Prostate Cancer Screening Strategy

Confidential Example Report

September 14, 2017

This report presents the results of speculative calculations
that are based on data supplied as an example.

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for our Prostate Smart services to inform discussions with their physicians.

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For:_____

Consider writing your name here on a copy for your physician.

This report informs discussions with physicians and confidants about prostate cancer screening strategy. It is based on speculative scenarios created through analysis of example data in comparison to published results of medical studies. These scenarios are speculative because of: 1) Imperfect knowledge about prostate cancer, its risks and the effectiveness of screening actions; and 2) Assumptions that must be made to complete the analysis, such as the growth rate in prostate cancer risk. Interpretation depends on life expectancy, personal risk preferences and prostate cancer screening strategy. Consult your physicians before considering any actions.

Prostate Cancer Screening Challenge and this Report

Many men greatly overestimate the deadliness of prostate cancer, which can trigger decisions that lead to over-diagnosis and over-treatment, per a recent medical journal article. Compared to some of the most aggressive other cancers, prostate cancer is:

- Highly prevalent – perhaps as high as 60% of men in their 60s.
- Not very deadly on average.
- Slow growing on average.
- Rarely kills as fast as the worst other cancers.

This report is designed to inform you and your physicians as you discuss developing a smart screening strategy that balances early detection of the deadliest cancers with limiting the risk of over-diagnosis and over-treatment. It considers new screening technologies, reflects risk analysis in the medical literature and informs discussions with your physicians based on your personal risk preferences. Quantitative results are calculated for speculative scenarios and presented for consideration and discussion.

Contents

Tips on How to Master this Strategy Report

Men who have used these strategy reports find they are valuable and informative but require work and persistence to master fully. They suggest tips for your consideration:

Read Twice – First for an Overview and Second to Study Relevant Sections

Many men become familiar with the report on first reading but require a second or third reading to achieve a deep understanding of their strategy and implications. They suggest a brisk first read without bogging down to see the full picture before returning to study sections of most interest and relevance to your next decisions.

Print the Report for Mark Up and Use the Glossary

Many men like to mark up the report with highlights, questions and notes that they can return to later. Most prefer to print the report for ease of mark up, but some are comfortable doing that online. Many men find it difficult to retain all the new terms and abbreviations while learning new screening strategy concepts. They suggest referring to a printed copy of the *Glossary* next to the report while you are reading.

Study the Overview

Some men find that section *1. Screening Strategy Overview* provides enough information and summary results to start a discussion with their physicians, especially if their risks are low. Most men suggest studying the *Overview* to make sure that you understand your screening strategy options and their implications.

Selectively Focus on the Sections Relevant to Your Next Decisions

The report is long because it is designed to support men from the beginning to the end of the screening process using a full range of screening technologies. Men suggest focusing your attention on the sections most relevant to your next decisions:

- Use section *2. Informative Screening Actions before Biopsy or MRI* to help you choose your next screening action and its timing. If you are considering an informative screening action next, then scan the remaining sections to learn what comes later if your risks increase.
- If you are considering a biopsy after using all informative screening actions, then read sections:
    3. *Conventional Pattern Biopsy*
    4. *MR Imaging*
    5. *MRI Targeted Biopsy*
    6. *Screening MRI*
- Skim *Appendix A. Speculative Prostate Cancer Scenarios* to see if detailed results with tables and charts interest and inform you. If not, then skip *Appendix A*.
- Only refer to *Appendix B. Biopsy and Treatment Risk Assessment Adjustments* if you want to fine-tune your risk assessments for biopsy and screening MRI timing.

Background on Subscriptions to Example Speculative Screening Strategy Reports

Skim this section to put this *Example* report in context. Prostate Smart offers subscriptions to 72 example speculative prostate cancer screening strategy reports based on combinations of: life expectancy/age, PSA, cancer risk and its growth rate. One or more reports may reflect your situation and inform your screening strategy discussions with your physicians.

See *ProstateSmart.info* to learn more. There, we describe a 6-step process to select and use example strategy reports, as outlined below.

1. Estimate your life expectancy

Example report choices are: 25-year life expectancy at age 58, 20-year life expectancy at age 64 and 15-year life expectancy at age 71. See online life expectancy calculators.

2. Adjust your PSA values and estimate your PSA trend

Example report choices for calibrated and adjusted PSA are: 3 PSA and 6 PSA. Our site shows you how to calibrate and adjust your PSA values and estimate your PSA trend.

3. Estimate your cancer risk factor using risk calculator(s)

For each combination of age/life expectancy and PSA, Base risk is estimated for a Caucasian man with no risk factors. *Example* report risk factor choices are: 1X, 2X, 3X and 4X times Base risk. To estimate your risk factor, our site helps you use and interpret two online risk calculators from: the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate Cancer Prevention Trial (PCPT) - plus 4Kscore.

4. Choose your growth rate in cancer risk

Example report choices for the growth rate in cancer risk are: 20% moderate growth, 40% high growth and 60% very high growth. Your choice of growth rate can be informed by your estimated growth rate in PSA from cancer from your PSA trend analysis.

5. Select and download an *Example* report for you

72 *Example* reports are available as combinations of the four variables above.

6. Use the *Example* report to learn and discuss your screening strategy

Your *Example* report can help you learn about your prostate cancer screening strategy options and implications and inform your discussions with your physicians and confidants.

Thoughts on Developing a Screening Strategy

A comprehensive prostate cancer screening strategy can become increasingly complicated and time consuming if risks increase and the stakes become greater, as you will learn in this report. Few physicians have the time to do the analysis required or even read your lengthy strategy report. Therefore, you probably will have to assume leadership of the strategy development process and do much of the analysis and report evaluation.

Team Approach

Teamwork is needed to develop a prostate cancer screening strategy that reflects your personal preferences and risk tradeoffs. Choosing your team is crucial to success.

Analyst and Report Master - You

Only you are likely to have enough time to analyze your results, choose the appropriate Example report and master its contents. For example, few urologists and fewer primary care physicians use the online risk calculators that consider your medical results.

Knowledgeable Personal Confidant

There can be great value in finding a personal confidant who will become knowledgeable and work through the screening strategy process with you. A close friend with prostate cancer concerns is a likely candidate, but it may be your spouse, partner or adult child.

Primary Care Physician

Primary care physicians (PCPs) start the prostate cancer screening process and are concerned with your overall health. They can perform or order all the informative screening actions from PSA and DRE to other blood tests to TRUS ultrasound imaging. You can provide the analysis and summarize the implications of your *Example* report for discussion and medical advice by your PCP, who can refer you to a urologist if your risks increase.

