

# Mi-Prostate Score (MiPS)

## Frequently Asked Questions (FAQ)

### What is MiPS?

Mi-Prostate Score (MiPS) is an early detection test for prostate cancer that combines the amount of serum PSA, with the amounts of two genes in the urine. These two genes, TMPRSS2:ERG and PCA3, are specific for prostate cancer, meaning they are rarely present at high levels in the urine of men without prostate cancer. The MiPS combines serum PSA, urine TMPRSS2:ERG (also known as T2:ERG) and urine PCA3 to predict a patient's risk for having prostate cancer detected by standard biopsy. The test also predicts the patient's risk for having potentially aggressive prostate cancer. The MiPS test was developed and validated on almost 2,000 patients. The MiPS test is designed to help doctors and patients make a shared decision after PSA testing about whether to monitor PSA levels or pursue a prostate biopsy.

### When should a MiPS test be used?

MiPS is designed to provide more information to patients who are concerned about their risk for prostate cancer based on serum PSA testing. Patients with very low or very high PSA levels are unlikely to benefit from MiPS testing. The MiPS test should be used as a tool along with other clinical and physical examination findings, such as family history, previous history of a negative prostate biopsy, age, digital rectal examination findings, to help patients and their physician decide on management after serum PSA testing.

### Does MiPS replace PSA testing?

No. MiPS is not a screening tool, nor is it intended to replace PSA. The Mi-Prostate Score test is designed to provide additional information for patients who have undergone PSA testing. The performance in men who have not undergone PSA testing is unknown.

### What are the most important advantages of the MiPS test?

By combining three markers, MiPS provides a much more accurate prostate cancer risk assessment than serum PSA, PCA3 or T2:ERG alone. Although arbitrary cutoffs are used to say that a patient's PSA is "normal", a normal PSA value does not mean the patient does not have prostate cancer. Similarly a "high" PSA value does not mean the patient has prostate cancer. Therefore, the MiPS test provides an estimate of the patient's chances for having cancer detected, ranging from 0 to 100%. This will allow the patient and their physician to make the most informed choice about undergoing biopsy.

### What does the MiPS test risk score mean?

The MiPS prostate cancer risk score provides a quantitative risk of having prostate cancer detected on a biopsy. For example, a MiPS prostate cancer risk score of 10% (95% confidence interval 6%-13%) indicates that the patient has a 10% chance of having prostate cancer detected on biopsy. The 95% confidence interval indicates the reliability of the estimated risk score. The MiPS high grade cancer risk score provides a quantitative risk of having potentially aggressive prostate cancer detected on biopsy. Individual patients may elect to undergo or delay biopsy at different MiPS risk levels so we do not provide a "positive" or "negative" cutoff. As with any early detection test, aggressive prostate cancer may be present in patients even with very low MiPS cancer risk or high grade cancer risk scores. Models used in generating MiPS scores were generated from a large population of patients, however an individual patient's actual risk of having prostate cancer is influenced by a number of factors. The MiPS test risk scores should be interpreted by patients and their physicians with other clinical information, including serum PSA, family history of prostate cancer, patient age, race/ethnicity and previous history of negative biopsy, among others.

## Does the MiPS test only help in deciding whether a biopsy is needed or can it also aid in differentiating significant (aggressive) from insignificant (indolent) cancer?

MiPS provides a risk estimate for detecting prostate cancer on biopsy. Due to concerns about detecting slow growing cancers that may never cause symptoms, MiPS also provides a risk estimate for detecting high grade (potentially aggressive) cancer. Michigan Medicine defines aggressive cancers as those with Gleason score greater than 6, which most clinicians feel should be treated. The Gleason score is a measure of tumor grade, with higher scores indicating more aggressive cancer.

## How does a physician explain the value of the MiPS test to a patient?

The MiPS test provides patients with an individualized risk estimate for having prostate cancer. The MiPS test, which combines serum PSA, urine PCA3, and urine T2:ERG, is more accurate than serum PSA or PCA3, either alone or in combination. Although patients with very low or very high serum PSA will likely not benefit from MiPS testing, MiPS provides a more accurate prostate cancer risk estimate for patients who are concerned about their serum PSA levels.

