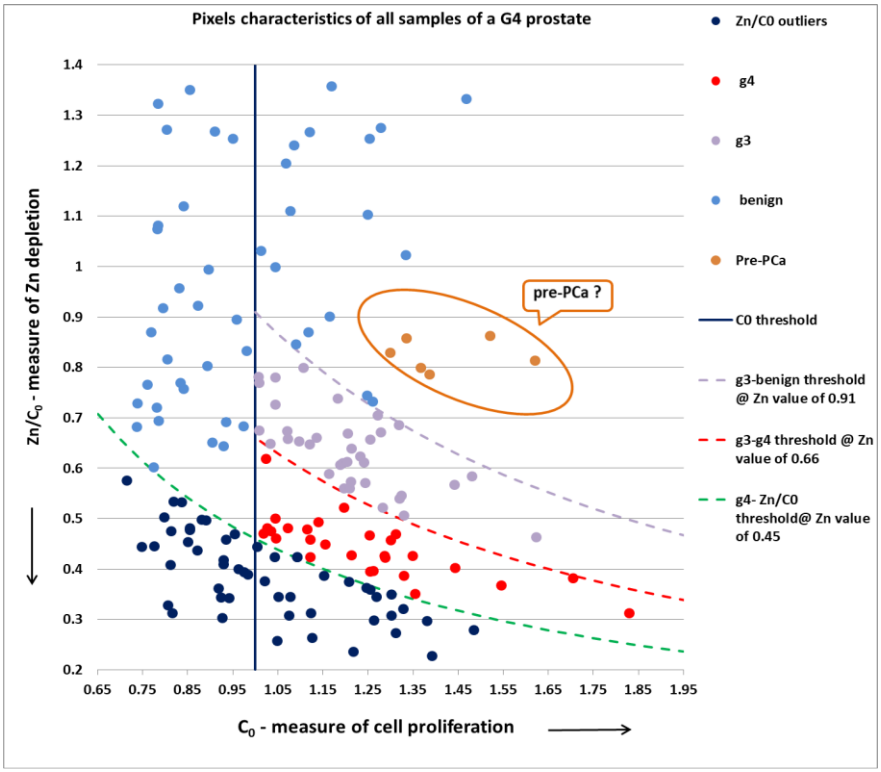

Figure 5. Pixel characteristics and thresholds in a high PCa malignancy score, G4 Prostate (one single benign sample, and several g34, g43 and g44; pixels: benign, g3 and g4).

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The positive pixels — g3 and g4 in this case — have a common C_0 threshold level = 0.97 (for this specific prostate), and have values of C_0 and Zn/C_0 bounded between the three Zn threshold lines: lower threshold boundary between g4 and outlier low pixels corresponding to a Zn value of 0.45; a middle threshold boundary between g4 and g3 pixels corresponding to a Zn value of 0.66; and the upper threshold boundary between g3 and benign pixels corresponding to a Zn value of 0.91.

Regarding the "pre-PCa" pixels in both graphs above: *since Zn depletion precedes the morphology changes*, it seems reasonable that in the near future, the algorithm will have the ability to identify such cases and further improve sensitivity.

Such a "template" of thresholds is generated for each prostate.

2.4.3 Biopsy Metrics

The accuracy of our non-blinded analysis is measured vis-a-vis the pathology findings that serve as an absolute reference against which the analysis quality metrics are calculated. Below, in Table 3, all biopsy quality metrics are tabulated.

Table 3. Analysis — Biopsy Quality Metrics

Metrics	Prostate Level	Sample Level
After Data Cleaning [3]	20	308
P	10	64
TP (true positive)	10	57
N (including Inflamed)	10	244
TN (true negative)	10	240
Inflamed Prostates (out of TN)	2	32
False N	0	7
False P	0	4
Sensitivity	100%	89%
Specificity	100%	98%
Accuracy	100%	96%

As the Zn depletion precedes the morphology changes on which the pathology findings are based, note that indeed, at the sample level, FP/P is much lower than FN/N (about 10% vs 3%).