Personal Urologist

Collaborative teamwork with your urologist is crucial to a successful screening strategy. Your personal urologist can perform or order all the informative screening actions from PSA and DRE to other blood tests to TRUS ultrasound imaging. However, many urologists do not routinely order all these tests before biopsy and most do not have the time to use online risk calculators. Most do not yet offer MRI targeted biopsies or screening MRIs.

Specialist Urologist for MRI Technologies and Perhaps Ultrasound Imaging

If necessary, your personal urologist can refer you to a specialist urologist if you are interested in MRI technologies or perhaps even TRUS ultrasound imaging. For MRI technologies, you might consider shopping for the appropriate combination of quality and price along with a willingness to consider a screening MRI if you are interested.

1. Screening Strategy Overview

In this section, you will learn about your prostate cancer screening choices and how speculative analysis results might inform your screening strategy discussions with your physicians and confidants. To learn more, consult the other major sections of this report and then our website: *ProstateSmart.info*.

Example Individual Information

The *Example* **I**ndividual information {**I**} for this report is:

{I1a}	20	year life expectancy at
{I1b}	64	years of age
{I2}	3.0	PSA (prostate-specific antigen level calibrated and adjusted
{I3}	1X	times Base risk for a Caucasian man with no risk factors
{I4}	20%	growth rate of cancer risk that is used to calculate results for the speculative scenarios. It is informed by an estimated growth rate in cancer PSA for a PSA trend above a no-cancer baseline.

This *Example* report is one of 72 different *Example* reports based on variations of these variables. Consult our website, *ProstateSmart.info*, for help choosing an *Example* report or to explore how changes of each variable affect the results. We also offer *Premium Screening Strategy Reports* based on information that you supply.

Speculative Strategy Analysis

The *Example* individual information above has been analyzed based on published studies of prostate cancer. The analysis is speculative because medical studies are available to inform only parts of the analysis and assumptions must be made to complete the analysis, such as the growth rate in prostate cancer risk. See *Appendix A. Speculative Prostate Cancer Scenarios*.

Biopsy, Possible Cancer Diagnosis and Treatment if Warranted

A biopsy of the prostate is the pivotal cancer screening step. It is needed to diagnose cancer that can lead to treatment with possible life saving benefits. However, most prostate cancers are not very life threatening with little or no benefit of treatment. A biopsy also has negative consequences, including: 1) Discomfort and the risk of potentially life-threatening sepsis (infection), 2) Emotional costs that accompany a possible diagnosis of cancer and 3) Potential side effects of treatment if warranted, such as impotence and incontinence.

Decisions: Now or Delay for Each Screening Action

Each screening action can be taken now (or soon) or delayed. In this report, we consider a 1-year delay that is convenient for analysis and discussion. Ultimately, a 1-year delay in

screening actions delays a subsequent biopsy, possible diagnosis and treatment if warranted. The consequence is a reduction in life expectancy from a delay in treatment that may allow prostate cancer to progress. The benefit of delay is deferral of the negative consequences of a biopsy, possible diagnosis and treatment.

Average Outcomes for a Delayed Biopsy

For the *Example*, we estimate average reductions in life expectancy from a 1-year delay in **B**iopsy {**B**}, possible diagnosis and treatment if warranted. Consider the results step-by-step. The overall reduction in life expectancy from delay is:

{B1}	0.01	year overall reduction in life expectancy from delay

This overall reduction can be compared to the overall effect of other health and medical decisions. It is pulled down toward 0.00 by the probability that a biopsy will **not** find cancer:

{B2a}	79%	probability a biopsy will not find cancer

In contrast, the overall reduction, {B1}, is pulled up by the probability that a biopsy **will** find cancer:

{B2b}	21%	probability a biopsy will find cancer

If cancer is found by biopsy, then the overall reduction, {B1}, is increased to the conditional "if-cancer" reduction in life expectancy from delay:

{B3}	0.07	year if-cancer reduction in life expectancy from delay

You might wonder why the overall reduction is less than the conditional "if-cancer" reduction. The overall reduction is a "weighted average", where we multiply the larger "if-cancer" reduction, {B3}, by the (less than 100%) probability a biopsy will find cancer, {B2b}, to calculate the smaller overall reduction:

{B1}	0.01	year overall reduction in life expectancy from delay

CAUTION: These are estimated reductions in life expectancy from delay based on the example growth rate in cancer risk. They are in addition to any decreases in life expectancy from prostate cancer that is diagnosed now with treatment that may not be successful. See *Appendix A. Speculative Prostate Cancer Scenarios*.

Speculative Scenarios

Average outcomes above do not fully describe the range of prostate cancer scenarios. For this *Example* report, 100 equally likely speculative scenarios for prostate cancer have been estimated. See *Appendix A. Speculative Prostate Cancer Scenarios* to view the 100 **S**cenarios {**S**} for this example report. There are two categories of scenarios:

{S1}	79	scenarios where no cancer is found by biopsy
{S2}	21	scenarios where cancer is found by biopsy

Rare Alarming Speculative Scenario Outcomes

Average outcomes summarize some relatively low risk scenarios and a few alarming scenarios. For this *Example* report, the five most **A**larming prostate cancer scenarios {**A**} are summarized below, where each has a 1 of 100 chance of being true (1% probability):

{A1}	0.17	year reduction in life expectancy from 1-year delay (1% probability)
{A2}	0.14	year reduction in life expectancy from 1-year delay (1% probability)
{A3}	0.13	year reduction in life expectancy from 1-year delay (1% probability)
{A4}	0.12	year reduction in life expectancy from 1-year delay (1% probability)
{A5}	0.11	year reduction in life expectancy from 1-year delay (1% probability)

You may want to consider some of these rare alarming cancer scenarios when you choose the timing of screening actions. For perspective, the life expectancy reductions of these rare alarming prostate cancers are typically much less than for the most aggressive other cancers that can kill within months or years and reduce life expectancy by 75% to 90%, such as a 15 to 18-year reduction of a 20-year life expectancy.

CAUTION: Scenario {A1} above is a rare scenario (1 of 100 or 1% probability) but not a worst case. There is always a very small probability of very deadly prostate cancer where the risk of delay can be higher than for Scenario {A1}.

Informative Screening Actions before Biopsy or MRI

For the most effective screening strategy, consider taking all informative screening actions before considering a biopsy or before considering a screening MRI and possible targeted biopsy. Informative screening actions are:

- Life Expectancy estimation.
- PSA (prostate-specific antigen) annual blood tests with Hybritech calibration.
- DRE (digital rectal exam) with prostate volume estimate by your doctor.
- PHI (Prostate Health Index) blood test (used with ERSPC-RC) or 4Kscore.
- Ultra-Sound imaging for prostate volume and cancer risk (used with ERSPC-RC).
- Risk Calculator analysis of all variables (ERSPC-RC and PCTP-RC).
- PSA Trend analysis using a process described in *ProstateSmart.info*.
- Growth rate in cancer risk estimation.

