AdMeTech FOUNDATION the manogram® project a whole new look at prostate cancer

THIRD GLOBAL SUMMIT ON PRECISION DIAGNOSIS AND TREATMENT OF PROSTATE CANCER
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CONSENSUS STATEMENT ON THE CURRENT STATE AND FUTURE VISION FOR PRECISION CARE:
EMERGING PRACTICES AND RELATED ASSUMPTIONS, HYPOTHESES AND NEEDS

MISSION: Individualizing patient care through the advancement, integration, evaluation and implementation of diagnostic tools for improved detection of clinically significant prostate cancer (PC) and its differentiation from indolent, subclinical disease for selection of patients for biopsies and appropriate treatment. Clinically significant PC is defined by its propensity to progress, cause recurrent and advanced local and regional disease, distant metastases and deaths.

BACKGROUND AND RATIONALE: Prostate cancer has the highest incidence and the second highest mortality rates in men among major non-cutaneous malignancies and is a leading health disparity in Black (including Hispanic) men in the U.S.[1] Standard diagnostic tools, such as screening with Prostate Specific Antigen (PSA) and transrectal ultrasound (TRUS) biopsies, have led to a significant decline in mortality rates (over 50%), with greater annual percent change compared to all other malignancies between 1998 and 2007.[1] However, PSA screening has been associated with such risks as over-diagnosis and over-treatment of indolent PC, which is unlikely to cause significant morbidity or mortality in a man's lifetime.[2,3] Poor tissue sampling with standard TRUS biopsies can under-estimate PC aggressiveness and stage, leading to under-treatment of clinically significant disease, or miss it altogether.[2,3] Current standard pathologic assessment of PC aggressiveness using Gleason Pattern or Scores, while improved over the last decade, provides primarily histologic rather than biologic assessment. The National Institutes of Health consensus has endorsed these concerns and recognized the advancement of diagnostic tools as a national research priority.[3]

More recently, the National Comprehensive Cancer Network (NCCN), consisting of the key opinion leaders representing top cancer hospitals, developed guidelines for improved screening, detection and treatment of PC, based on the best available evidence and clinical consensus.[4,5] Indeed, new and emerging diagnostic approaches, including better liquid (blood and urine) biomarkers, improved imaging for visualization and localization of significant and recurrent PC, and advanced epigenetic and genomic profiling of biopsy and post-surgical tissue samples can improve risk assessment, early detection of PC and its recurrence, prediction of progression and treatment planning. These novel precision diagnostics are expected to increase the benefits and reduce the risks and costs of patient care.

To improve risk assessment in men with suspicious screening and before diagnosis of PC, NCCN guidelines recommended PSA isomers (e.g., Free/Total Percent PSA, *phi,* 4K Score testing) and multi-parametric (mp) MRI prior to and after the initial biopsy, liquid molecular marker PCa3 and/or tissue analysis with Confirm MDx after a negative biopsy to improve prediction of clinically significant PC and reduce unnecessary and/or repeated biopsies, and mpMRI fusion with TRUS to improve tissue sampling.[4-6] More clinical evaluation and consensus are needed to determine the clinical utility of emerging biomarkers (e.g., STML3, ExoDx, Select MDx, Mi-Prostate Score, etc.) [5] and advanced imaging, including high resolution ultrasound with and without contrast agents.

For men with proven PC, NCCN advised to consider germline testing, particularly in individuals with family history, to improve identification of patients at higher risk of aggressive PC and treatment planning, as well as CT or mpMRI in higher-risk men for local and regional staging, and a radionuclide scan for distant metastases.[5] NCCN also recommended tissue analysis of either biopsy samples with Oncotype Dx, Prolaris and ProMark for selecting men for appropriate care (active surveillance, or AS vs. immediate appropriate treatment), or post-surgical pathology with Decipher for improving prediction of progression and optimizing management.[5] Molecular *in vivo* PET imaging with C11-Choline and 18F-Fluciclovine may be used for early diagnosis of recurrent disease, and F18-Sodium Fluoride for further evaluation of distant metastases when findings on standard bone scans are equivocal. [5] Further research is needed to determine clinical utility of other biomarkers (e.g., Ki-67, Biopsy Decipher, etc.) and PET imaging agents (e.g., Prostate-Specific Membrane Antigen-targeted probes, Fluorodihydrotestosterone, etc.).

AdMeTech Foundation's Global Summit and Brain Trust on Precision Diagnosis of PC, which have taken place over the last two years, brought into sharp focus that radiogenomics – integrating quantitative *in vivo* imaging (radiomics) with *in vitro* liquid and tissue molecular and genomic diagnostics - may improve risk assessment before and after diagnosis of PC and help with selection of patients for AS, image-guided focal interventions and appropriate treatment in the future. Another area of intense investigation is the application of machine learning tools, which are likely to be fundamental to the integration of a comprehensive, multi-modality and multi-factorial diagnostic evaluation, including early detection of clinically significant localized PC and clinical assessment of advanced and recurrent disease.