3. Considerations on the Routine Use of ScoRisk in the Clinic

Unlike the clinical study — where real time grading and guidance wasn't required and samples were scanned in batches — during routine use in the clinic, the biopsy samples are introduced one by one into a desktop X-ray fluorescence (XRF) device for scanning, immediately after removal from the prostate.

While the urologist removes the next sample, the grades/score of the previous sample is graphically displayed on the ultra-sound (US) screen (which is used in ALL types of biopsies), superimposed on the US image, in tandem with the "rolling/evolving" prostate malignancy score — both, along with the statistical certainty; the more samples are extracted, the higher the certainty.

After scanning, the samples are placed in the formalin bottles for histopathology as done routinely, with negligible impact on the flow and without losing time.

3.1 Flowchart — as Part of Routine Clinical Flow

The flowchart in Figure 6 below, outlines the real-time algorithm of ScoRisk that is to be used during a biopsy for the prostate malignancy scoring, sample/pixel grading and during-biopsy interactive guidance.

Additional details are described below the flowchart, according to the numbering of selected blocks.

[3] Samples with very few pixels (<4) and/or missing in the pathology report

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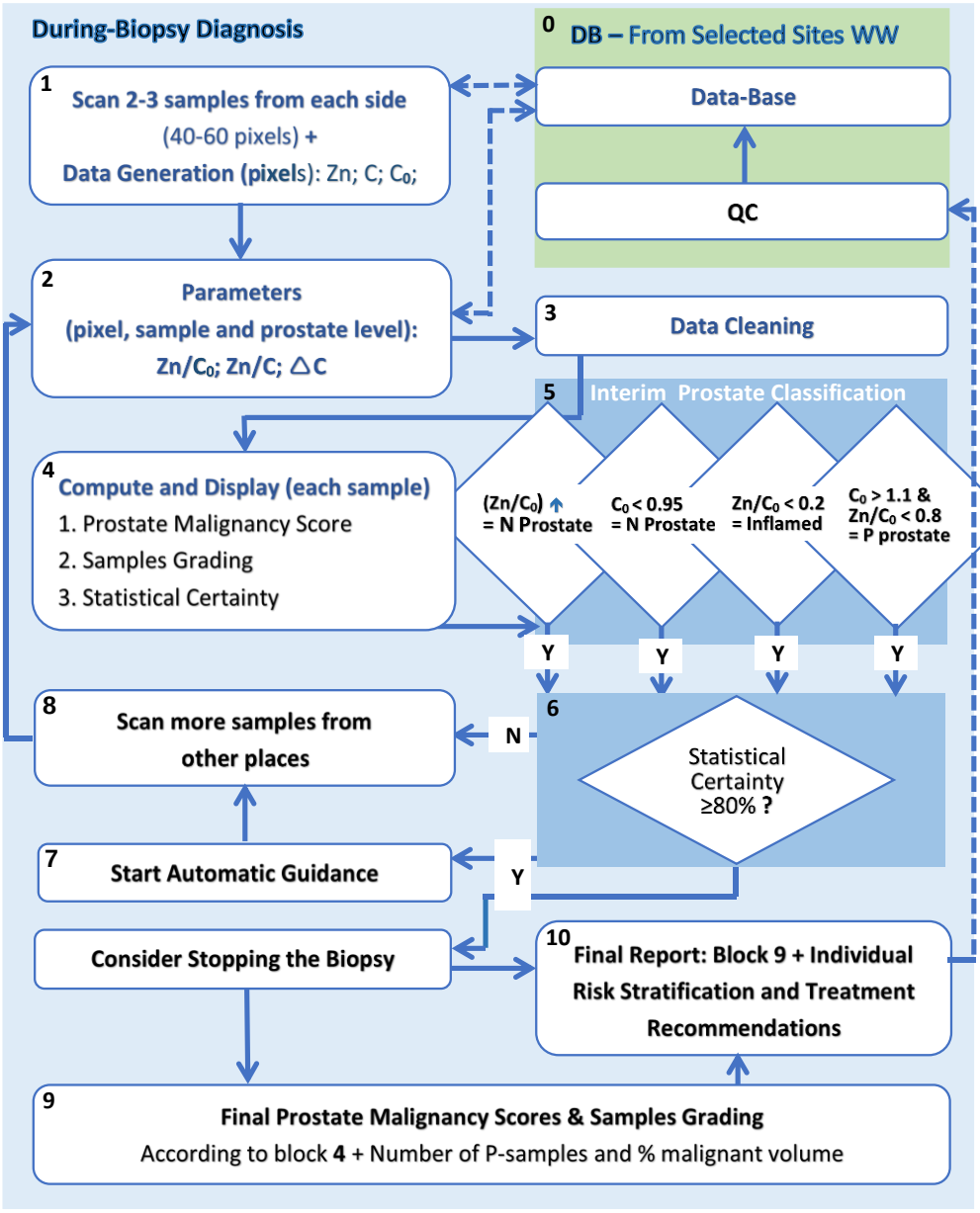