## Will the MiPS test give a final diagnosis?

No. A MiPS report will provide an estimate of the patient's risk for having prostate cancer diagnosed on a prostate needle biopsy. The patient's risk for having potentially aggressive cancer diagnosed on biopsy is also provided. The MiPS does not replace a prostate biopsy.

## Can the MiPS test be used to monitor progression of prostate cancer during active surveillance?

MiPS was developed and validated in patients who had not previously been diagnosed with prostate cancer. It has not been evaluated in patients on active surveillance. Researchers are studying the utility of MiPS in patients on active surveillance and in patients newly diagnosed with prostate cancer considering active surveillance.

## Can the MiPS test be used to monitor disease response and/or recurrence of prostate cancer after local or systemic therapy?

No. The MiPS test is designed to provide a risk estimate for prostate cancer detection on biopsy. MiPS is not designed for patients who have been treated for prostate cancer by surgery or radiation. Such patients also do not have sufficient amount of prostate derived genes in their urine to calculate MiPS risk scores.

## How will the MiPS test be done?

The patient's physician will perform a digital rectal exam (DRE). Within 1 hour of the DRE, the patient will provide a urine specimen collecting the first 20 - 30 mL of voided urine. The specimen will be transported to the Michigan Medicine-MLabs for testing. The physician will receive the MiPS report generally within 7 days.

## How does a patient get this test done?

The test must be ordered by the patient's physician and specific collection and transportation requirements are needed. The patient's physician must also provide the result of a recent serum PSA test. If the patient and their physician are interested in having this test performed, the physician's office should contact MLabs at 800-862-7284 to request a MiPS Collection Kit and further instructions on how to send the specimen.

## Are urine specimens collected by catheterization acceptable for testing?

No, a voided urine collected following an attentive DRE is required for testing.

## Which physician should a patient consult with to perform a MiPS test?

MiPS can be ordered by any physician but the test is performed only at Michigan Medicine - MLabs. As the MiPS test requires previous serum PSA testing, patients should typically consult with the physician who ordered this test to allow for shared decision making based on the results of MiPS testing. Physicians will need to contact MLabs (800-862-7284) to receive instructions and specialized test kit prior to performing the MiPS test. Physicians will perform a digital rectal exam prior to urine collection to ensure enough prostate genes are released into the urine for MiPS testing.

## Who can order the MiPS test?

Any physician can order the MiPS test. Please see the previous question for detailed instructions.

## How much does the MiPS test cost and is the MiPS test covered by health insurances?

The cost of the test is currently \$783.00 (7/1/2017), which will be billed to the patient's insurance by The University of Michigan Health System. The cost includes individually running PCA3 (Progenesa) and T2:ERG which is combined with serum PSA in a risk model that generates a MiPS score.

## Will insurance pay for the test?

Every insurance plan is different; your insurance may pay for some of the cost, but possibly not all. The patient will be financially responsible for the remaining balance. Most insurance carriers require prior authorization for payment of PCA3 or MiPS testing. Benefits, copays, referral, and prior authorization requirements vary by individual policy. MLabs recommends that the patient contact his insurance provider for specific details regarding coverage for this testing (CPT code 81313). Patients are responsible for any expenses not covered by insurance.

## Will Medicare pay for the MiPS test?

Medicare may pay for a portion of the testing but not the total cost. The patient will be responsible for any remaining balances. A Medicare ABN (Advance Beneficiary Notice) signed by the patient is required for MLabs to bill Medicare. The ABN is a document that states the actual cost the patient agrees to pay if Medicare does not pay for the testing.

If the ordering clinician's facility is part of a hospital or health system that is billing the patient's insurance for an office visit, Medicare patients are considered registered outpatients and MLabs cannot bill Medicare for laboratory testing. In these cases, MLabs can bill either the referring facility or the patient directly (a signed ABN is required for MLabs to bill the patient).

## How long does it take to receive the MiPS test results?

It will take approximately 7 days for the analyzed return of results to the patient's physician.

## Does the volume of the urine sample that is collected influence the MiPS test?

At least 20-30mL of urine is required to perform the MiPS test. Otherwise the amount of urine collected does not influence the MiPS test.

## 5 $\alpha$ -reductase inhibitors, such as finasteride and dutasteride, decrease the size of the prostate and the serum PSA level. Do these agents also impact on the MiPS Test?