GOAL: Advances in precision diagnostics will make it possible to deliver personalized PC care and improve individual outcomes with decreased morbidity and at a lower cost. Furthermore, precision diagnostics will increase the benefits and cost-effectiveness of patient care and reduce over-diagnosis and over-treatment, as well as under-diagnosis and under-treatment of PC, by enabling novel strategies for:

- Screening;
- Risk stratification before and after PC diagnosis in order to decrease unnecessary and failed clinical interventions, such as biopsies and treatment, which reduce quality of life and inflate health care costs;
- Early detection of clinically significant disease, which can reduce the mortality and morbidity of advanced and metastatic disease; and
- Individualized treatment for localized, recurrent and advanced PC.

APPROACH: Population-based accurate diagnostic assessment to improve and individualize patient selection for screening, biopsies and treatment.

I. General Population of Asymptomatic Men: While patient selection for screening remains controversial, it should be based on informed and shared decision making by men and their physicians, which will consider the individual patient's health status and risk factors for PC, including aggressive disease (e.g., race/ethnicity, family history, genetic predisposition, and age). Family Practice physicians who order over 90% of the PSA tests need a simple message on the evaluation of the PSA testing results, including the age-appropriate, evidence-based cut-off point (e.g., ≥1.5 ng/mL in mid-life), and follow up strategy. For example, there are no current data and/or clinical consensus to support PC screening in asymptomatic healthy men younger than 40 years of age, or in men aged 75 and older who are in poor health.[4]

Assumptions, Hypotheses & Needs: Screening will include testing for PSA (with a focus on a baseline level in mid-life to refine risk assessment), more specific validated PSA variants, and digital rectal exam (DRE) in the near term. Screening will require development and validation of the approach, which incorporates a simple message to primary care practitioners who order PSA. There is rapidly growing evidence and consensus supporting PSA cut-off of 1.5 ng/mL in mid-life to help physicians identify men at low vs. high risk of lethal PC and have informed and shared decisions with patients regarding the follow up testing.[4]

Recent data indicate that baseline PSA of ≥1.5 ng/mL in mid-life may be the most essential risk factor for lethal PC, outweighing even family history and race and playing an important role in selecting the frequency of the follow up testing.[4] Men aged 60 and older who have low PSA (≤ 1 ng/mL) have a very low risk of metastases or death from PC and may not benefit from further screening.[4] Current clinical consensus recommends screening in men aged 75 and older only when they are very healthy and have little or no co-morbidity.[4]

Novel, emerging liquid molecular and imaging biomarkers require further research and may be utilized in the future to improve prediction (and exclusion) of high-grade, aggressive disease. Germline variants in DNA also hold promise for identifying men at higher risk of biologically significant disease and designing treatment.

II. Population of Men with High Risk(s) for and/or Clinical Suspicion of PC During Screening will be identified in the short term based on risk factors (e.g., family history, race, baseline PSA levels higher than expected for a man's age, suspicious DRE exam), abnormal PSA variants, germline genetic variants and/or mpMRI.[4] In the long term, these patients may be selected for novel advanced diagnostics, including emerging *in vitro* molecular markers and/or imaging tools that require further research.

Assumptions, Hypotheses & Needs: Baseline PSA testing, validated PSA variants and emerging liquid and imaging biomarkers (e.g., mpMRI) may improve risk assessment and selection of patients for biopsy.[4,5] Further research is needed to determine:

A. The sequence of testing (liquid biomarkers vs. imaging tools) that may increase confidence in low risk disease and improve prediction of aggressive PC;
B. When liquid biomarkers and/or imaging tools indicate a low risk of biologically significant PC, no further testing may be needed, and standard monitoring protocols will be followed; and

C. When emerging liquid biomarkers and/or non-invasive imaging suggest the presence of biologically significant disease, patients will be referred for further procedures:
    a. If non-invasive imaging shows suspicious lesions, targeted biopsies will be recommended;
    b. If non-invasive imaging is negative while liquid biomarkers are suspicious of aggressive PC, systematic TRUS biopsy will be recommended; and
    c. If non-invasive imaging is ambiguous while liquid biomarkers are suspicious of aggressive PC, image-targeted biopsies in combination with systematic TRUS biopsies will be indicated.[6]

III. Patient Selection for Biopsies will be based upon the results of screening, including PSA level, validated PSA variants and mpMRI[4], as well as their integration and multi-factorial modeling in the near term, to assess probability of clinically significant cancer vs. benign diseases and indolent malignancy, which is not likely to cause short-term harm but may need to be monitored for progression to biological significance. Research to develop, validate and integrate advanced *in vitro* liquid and tissue biomarkers and imaging tools will be critical for further refinement of risk assessment in the future.