Skipping any of these informative screening actions can lead to poor decisions including: 1) Late diagnosis and treatment, 2) Over-diagnosis and over-treatment with the risk of side effects, and 3) Excessive financial cost. All these actions are either free or relatively low cost and often reimbursed by health insurance. Therefore, you can comfortably take any of them based on your gut reaction to the quantitative results of analysis. See section *2. Informative Screening Actions before Biopsy or MRI* to learn more.

Conventional Pattern Biopsy without MRI

Currently, most men will choose a conventional pattern biopsy rather than MR imaging for a variety of reasons, including urologist preference and potentially high cost of MRI that is not reimbursed. See section *3. Conventional Pattern Biopsy* to learn more, including about the biopsy timing decision.

MR Imaging Is Effective but Can Be Expensive

MRI (multi-parametric magnetic resonance imaging) is very effective at identifying the large, aggressive (high-grade) cancers that are deadliest while reducing over-diagnosis of insignificant cancers. However, it can be expensive and may not be reimbursed by health insurance. You may choose to shop for the best combination of quality and price. See section *4. MR Imaging* to learn more.

MRI Targeted Biopsy vs Pattern Biopsy

An MRI targeted biopsy is more effective than a conventional pattern biopsy that is not targeted. A pattern biopsy uses a template for up to 12 or more needles to sample your prostate. In contrast, a targeted biopsy typically directs fewer needles at a high suspicion tumor target(s) visible on MR images and does not sample the rest of the prostate. MRI targeted biopsies often find high-risk prostate cancers while reducing the chance of finding low-risk cancers that lead to over-diagnosis and over-treatment. See section *5. MRI Targeted Biopsy* to learn more.

If you plan to choose an MRI targeted biopsy rather than a pattern biopsy, then the MRI results can be used for screening prior to making a biopsy decision.

Screening MRI before Targeted Biopsy

A screening MRI is effective at identifying the large, aggressive (high-grade) cancers that are deadliest while reducing over-diagnosis of insignificant cancers. The benefits of a screening MRI depend on your tentative conclusion in section *3. Conventional Pattern Biopsy* about a biopsy now vs a 1-year delay, either: A. Justification or B. No Justification for a conventional pattern biopsy now:

A. Justification for a conventional pattern biopsy now by your risk assessment: In this case, a screening MRI often can support delaying or avoiding a biopsy and all its negative consequences if your physicians see little or no evidence of a tumor and assign a low MRI Suspicion Score.

B. No Justification for a conventional pattern biopsy now by your risk assessment: In this case, a screening MRI sometimes can justify an MRI targeted biopsy if your physicians see strong evidence of a tumor and assign a high MRI Suspicion Score.

See section *6. Screening MRI* to learn more.

Next Steps

We encourage you to skim the remaining major sections to learn more about the *Example* results and decision options and to prepare for a discussion with your physicians and confidants:

- If you have **not** used all informative screening actions then read:
  - Section *2. Informative Screening Actions before Biopsy or MRI* to learn more about choosing your next screening action and its timing.
- If you **have** used all informative screening actions then read:
  - Section *3. Conventional Pattern Biopsy*
  - Section *4. MR Imaging*
  - Section *5. MRI Targeted Biopsy*
  - Section *6. Screening MRI*

2. Informative Screening Actions before Biopsy or MRI

For the most effective screening strategy, consider taking all informative screening actions before considering a conventional pattern biopsy or before considering a screening MRI and possible targeted biopsy. Informative screening actions are:

- Life Expectancy estimation.
- PSA (prostate-specific antigen) annual blood tests with Hybritech calibration.
- DRE (digital rectal exam) with prostate volume estimate by your doctor.
- PHI (Prostate Health Index) blood test (used with ERSPC-RC) or 4Kscore.
- Ultra-Sound imaging for prostate volume and cancer risk (used with ERSPC-RC).
- Risk Calculator (RC) analysis of all variables (ERSPC-RC and PCTP-RC).
- PSA Trend analysis using a process described in *ProstateSmart.info*.
- Growth rate in cancer risk estimation.

Skipping any of these informative screening actions can lead to poor decisions including: 1) Late diagnosis and treatment, 2) Over-diagnosis and over-treatment with the risk of side effects, and 3) Excessive financial cost.

Choosing Next Screening Action(s) and Timing

All these informative screening actions are free or relatively low cost and often reimbursed by health insurance. Therefore, you can comfortably take any of these actions based on your gut reaction to your analysis results. Use annual PSA testing as your foundation. Consider a follow-up PSA test if you suspect that a recent increase in PSA was caused by temporary prostatitis due to infection or inflammation. You may already have a DRE (digital rectal exam) or can get one at your next physician visit. Consider a low-cost and often reimbursed PHI blood test when your risks increase to a concerning level with a follow-up PHI test if your risk level is elevated and temporary prostatitis might be the cause. Alternatively, consider a potentially more expensive 4Kscore test. Consider ultra-sound imaging when your risks increase and you are not ready to choose a higher stakes biopsy or more expensive screening MRI.

There is no financial cost to using risk calculators. Use them whenever you want a more complete risk analysis. PSA trend analysis may provide a sense of how fast cancer might be progressing.

Life Expectancy Estimation

Life expectancy determines your exposure to prostate cancer risk. The longer you expect to live the greater the opportunity for prostate cancer to progress and shorten your life. The US Social Security Administration offers a life expectancy calculator for average men at: *https://www.ssa.gov/oact/population/longevity.html*. With your physician's help, you can adjust the average result for you based on your health, or you can search the Internet for more sophisticated life expectancy calculators.

PSA Annual Blood Tests

The PSA (prostate-specific antigen) blood test is the low-cost foundation of prostate cancer screening. PSA testing is controversial because simplistic use of the test results can lead to over-diagnosis and over-treatment. However, increasing PSA can provide invaluable early warning of prostate conditions that may be progressing cancer. A PSA test can be ordered on-line for $40 to $60 per test. Prices as high as $200 to $400 at some hospitals have been reported. PSA testing is often reimbursed but some insurance providers are starting to resist, especially for men over age 70.

Annual PSA testing can provide useful information about the likelihood of prostate cancer and allows estimation of a trend and the rate at which PSA from cancer may be growing. PSA increases caused by non-cancer temporary conditions may be followed by a later drop. Therefore, a near-term follow-up test can provide valuable additional information, especially if you do not have a long history of annual tests.