The MiPS test may be influenced by 5 $\alpha$ -reductase inhibitor use, given the known effect on lowering serum PSA. Although data is limited, PCA3 scores and T2:ERG scores do not appear to be influenced by 5 $\alpha$ -reductase inhibitor use. The MiPS test does not correct serum PSA levels in patients on 5 $\alpha$ -reductase inhibitors, and hence it may underestimate cancer risk in such patients.

## Is the MiPS test age-dependent?

There is no evidence that the MiPS test is significantly influenced by age. The MiPS test was trained and validated in large numbers of patients where the average age was 64 years old. Half of the patients were between the ages of 58 and 69.

## Can the MiPS be used for patients with prior negative prostate biopsy(ies) or only for patients who have never had a prostate biopsy?

The components of the MiPS have been studied extensively among patients coming in for their first biopsy and for those who had a prior negative biopsy. In both settings, they have been found to be valuable.

## Does testosterone replacement therapy influence the MiPS Test?

Michigan Medicine has very little data on the effects of testosterone replacement therapy on the MiPS test. Although the effects of testosterone replacement therapy on urine T2:ERG and PCA3 have not been well studied, there is no known biological explanation for how testosterone therapy could elevate these markers. By incorporating three biomarkers, the final MiPS risk score will be minimally affected by small changes in serum PSA, urine T2:ERG or urine PCA3 caused by testosterone replacement therapy.

## The report interpretation states: "Urine PSA is at the lower end of the reportable range. This may be due to therapies that inhibit testosterone/androgen synthesis and may impact risk estimates provided by the MiPS algorithm." What does this mean?

The urine T2:ERG and PCA3 scores used in the MiPS algorithm normalize the amount of T2:ERG (or PCA3) to the amount of urine PSA to account for the amount of isolated prostate derived mRNA. Therapies that inhibit testosterone or androgen synthesis (such as 5 $\alpha$  reductase inhibitors) may impact urine PSA as well as serum PSA levels. Likewise, inattentive digital rectal exams may also lead to low isolated prostate derived mRNA. Although the impact of therapies that inhibit testosterone or androgen on the clinical utility of MiPS has not been well studied, we include the above comment when urine PSA is at the lower end of our reportable range. As in all cases, the MiPS score should be used along with other clinical parameters to determine patient management, including therapies that inhibit testosterone or androgen.

## Is the MiPS test affected by the presence of a urinary tract infection?

A urinary tract infection can elevate serum PSA levels, and thus influence the MiPS test. The serum PSA provided for the MiPS test should be drawn when the patient does not have a urinary tract infection. Infection has not been shown to influence urine PCA3 scores. The effect of inflammation on urine T2:ERG score is unknown, although there is no known biological mechanism where inflammation would elevate T2:ERG score.

## Does recent ejaculation affect the MiPS test?

There are conflicting reports on the effects of recent ejaculation on serum PSA. There is no evidence that recent ejaculation affects urine T2:ERG and PCA3 scores. However, there is no known biological mechanism where recent ejaculation could affect T2:ERG or PCA3 scores. By incorporating three biomarkers, the final MiPS risk score will be minimally affected by small changes in serum PSA, urine T2:ERG or urine PCA3 caused by recent ejaculation.

## Does treatment with antibiotics influence the MiPS test?

There is no evidence that antibiotic use influences the MiPS test.

## Can the MiPS test aid in the decision whether a biopsy is needed in patients suspected of having prostate cancer but who have been previously treated for prostatitis?

Prostatitis can increase serum PSA. The serum PSA provided for the MiPS test should be drawn when the patient does not have active prostatitis. There is no evidence that prior treatment for prostatitis influences urine PCA3 or T2:ERG.

## Can the MiPS test aid in the decision whether a biopsy is needed in patients suspected of having prostate cancer but who have previously undergone transurethral resection of the prostate (TURP) for benign prostatic hyperplasia (BPH)?

The effects of previous surgical treatment for benign prostatic hyperplasia (BPH), including transurethral resection (TURP), laser ablation or transurethral needle ablation (TUNA) on the MiPS test are unknown. Few patients with a history of these procedures were included in the groups of patients used for training and validating the MiPS test.

## Can the MiPS test aid in the decision to perform a prostate biopsy in patients who have known genetic variations linked to an increased prostate cancer risk (e.g. a BRCA2 mutation) either themselves or in their immediate family?