Figure 6. Clinical Flowchart – Malignancy Scoring, Sample Grading/Scoring and guidance during biopsy

Block 0: Data-Base — The following is included in the Data-Base for reference during the biopsy session: data (block 1), parameters block 2); pathological conditions, as gathered from selected sites, following QC; pixels and samples' grades and prostate malignancy scores; compartmentation (such as ethnicity, age, etc.); clinical data that might improve the accuracy in due course (such as PSA, PSA density, PSA velocity, etc.).
Block 1: Scan + data generation — The same XRF scanning scheme used in the clinical study is employed following the removal of each sample.
Block 4: Compute and Display — When establishing the Prostate Malignancy Score the calculations are at the population level in the DB. When establishing the pixels and samples Grades, the classifications are at the combined population and prostate (biopsy) levels.
Block 5: Interim Prostate Grading

Following the removal and scanning of 2-3 samples (ca. 10 pixels each) from each side of the prostate (40-60 pixels) an interim prostate classification is established according to the malignancy score rules at the prostate level.

Once the analysis for the prostate is generated, all pixel parameters are normalized and classified in relation to the prostate parameters.

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In some clear-cut cases it could be established quite early in the process that the prostate is benign and the biopsy could be stopped to avoid unnecessary risk of complications to the patient.

In cases of MRI-guided biopsy, an additional interim classification could be considered for stopping the biopsy — upon confirming one or two positive g7(43) samples in an ROI (region of interest).

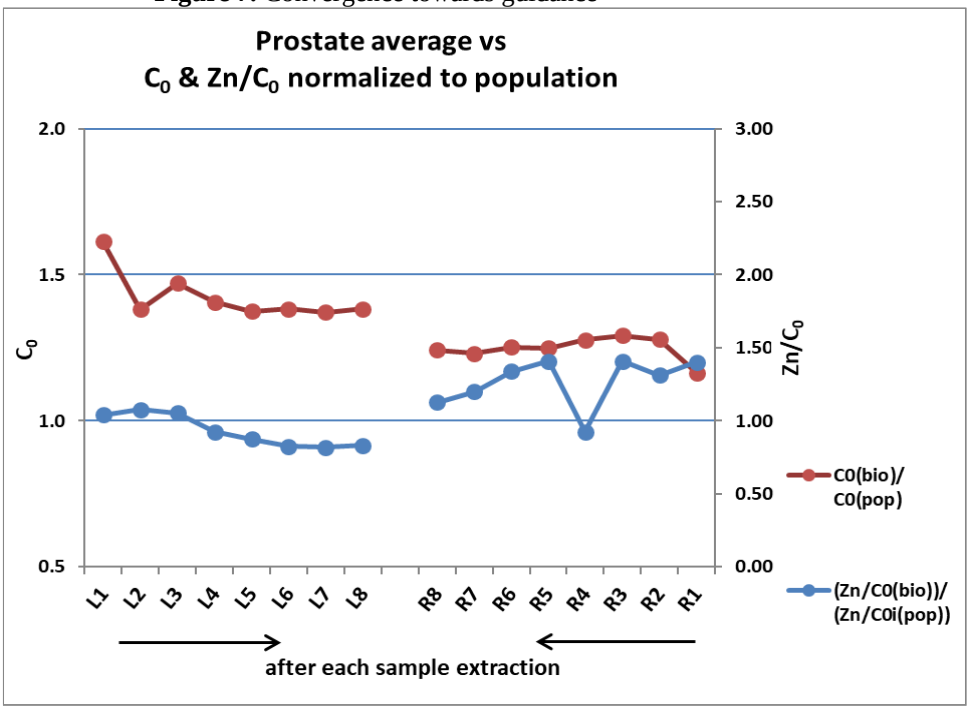
Block 9: Final Prostate Malignancy Score