For use with the risk calculators, all your PSA tests should be Hybritech calibrated and not WHO calibrated. Two very different calibrations are used for PSA with WHO calibration about 20% below Hybritech calibration. For example, a 4.0 Hybritech calibrated PSA is the same as a 3.2 WHO calibrated PSA. Both major risk calculators are based on Hybritech calibrated PSA levels (PCPT-RC and ERSPC-RC). Multiply all WHO calibrated PSA values by 1.25 for Hybritech calibration or see *ProstateSmart.info* for a calibration table. In addition, Proscar (finasteride) or Avodart (dutasteride) treatment for BPH (prostate enlargement) reduces PSA by about 50% on average. In this case, PSA test levels should be doubled for use in risk calculators or see our website. Flowmax (tamsulosin) does not have this effect.

DRE (Digital Rectal Exam) with Prostate Volume Estimate

Your physician can perform a digital rectal exam of your prostate during a physical exam with two objectives: 1) Check for a hard lump that might suggest the possibility of cancer, and 2) Estimate the size of your prostate. Both results are valuable information for use in the ERSPC Risk Calculator, which provides the following guidance:

> The digital rectal examination is less effective than the PSA blood test at finding prostate cancer but it can sometimes find cancer in men with normal PSA levels. A DRE is considered abnormal if the examination reveals marked asymmetry, obvious induration, nodularity or a hard mass.
>
> On the basis of DRE the volume of the prostate is estimated to be in the range of < 30 cc (walnut), between 30-50 cc (*[small]* tomato) and >= 50 cc (mandarin *[small orange]*).

If a prostate cancer tumor is large enough to be felt by digital exam, it may be large enough to be imaged. Therefore, a positive digital rectal exam may suggest follow-up with either TRUS ultrasound imaging or MR imaging to look for the possible tumor.

PHI (Prostate Health Index) Blood Test with ERSPC-RC or 4Kscore

New panels of blood tests and a urine genetic test provide more information than PSA alone.

Free PSA is blood test used in conjunction with PSA to calculate the Free PSA percentage (Free PSA %), which has informed screening decisions for many years. Free PSA is a component of PSA that is not bound to other proteins. It is a component of both PHI and 4Kscore. A low Free PSA % suggests an increased probability of prostate cancer but may be caused by a prostate infection.

PHI (Prostate Health Index) is a calculation based on a panel of three blood tests produced by Beckman Coulter. The PHI panel includes PSA and two other components of PSA, which means the PSA component can be used with the ERSPC risk calculator and to extend your PSA trend. PHI is more effective than PSA alone. One study suggests that the trend for multiple PHI tests provides additional information. PHI can be obtained at many labs or from ACCU Reference Medical Lab for $100+. There are indications that PHI cost can be reimbursed, but you should check your health insurance plan. When you want more information about your prostate, there are four reasons for using PHI (Prostate Health Index):

- PHI (and 4Kscore) are most effective for screening and better than PCA3.
- PHI can be used with the ERSPC-RC.
- PHI can be much lower cost than others and is often reimbursed by health insurance.
- PHI provides a Hybritech calibrated PSA result as one of its components along with Free PSA, which may be compared to past Free PSA tests if available.

4Kscore is a proprietary calculation based on a panel of four blood tests plus age, DRE and previous biopsy that can provide valuable information. It is produced and provided by OPKO Health, Inc. The 4Kscore panel includes PSA and three other components of PSA. 4Kscore is more effective than PSA alone. However, studies suggest that when used with risk calculators 4Kscore PSA components add no more value than PHI PSA components. The ERSPC-RC does not consider 4Kscore, which limits its usefulness. Moreover, the reported PSA is based on the Roche assay, which suggests WHO calibration. 4Kscore can be obtained from BioReference Laboratories, a subsidiary of OPKO, for reported prices ranging from $500 to $1,000. It is supplied as a Laboratory Developed Test from a CLIA lab and is not approved for screening by the FDA, which may affect reimbursement. You should check if your health insurance plan will reimburse the cost of a 4Kscore. On their website, BioReference Laboratories offer help with insurance carriers and self-pay and payment plan options if 4Kscore is not reimbursed.

Follow-Up PHI or 4Kscore may be valuable if the first test shows elevated risk. A follow-up PSA test is recommended by many physicians and organizations as best practice. An elevated PSA test, including a surprise increase, may be the result of a temporary condition such as prostatitis caused by infection and/or inflammation. After elevated PSA tests, follow-up tests often decrease as the temporary condition weakens and biopsies

may be deferred. PSA is a primary component of PHI and 4Kscore, which suggests that a temporary condition that increases PSA may increase PHI and 4Kscore temporarily. In addition, the Free PSA component of PSA is considered by both PHI and 4Kscore because it is well known that prostate cancer tends to decrease the ratio of Free PSA to PSA. There are indications that a prostate infection also tends to decrease that ratio, which suggests that an infection may increase both PHI and 4Kscore by increasing PSA and by decreasing Free PSA %.

For these reasons, it is worth considering a follow-up PHI or 4Kscore before considering a biopsy or other more aggressive action, especially if the:

- Estimated reduction in life expectancy is very low for a delay of a month or two:
    - Check estimated overall reduction in life expectancy from 1-year delay.
    - Divide estimated reduction by 12 for 1-month delay.

PCA3 is a genetic urine test produced by Hologic, Inc. The FDA has licensed it for informing the repeat biopsy decision but not screening, which may affect reimbursement. However, many doctors use it for screening. It does not provide a PSA value, which must be obtained separately. Some studies suggest that PCA3 is somewhat less effective than PHI and 4Kscore. The ERSPC-RC does not consider PCA3, which limits its usefulness. We have seen reports of $350 to $500 per test. You should check if your health insurance plan will reimburse the cost of PCA3.

Other companies are working on competing biomarkers for prostate cancer screening and some may be available. None are proven to be as effective as PHI and 4Kscore and none are considered by the ERSPC-RC.

TRUS - Ultra-Sound Imaging with ERSPC-RC

Consider transrectal ultra-sound (TRUS) imaging prior to a conventional pattern biopsy or screening MRI. At relatively low cost that is often reimbursed, TRUS provides valuable information about your prostate volume and possible abnormal areas that can strongly affect estimates of your cancer risk by the ERSPC risk calculator.