Yes, the MiPS test is appropriate for patients at a high risk of prostate cancer due to family history. The MiPS test reports a risk estimate of cancer being detected on immediate biopsy, rather than a lifetime or future risk of prostate cancer.

## Would the MiPS test be a good option for patients with a high prostate specific antigen (PSA) level and an enlarged prostate who have had a colostomy, i.e. in whom a prostate biopsy by means of a rectal approach cannot be performed?

A digital rectal exam is generally required prior to urine collection for the MiPS test. The rectal exam ensures sufficient genes from the prostate are collected to give a valid MiPS test. Although a MiPS test can be attempted on urine collected without a rectal exam, we anticipate that approximately 50% of urine samples will be insufficient to report MiPS risk scores due to insufficient prostate derived genes.

## How was the MiPS test discovered?

Serum PSA has been used as a prostate cancer early detection test since the late 1980's. PCA3 was discovered in 1999 as a gene that is expressed at high levels in most prostate cancers, but not expressed in normal prostate tissue. T2:ERG gene fusions were discovered by researchers at the University of Michigan in 2005. T2:ERG gene fusions are present in ~50% of prostate cancers. However, as most patients with prostate cancer actually have multiple distinct prostate cancers in their prostate (called multifocal disease) ~75% of men have T2:ERG gene fusions in their prostate cancer. T2:ERG gene fusions have not been found in any other cancer and are almost never detectable in normal prostate tissue. The MiPS test uses commercial grade assays to quantify the amount of T2:ERG and PCA3 in the urine. The MiPS test was developed by measuring serum PSA, urine T2:ERG and urine PCA3 in men immediately before prostate biopsy. Models were then developed that optimally combine these three biomarkers to predict the presence of prostate cancer, or high grade cancer, on biopsy. Finally, the performance of the models was validated in a new set of patients.

## Are T2:ERG fusions present in only half of all prostate cancers?

The T2:ERG gene fusion is one of the best studied biomarkers in prostate cancer. A summary of published studies reported that 47% of more than 10,000 prostate cancers had T2:ERG fusions. Up to 90% of men with prostate cancer at the time of surgery actually have prostate cancers, with multiple distinct cancers in their prostate. In studies that have carefully assessed all prostate cancers in a single prostate, ~75% of all men with prostate cancer have at least one cancer with a T2:ERG fusion. The urine T2:ERG score used in MiPS is highly correlated to the total amount of T2:ERG+ cancer in a patient's prostate. As benign prostate tissue produces no T2:ERG, there is no known biological explanation for markedly elevated urine T2:ERG besides prostate cancer.

## What types of patients were used to develop the MiPS test?

The MiPS cancer and high grade cancer risk models were developed on a multi-institutional cohort of 711 total patients. The median patient age was 63 years, the median serum PSA was 5.1 ng/mL, 14% had an abnormal digital rectal exam, 25% had a history of previous negative biopsy, 23% had a first degree relative with prostate cancer, 82% were Caucasian, and 97% had no previous history of prostate cancer. The median Prostate Cancer Prevention Trial (PCPT) risk calculator risk for the presence of prostate cancer was 40%, and the median high grade PCPT risk calculator risk for the presence of high grade prostate cancer was 10%. Of the 711 patients, 53% underwent 12 core biopsy, 44% underwent >12 core biopsy, 46% of patients were diagnosed with cancer on biopsy and 27% were diagnosed with high grade (Gleason score >6) cancer.

The MiPS cancer risk and high grade cancer risk models were validated in a separate multi-institutional cohort of 1,225 total patients. The median patient age was 64 years, the median serum PSA was 4.7 ng/mL, 23% had an abnormal DRE, 20% had a history of previous negative biopsy, 20% had a first degree relative with prostate cancer, and 73% were Caucasian. No patients had a previous history of prostate cancer. The median PCPT risk calculator risk for the presence of prostate cancer was 40%, and the median PCPT risk calculator risk for the presence of high grade prostate cancer was 11%. Of all 1,225 patients, 89% underwent 12 core biopsy, 10% underwent >12 core biopsy, 42% of patients were diagnosed with cancer on biopsy and 18% were diagnosed with high grade cancer.