The thresholds derived from Table 1 — adjusted to the individual prostate, along with the number of positive samples and % of malignant volume — are reiterated and used for final-grading the samples and generating the final malignancy score, out of which the individual risk stratification and treatment recommendations are generated in the Final Report (block 10).

3.2 Interactive Biopsy Guidance

Following extraction of 2-3 samples from each side, the system starts automatic guidance, suggesting changes in the original plan (which is random in the systematic biopsies). The below graph in Figure 7 exemplifies a typical quick convergence of parameters.

Figure 7. Convergence towards guidance



Note that after 2-3 samples on the left (L) and right (R) sides, the "rolling" prostate-level averages reach close-to-final values, therefore allowing guidance. It is quite clear that the left side is positive and right side is negative.

Some examples of guidance (not specifically in the case of Figure 7): take one or more samples from a certain area; or move to a different region, if the area is not malignant; or possibly stop the biopsy, in case sufficient reliable information is gathered following guidance and avoid taking additional unnecessary samples.

Below is an initial partial list, of how the urologist could use ScoRisk during-biopsy for better biopsy outcome and for deriving individual risk stratification and treatment recommendations at the conclusion of the biopsy.

3.2.1 Interactive Guidance Examples

- Low prostate malignancy score in tandem with low grade samples: recommendation to abandon the current region and continue to the next;
- In case of mid-high malignancy score in tandem with low-mid grade samples: continue taking more samples from the same region to increase the positive yield (cancer volume) and sharpen index lesion;
- In case inflammation (prostatitis) is detected: consider stopping the biopsy and avoid the extraction of additional unnecessary samples.

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3.2.2 Personalized Treatment Recommendations

Current NCCN / AUA / ACS guidelines are quite coarse. With ScoRisk, finer and sharper malignancy scores for comparable index lesion samples could lead to different, more specific personalized treatment recommendations.

In doubtful cases this offers the possibility to decide more safely that for example radical prostatectomy (RP) can be postponed, or in case of negative biopsy, in support of Active Surveillance, postpone or pull-in repeat biopsy.

4. Discussion

The scientific puzzle of how to take advantage of the best PCa indicator for routine clinical use — Zn depletion — seems to have been solved; all the pieces seem to be in place: a novel measure of prostate aggressiveness — Malignancy Score — on top of sample grading; the ability to get and use this information in real-time during the biopsy; the accuracy required for individual aggressiveness determination; the non-destructive, workflow-neutral nature of the modality.

The analysis clearly corroborates the metabolic signs of PCa - seemingly before any other existing method and seemingly with much higher fidelity. The higher accuracy is based on unique characteristics of the new modality:

- It is a direct measurement of the most reliable prostate cancer malignancy indicator known to science – Zn depletion – accurately measured by XRF
- The newly discovered ability of XRF to discriminate tissue-related signs of cancer (including tissue proliferation), which is in fact an additional marker of PCa and further improves the accuracy of ScoRisk
- Our ability to remove and scan the most suspected samples – thanks to real-time guidance during the biopsy, in order to extract as much positive or "closest" to positive biopsy cores
- Zn depletion precedes the morphology changes the current pathology is based on – thereby providing earlier detection
- Our measurements are on the full depth (3D) of the needle biopsy core, providing inherently more representative results than looking at a 25-micron thin microscopy slide sample (over 1/50 thinner than the original biopsy core – in fact on the surface of it only)
- Our ability to determine the prostate-level Malignancy Score - which is a higher granularity prostate grading capability, effective especially in doubtful cases, where the urologists/oncologists seek support in decision making - beyond Epstein's grading scheme. Concurrently, our modality is designed to generate higher granularity sample grading – both through continuous reference to an AI-enhanced, large, continuously updated population database, incorporating the various pathologies and the corresponding XRF parameters.

The results demonstrate the potential impact of ScoRisk in prostate cancer (PCa) biopsy, risk stratification and treatment management by providing new evidence-based data that will lower uncertainty in many cases.

Accordingly, in case of doubt, the urologist has additional information at his disposal for getting more decisive and safer decisions at a much lower cost than utilizing expensive and quite inaccurate genomic, or other risk prognosis methods, that in addition to their inherent inaccuracy can – in the best case – only be as good as the biopsy samples quality. Moreover, genomic tests for lower malignancy score prostates are not as meaningful, while ScoRisk can provide accurate information for low-malignancy and even benign prostates.

4.1 Short Term Plans

The foundations of a device for clinical use realizing the potential of ScoRisk were cast in this work. The following are non-exhaustive clinical steps and improvements suggested for the device, prior to releasing a commercial product:

- In addition to the clinical trials for the regulatory steps, conduct on-going systematic retrospective follow-up on treatment recommendations, for solidifying the fidelity of the prostate malignancy score in providing improved risk stratification for better treatment recommendations.
- Implement a real-time Guidance and Grading digital code – centered on multivariate statistical analysis and deep learning tools – including a large-scale accessible population database and real-time diagnosis, grading/scoring and guidance during the biopsy.
- Implement a built-in camera for simultaneously measuring the volume for each pixel during the XRF scan for further improving normalization.

- Take advantage of Digital Pathology during the next studies/trials, as it is not practical for the pathologists to perform pixel-by-pixel analysis.

4.2 Long Term Plans

- As Zn depletion precedes the morphological changes, conduct on-going follow-up studies for solidifying ScoRisk's sample grading as an independent standard by gathering statistical information rather than solely comparing to pathology findings.
- Introduce a dedicated tool for analyzing a prostate following prostatectomy for completely automatic analysis of Whole Mount samples, that will be much thicker than today's microtomes and then - creating much more accurate 3D malignancy maps reconstruction of the whole prostate.

4.3 One-Stop-Shop

We set the ground for a one-stop-shop clinical routine that translates the most direct PCa severity predictor — Zn depletion — into a single, accurate method for PCa aggressiveness, individual risk stratification and treatment recommendations, to improve any type of biopsy, dramatically reduce repeat biopsies, avoid overtreatment, decrease morbidity and mortality and reduce the overall economic burden of treating PCa.

5. Patents

- Granted, US 9,052,319 — METHOD OF GUIDING PROSTATE BIOPSY LOCATION — SIMON Avi et al.
- Pending, WO2021/009762 — METHOD AND SYSTEM FOR ANALYZING PROSTATE BIOPSY— WEKSLER Meir et al.
- Pending, 2022 — WEKSLER Meir et al.

Author Contributions: Conceptualization, Investigation, Formal analysis, Meir Weksler; Conceptualization, methodology, drafting, Avi Simon; Validation, review and editing, Robert Lenkinski; XRF measurements and Data Extraction, XRF/algorithm interfaces, Hagar Landsman; Project administration, clinical study, biopsies and results management: Haim Matzkin (PI) and Nicola Mabjeesh; Clinical support and guidance, Ilan Leibovitch. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki; document number 0333-13-TLV; Company: Prosight Ltd. The document can be provided upon request.

Informed Consent Statement: Informed consent was obtained from all patients involved in the study.

Data Availability Statement: The raw data, on which this article is based is available upon request.

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