Cancer risk increases substantially for small prostate volumes and for abnormal areas on TRUS images. The ESPC-RC says that “Trans-rectal ultra-sound (TRUS) allows the visualization of the prostate. It uses a small probe, about the size of a finger, that is inserted into the rectum. This probe uses ultrasound to evaluate the prostate, in the same way, for example, that ultrasound is used during pregnancy to evaluate the fetus. The evaluation may show enlargement of the prostate or other abnormalities, that may be related to several conditions, such as prostatitis, BPH or prostate cancer. Abnormal is defined as a hypoechoic lesion.” A hypoechoic lesion is an abnormal area that can be seen during an ultrasound examination because it is darker than the surrounding tissue.

Financial cost and incremental decision making provide reasons to consider ultra-sound (TRUS) imaging before a conventional pattern biopsy or screening MRI. Ultra-sound imaging is relatively inexpensive and often reimbursed by health insurance. MRI can be

relatively expensive and may not be reimbursed for screening. TRUS can be used as a potentially low-cost way to improve your risk assessment prior to making an MRI decision. Moreover, TRUS results may help your doctors make the case for MRI reimbursement by your health insurance carrier.

Choosing an MRI is a major decision because it can be costly and starts a process that is hard to control. It is impossible to undo the decision after your MRI is evaluated. At that point, the medical process will tend to sweep you along if you receive a high MRI suspicion score [4 or 5] that will lead to very strong pressure to biopsy.

TRUS is a valuable and relatively low-cost way to gain more control over the MRI decision process and make better decisions. For example, you may feel comfortable delaying an MRI if your risks decrease because your prostate volume is moderate to large with no abnormal areas on TRUS. Alternatively, you may feel more comfortable choosing an MRI if your risks increase because your prostate volume is small and/or there is an abnormal area on TRUS.

Risk Calculator Analysis of All Variables (ERSPC-RC & PCPT-RC)

Risk calculator (RC) analysis should be used every time new information is collected.

Two prominent prostate cancer risk calculators are available at no charge on the Internet:

- ERSPC-RC – European Randomized Study of Screening for Prostate Cancer Risk Calculator by the Prostate Cancer Research Foundation, Rotterdam:
  - http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators
- PCPT-RC – Prostate Cancer Prevention Trial Risk Calculator:
  - http://myprostatecancerrisk.com

We encourage you to consider both risk calculators to help you and your physicians assess your prostate cancer risks. The substantial differences between the two risk calculators are summarized below. We suggest using the ERSPC-RC and supplementing it with results from the PCPT-RC if you are African American or have a Family History of prostate cancer.

High Grade Cancer or Significant Cancer

The PCPT-RC considers high-grade cancer. The ERSPC-RC adds very large low-grade tumors to its Significant Cancer Risk category. The ERSPC-RC reports: 1) Detectable cancer risk by biopsy and 2) Significant cancer risk, defined as: “Significant Cancer Risk – A clinically significant prostate cancer is defined as a tumor stage greater than T2b, which means that the tumor is more than half of at least one lobe, and/or having a Gleason biopsy score equal or greater than 7.” In practice, the PCPT-RC and ERSPC-RC categories are likely to be similar because only a small percentage of low-grade cancers are very large.

PSA, DRE and Previous Biopsy Are Used by both ERSPC-RC and PCPT-RC

Hybritech PSA calibration is implicit in both risk calculators because it was used by both the ERSPC and PCPT studies. WHO calibrated PSA values should be calibrated to Hybritech, as noted. The PCPT-RC is based on a study of U.S. men and U.S. physicians, which may account for some differences between the PCPT-RC and the ERSPC-RC for European men. For example, the difference in risks between a normal and abnormal DRE are much greater for the ERSPC-RC than for the PCPT-RC. U.S. men should be careful accepting the strong (high-risk) implications of an abnormal DRE using the ERSPC-RC. Previous biopsy is used by both with a stronger effect for the ERSPC-RC.

ERSPC Risk Calculator for Prostate Volume, TRUS and PHI

Consider using ERSPC-RC 3 and 4 with TRUS or DRE and the PHI version if a PHI (Prostate Health Index) test result is available.

The ERSPC-RC is valuable because it incorporates three additional variables of high influence (prostate volume, PHI and TRUS cancer result) that are not considered by the PCPT-RC. See *ProstateSmart.info*. Prostate volume strongly affects the interpretation of an elevated PSA. For a given PSA level, such as 4.0, the probability of cancer is much higher for a small prostate than for a large prostate, which often produces elevated PSA at a slowly growing rate. PHI provides more valuable information than PSA alone. TRUS prostate volume is more accurate than a DRE estimate, and a TRUS cancer abnormality substantially increases the probability of prostate cancer.

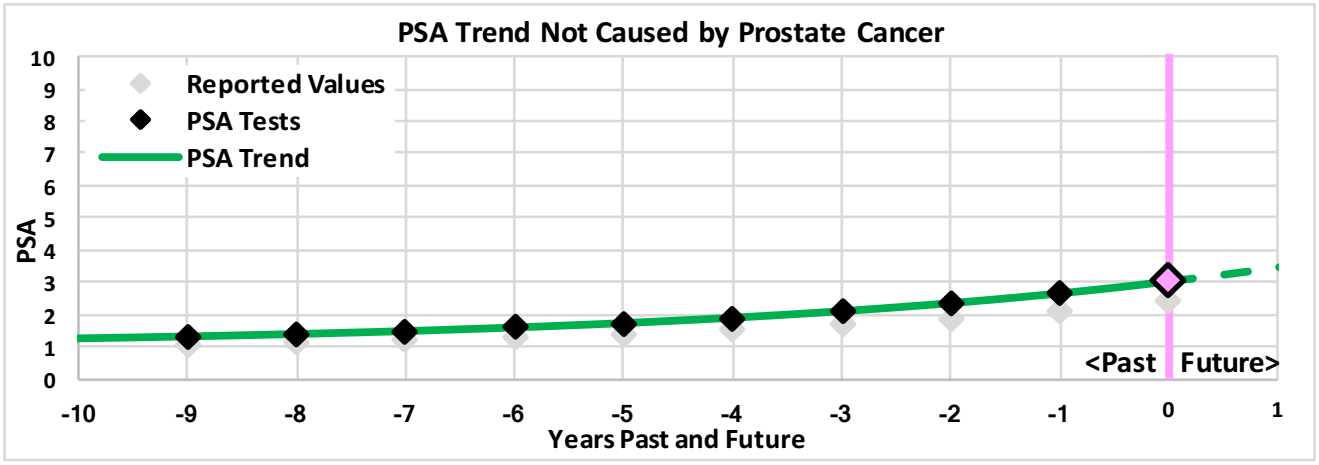
PCPT Risk Calculator for Race, Age and Family History

The current version of the PCPT-RC is 2.0. For a biopsy, it reports the chances of high-grade and low-grade cancer and no cancer (negative biopsy), where high-grade is Gleason 7 and greater and low-grade is Gleason 6 and lower.