Assumptions, Hypotheses & Needs: Integration of PSA and its more specific variants, novel liquid biomarkers and imaging data may improve prediction of aggressive disease and selection of patients for biopsies. Further research is needed to test the following hypotheses:

A. If imaging data show no visible lesions, benign or indolent disease and are in conflict with *in vitro* liquid testing, risk assessment, including probability modeling (nomograms) may be considered with the integrated information (PSA, biomarkers, imaging) to determine the likelihood of aggressive disease and assist with selection of patients for biopsies.
    a. If the risk is found to be low, non-invasive monitoring can be considered[4,5]; and
    b. If the risk is found to be high:
        i. image-targeted biopsies in combination with TRUS biopsies can be undertaken for definitive diagnosis when imaging findings show lesions of low risk or ambiguous significance;[4-6]
        ii. systematic biopsies will be undertaken if imaging shows no visible lesions.

B. If imaging data are in alignment with *in vitro* biomarker testing and indicates aggressive disease, mpMRI-guided tissue sampling in combination with systematic TRUS biopsies need to be performed for definitive diagnosis. [6]

IV. Population of Men with Initial Presentation of Proven PC will be evaluated to select patients who need immediate treatment, AS or focal treatment. In the near term, this evaluation may be based on standard pathologic evaluation (including Gleason Score), germline testing, and imaging for higher risk patients.[5] For example:

A) In men with the NCCN Favorable Intermediate Risk and above, pelvic and abdominal imaging (e.g., CT, mpMRI) may be performed to study local and regional PC extent; [5] and

B) In men with the NCCN Unfavorable Intermediate Risk and above, a radionuclide bone scan may also be performed to identify distant metastases.[5]

In the longer term, these standard tools will be integrated with advanced diagnostic assessment of cancer aggressiveness and stage, employing novel liquid biomarkers, multi-modality imaging (e.g., mpMRI, PET), image-guided biopsies and molecular, proteomic, genomic (DNA) and gene expression (RNA) profiling, and/or multi-factorial modeling to assess probability of aggressive disease.

Assumptions, Hypotheses & Needs: Integration of PSA, validated liquid biomarkers, germline testing, imaging, image-guided biopsy data and tissue analysis (e.g., Gleason Score, morphometry, quantitative molecular, genetic, genomic evaluation) may improve selection of patients for appropriate treatment (including adjuvant therapy) in the near term.[6] Research, development and validation of novel emerging liquid and tissue biomarkers (including germline testing) and their integration with imaging are critical for further refinement of risk assessment and related multi-factorial modeling.

Further investigation is needed to test the following hypotheses in men with proven PC:

A. If the initial *in vitro* and *in vivo* diagnostics are aligned and indicate low risk disease, and standard pathology shows Biopsy Gleason Score 3+3 or lower, patients will be referred for AS;

B. If the initial *in vitro* and/or *in vivo* testing predicts high grade disease, while Biopsy Gleason Score is 3+3 or lower, patients will be referred for further image-guided tissue analysis for molecular, proteomic, genetic and genomic markers:
    a. If the targeted biopsy tissue analysis shows a genetic profile indicating low risk of biologic progression, these men will be considered for AS; and
    b. If the targeted biopsy tissue analysis shows a genetic profile consistent with biologic aggressiveness, these men will be considered for immediate treatment;

C. If all of the initial *in vitro* and *in vivo* imaging diagnostic data are aligned (based on multi-modality testing) and indicate aggressive disease, and standard pathology shows higher grade disease (Gleason 4+3 and above), no further diagnostic evaluation may be needed, unless it would be directed at planning definitive treatment; and

D. In situations where conflicting data and/or clinical uncertainties exist (including Gleason Score 3+4 and/or large volume Gleason Score 3+3), patients can be selected for image-guided genetic tissue analysis and/or further molecular pathologic assessments. Probability modeling may be considered with the integrated information (PSA and variants, emerging liquid biomarkers, imaging, tissue analysis) to determine the likelihood of aggressive disease and assist with selection of patients for individualized treatment, including image-guided focal interventions or standard whole grand treatment, with and without adjuvant therapy.

V. Population of Men After Treatment for Prostate Cancer will be evaluated for the probability of progression and accurate diagnosis of recurrence, with a focus on identifying advanced and/or lethal disease early in order to design individualized strategies for treatment administration and close monitoring. [6]

Assumption, Hypotheses and Needs: Integration of pre-treatment and post-treatment diagnostic assessments (including post-surgical pathology, tissue analysis and imaging) may assist with designing individualized follow up strategies. Further research is needed to test the following hypotheses:

A. If all the diagnostic data indicate an early stage, localized prostate cancer without adverse pathologic features, absence of molecular markers of aggressive disease and a genetic profile consistent with low probability of progression, no further interventions in addition to non-invasive monitoring with standard tools (e.g., PSA) and/or novel diagnostics (e.g., liquid markers and imaging) may be indicated; and
B. If post-treatment diagnostic data indicate advanced and aggressive disease (e.g., extra-prostatic extension, regional or metastatic disease), imaging and molecular, proteomic, genetic, genomic evaluations will be undertaken throughout the clinical course to design individualized patient management strategies that maximize disease control and early detection of tumor recurrence and progression while preserving health status.

References

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