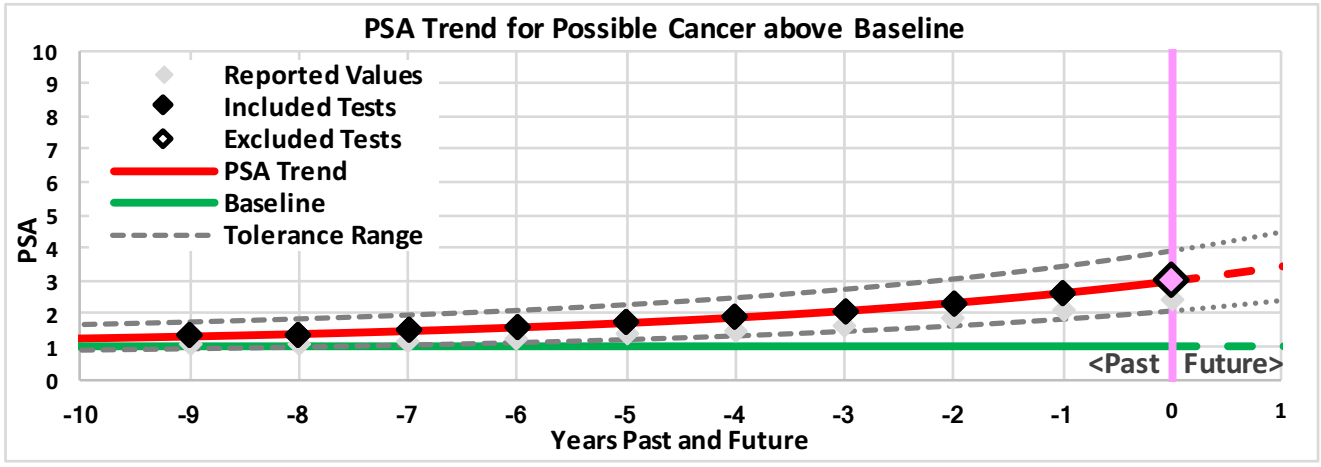
Race, Age and Family History of prostate cancer are considered by the PCPT-RC but not by the ERSPC-RC. For the PCPT-RC: African American men are at much greater risk than other men. Older men are at somewhat greater risk than younger men. Men with a family history of prostate cancer are at modestly higher risk than men with no family history. In principle, African American men and men with a Family History of prostate cancer should adjust ERSPC-RC results upwards using PCPT-RC results. See *ProstateSmart.info*.

PSA Trend Analysis

For most men, increasing PSA is more likely caused by prostate enlargement (BPH) or prostatitis than by progressing prostate cancer, as suggested on the graph below. For this *Example* on the graph below, the gray diamonds show reported PSA values with WHO calibration, and the black diamonds show the corresponding Hybritech calibrations. The pink diamond shows the current (most recent) PSA test with a no cancer trend shown by the green curve through the black calibrated tests.



Alternatively, PSA trend analysis may be informative if progressing prostate cancer is the cause, as suggested on the graph below. Please see *ProstateSmart.info* to learn more. For the example on the graph below, the black (or pink) diamonds show PSA tests with the red estimated trend through them. In this example, the red trend is estimated for Hybritech calibrated PSA values with no adjustment for BPH treatment needed.



A PSA trend for progressing cancer typically increases to the current (most recent) test, shown by the pink diamond on the graph with value:

{T1} 3.0 PSA at current test calibrated and adjusted

PSA trend analysis starts with an estimated no-cancer baseline, shown by the horizontal green line on the graph with value:

{T2} 1.0 estimated no-cancer PSA baseline

Estimated PSA from cancer is the difference between the horizontal green no-cancer baseline and the upward curving red PSA trend that includes PSA from cancer in addition to no cancer PSA. At the current test (pink diamond), PSA from cancer is estimated to be:

{T3} 2.0 estimated PSA from cancer above baseline

PSA from cancer is calculated as the difference: {T3} (= {T1} – {T2}.

Finally, the (annual) growth rate in cancer PSA is estimated to be:

{T4} 20% estimated growth rate in PSA from cancer based on trend analysis

The estimated growth rate in cancer PSA, {T4}, is used to inform the choice of growth rate of prostate cancer risk for the speculative analysis, as described in the next subsection. See *ProstateSmart.info* to estimate the growth rate in cancer PSA for your PSA tests.

PSA trends help you and your physicians assess whether your elevated PSA might be caused by prostate cancer, prostate enlargement (BPH) or prostatitis. Studies have shown that an elevated PSA level is often followed by a drop for a follow-up PSA test. If your PSA trend is growing smoothly cancer is more likely than if your PSA is increasing and decreasing, which suggests temporary prostatitis caused by inflammation and/or infection. If your PSA trend is growing slowly then prostate enlargement (BPH) may be the cause rather than cancer – and if cancer is the cause, then slow growth is less alarming than fast growth.

Smooth, fast growth in PSA over a few years or more suggests considering rapidly escalating screening actions before potential PSA from cancer reaches high levels.

Growth Rate in Cancer Risk Estimation

In order to choose one of the 72 *Example* reports available by subscription, you will choose a growth rate in cancer risk from:

- 20% moderate growth - cancer risk doubles every 3.5 years
- 40% fast growth - cancer risk doubles every 1.7 years
- 60% very fast growth - cancer risk doubles every 1.2 years

Your choice helps determine the consequence of delay in terms of reduction in life expectancy:

- At 20% moderate growth, the consequences of delay tend to be relatively low.
- At 60% very fast growth, the consequences of delay are much higher.

Prostate cancer may not be found by biopsy and may not be progressing. This step focuses on the growth rate in risk if prostate cancer will be found and is the cause of increasing PSA. Most prostate cancers tend to grow slowly compared to many other

cancers. The challenge is estimating the growth rate in cancer risk if prostate cancer is progressing.

Prostate Cancer Risks Are Higher at Higher Levels of PSA

For most men, PSA tests over time offer the only clue about the growth rate in cancer risk – but this relationship is speculative. PSA trends may provide insights into how fast prostate cancer risk is growing because cancer risks are related to PSA. However, increasing PSA does not always mean that prostate cancer is present or progressing. Increasingly severe prostatitis and increasing prostate size due to BPH can also cause PSA to increase over time.

Probability of Prostate Cancer Found by Biopsy Is Higher at Higher Levels of PSA

Very many studies have shown that the probability a biopsy will find cancer is an increasing function of PSA. The probability is higher at higher levels of PSA. You can see this relationship using the ERSPC and PCPT risk calculators.

Probability of High Risk Cancer Found by Biopsy Is Higher at Higher Levels of PSA

Many studies have shown that the probability a biopsy will find high risk or high-grade cancer is an increasing function of PSA. The probability is higher at higher levels of PSA. You can see this relationship using the ERSPC and PCPT risk calculators.

Probability of Prostate Cancer Death Is Higher at Higher Levels of PSA

Many studies have shown that for prostate cancer found by biopsy the risk of metastasis and death is an increasing function of PSA. The risk is higher at higher levels of PSA. In our speculative analysis, we use relationships between prostate cancer death risk and PSA prior to diagnosis found in the large study led by the Cleveland Clinic.

Implied but Unproven Relationship between Growth in Cancer Risk and in PSA

The strong relationships between prostate cancer risks (probabilities and death) and PSA levels suggest that increasing PSA for a man is an indicator of increasing cancer risk. However, this implication is a hypothesis that is difficult to prove for individual men because it is hard to measure increasing prostate cancer risk over time for individual men.

Choose Your Growth Rate in Cancer Risk

In order to choose one of the 72 *Example* reports available by subscription, you will choose a growth rate in cancer risk from:

- 20% moderate growth
- 40% fast growth
- 60% very fast growth

You may decide to inform your choice by your estimated growth rate in cancer PSA from trend analysis of your PSA tests because it is the best information available. Caution is advised no matter how you choose the growth rate in cancer risk.

3. Conventional Pattern Biopsy

After using all informative screening actions, the next step is to consider one of three alternatives:

- Conventional pattern biopsy (this section),
- MRI targeted biopsy (section 5) or
- Screening MRI (section 6).

A conventional pattern biopsy that uses a template for needles to sample your prostate is discussed in this section. MR imaging, an MRI targeted biopsy and a screening MRI are discussed in sections 4, 5 and 6, where you can learn about the substantial benefits of MRI and potentially high financial costs.

NOTE: The biopsy timing analysis of this section also applies to an MRI targeted biopsy if MRI is used for targeting but **not** for screening and the decision to biopsy. It also is the starting point for screening MRI timing analysis.

Biopsy vs More Information

A pattern biopsy uses a template for up to 12 or more needles to sample your prostate. It is the conventional option offered by urologists for the vast-majority of biopsies. If you can't justify a biopsy now, consider gathering more information with another PSA test or a PHI or 4Kscore blood test (that include PSA) in one year - or six months or even three months depending on your sense of urgency. Another PSA or PHI test in the future will provide new information for you to re-estimate your risks using the ERSPC risk calculator, and the additional PSA will allow better estimation of your PSA trend and its growth rate. Over time, periodic PSA or PHI or 4Kscore tests allow you to reassess your changing risks – which may go down or up enough to reconsider a biopsy.

Biopsy Timing Decision

Consider a biopsy now, or soon, if the risks of delay are high enough to justify the potentially high negative consequences of a biopsy. In this *Example* report, we consider a 1-year delay that is convenient for analysis and discussion. Ultimately, a 1-year delay in biopsy delays possible diagnosis and treatment if warranted that may allow prostate cancer to progress. The result is a reduction in life expectancy. The benefit of delay is deferral of the negative consequences of a biopsy, possible diagnosis and treatment.

Average Outcomes for a Delayed Biopsy

For the *Example*, we estimate average reductions in life expectancy from a 1-year delay in **B**iopsy {**B**}, possible diagnosis and treatment if warranted. Consider the results step-by-step. The overall reduction in life expectancy from delay is:

{B1} 0.01 year overall reduction in life expectancy from delay

This overall reduction can be compared to the overall effect of other health and medical decisions. It is pulled down toward 0.00 by the probability that a biopsy will **not** find cancer:

{B2a} 79% probability a biopsy will not find cancer

In contrast, the overall reduction, {B1}, is pulled up by the probability that a biopsy **will** find cancer:

{B2b} 21% probability a biopsy will find cancer

If cancer is found by biopsy, then the overall reduction, {B1}, is increased to the conditional "if-cancer" reduction in life expectancy from delay:

{B3} 0.07 year if-cancer reduction in life expectancy from delay

You might wonder why the overall reduction is less than the conditional "if-cancer" reduction. The overall reduction is a "weighted average", where we multiply the larger "if-cancer" reduction, {B3}, by the (less than 100%) probability a biopsy will find cancer, {B2b}, to calculate the smaller overall reduction:

{B1} 0.01 year overall reduction in life expectancy from delay

CAUTION: These are estimated reductions in life expectancy from delay based on the example growth rate in cancer risk. They are in addition to any decreases in life expectancy from prostate cancer that is diagnosed now with treatment that may not be successful. See *Appendix A. Speculative Prostate Cancer Scenarios*.

Overall Reduction in Life Expectancy in Context

The overall reduction in life expectancy from delay is:

{B1} 0.01 year overall reduction in life expectancy from delay

Let's put this reduction in context. There are many things that you can do this year to feel better now and live longer, including: improved diet, exercise, and stress reduction; healthier habits (stop if a smoker); and medical evaluation and possible changes of medication - with your heart near the top of the list. These health actions can add 1, 2, 3 or more years to your life expectancy as well as help make you feel better now. A biopsy now with a possible prostate cancer diagnosis with its emotional costs and treatment if warranted with potential side effects could make you feel worse in the near-term to avoid a reduction in life expectancy from a 1-year delay. During the next year:

- You might choose to invest your energy, time and money in other more valuable actions to feel better and live longer. Alternatively,
- You might be sufficiently concerned about increasing prostate cancer risk to consider a biopsy.

Deferral of Negative Consequences from Biopsy Delay

Biopsy delay defers the negative consequences of a biopsy:

- Discomfort and the risk of potentially life-threatening sepsis (infection).
- Emotional costs that accompany a possible diagnosis of cancer.
- Potential side effects of treatment if warranted, such as impotence and incontinence.

Delay can be evaluated from two complementary perspectives:

- Overall perspective, as above
- "If-cancer" perspective, below

The overall perspective is the big picture, where the often-low overall reduction in life expectancy may give you comfort and help you prioritize prostate cancer screening among your health and medical actions for the year.

However, the largest consequences of a biopsy are associated with diagnosis and treatment if warranted. These only occur if a biopsy **will** find cancer with probability:

{B2a} 21% probability a biopsy will find cancer

For an overall risk assessment of biopsy delay, this "if-cancer" probability should be multiplied by the consequences of diagnosis and treatment if warranted. Many men find this process of combining risks and probabilities awkward and not intuitive.

In practice, many men find it easier to assess their risk preferences for the "if-cancer" case described below because it minimizes the need to balance risks and probabilities simultaneously. Therefore, we will focus on personal risk assessment for the "if-cancer" case.

Personal Risk Assessment for the If-Cancer Case

Look into the future and imagine that your biopsy has found prostate cancer, which we call the "if-cancer" case. If you delay a biopsy, then you will also delay possible diagnosis and treatment if warranted. In other words, a delay in biopsy will delay this "if-cancer" case, which is our focus. For this "if-cancer" case, the reduction in life expectancy from a 1-year delay in biopsy, diagnosis and treatment if warranted is:

{B3} 0.07 year if-cancer reduction in life expectancy from delay

For this "if-cancer" case where prostate cancer has been diagnosed, delay defers two negative consequences:

- Emotional costs that accompany a possible diagnosis of cancer.

- Potential side effects of treatment if warranted, such as impotence and incontinence.

From this “if-cancer” perspective, your biopsy timing decision should be based on your assessment of these two consequences and the “if-cancer” reduction in life expectancy {B3}.

The assessment is very personal with wide variation among men and among physicians with potentially large differences between men and their physicians. For example, some urologists might be more concerned about the dangers of cancer while some primary care physicians might be more concerned about the side effects of biopsy, emotional costs of diagnosis and side effects of treatment. Different men seem to have highly divergent assessments of the risk tradeoffs.

Compare this reduction:

{B3} 0.07 year if-cancer reduction in life expectancy from delay

to your assessment of the benefits of deferring diagnosis and treatment if warranted:

- Some men might wait for a 1.0-year “if-cancer” reduction in life expectancy:
  - They place a high value on their currently high quality of life that would be disrupted by diagnosis and treatment if warranted and
  - Are much less concerned about losing life expectancy toward the end of life when they expect their quality of life may be low.
- Other men might only wait for a 0.25-year “if-cancer” reduction in life expectancy:
  - They are less concerned about disruption of their current quality of life from diagnosis and treatment if warranted and
  - Are more concerned about losing life expectancy, perhaps because they want to see their grandchildren grow up or live as long-as their spouse.

Consider a biopsy when the reduction in life expectancy, {B3}, exceeds your assessment of the benefits of delay, perhaps 0.25-year or 1.0-year or other benefit.

Biopsy and Treatment Risk Assessment Adjustments

For completeness, you might adjust your “if-cancer” risk assessment for the consequences of a biopsy and treatment strategies to reduce the risk of side effects, including active surveillance or even focal therapy. However, these adjustments work in opposite directions and tend to offset each other – often leading to small net adjustments. Therefore, we discuss them in *Appendix B: Biopsy and Treatment Risk Assessment Adjustments*, where you can learn more if you are interested.

Rare Alarming Speculative Scenario Outcomes

Finally, you may want to consider the possibility of rare alarming cancers, which might support a decision to biopsy. Average outcomes do not fully describe the range of prostate cancer scenarios, which tend to be skewed toward a few alarming ones. For this *Example* report, the five most **A**larming prostate cancer scenarios {**A**} are summarized below, where each has a 1 of 100 chance of being true (1% probability):

{A1}	0.17	year reduction in life expectancy from 1-year delay (1% probability)
{A2}	0.14	year reduction in life expectancy from 1-year delay (1% probability)
{A3}	0.13	year reduction in life expectancy from 1-year delay (1% probability)
{A4}	0.12	year reduction in life expectancy from 1-year delay (1% probability)
{A5}	0.11	year reduction in life expectancy from 1-year delay (1% probability)

You may want to consider some of these rare alarming cancer scenarios when you choose the timing of screening actions. For perspective, the life expectancy reductions of these rare alarming prostate cancers are typically much less than for the most aggressive other cancers that can kill within months or years and reduce life expectancy by 75% to 90%, such as a 15 to 18-year reduction of a 20-year life expectancy.

CAUTION: Scenario {A1} above is a rare scenario (1 of 100 or 1% probability) but not a worst case. There is always a very small probability of very deadly prostate cancer where the risk of delay can be higher than for Scenario {A1}.

Consider a biopsy now, or soon, if the reduction in life expectancy from delay is high enough to justify the potentially high negative consequences of a biopsy, possible diagnosis and treatment if warranted.

4. MR Imaging

MR imaging of the prostate can enhance your screening strategy and is worth serious consideration.

Multi-Parametric Magnetic Resonance Imaging (mpMRI or simply MRI)

Multi-parametric magnetic resonance imaging offers an improved way to identify large aggressive prostate cancers that are deadliest while also offering the potential to reduce over-diagnosis. MRI uses a magnetic field and radio waves to create images of the prostate. Multi-parametric MRI is a sophisticated method to identify prostate cancers that uses dynamic contrast-enhanced (DCE) MRI and diffusion weighted imaging (DWI) to supplement standard anatomical T1 and T2-weighted imaging. Because of its complexity and subtlety, extensive experience is needed to interpret the results effectively.

Three Ways to Use MR Images

Physicians are using MR images in three related ways:

MRI Targeted Biopsy

Many leading medical centers have adopted MRI targeted biopsies as their apparent standard of care. They use new technology that fuses (combines) MR images of the prostate with real-time ultra-sound images to guide biopsy needles to tumor target(s) visible on the images. See section *5. MRI Targeted Biopsy* to learn about the benefits compared to a conventional pattern biopsy. If you plan to choose an MRI targeted biopsy rather than a pattern biopsy, then it makes sense to consider using the MRI for screening prior to making a biopsy decision.

Screening MRI before Biopsy

Some leading medical centers are using MR images to screen for prostate cancer. The decision to biopsy depends on whether the images show a strong suspicion of prostate cancer. Biopsies, over-diagnosis and over-treatment can be delayed or avoided when the suspicion of cancer is low. See section *6. Screening MRI* to learn more about the benefits of a screening MRI.

MRI Targeted Focal Therapy

Some leading medical centers are using the results of MRI targeted biopsies to direct focal therapy at diagnosed prostate cancer tumors. Focal therapy is a new family of targeted treatments designed to destroy tumors but not damage the rest of the prostate in order to reduce the side effects of treatment. The long-term effectiveness of focal therapy is uncertain and its use is controversial. However, increasing numbers of men are choosing it as a low-side effect alternative between active surveillance and primary treatment, such as surgery or radiation.

Find the Right MRI Supplier for You Based on Quality and Price

A prostate MRI can be expensive, up to $3,000 to $10,000 or more at academic and research centers in the US, and may not be reimbursed by health insurance. Academic and research centers pioneered the use of multi-parametric MRI and remain the leaders in the field with continuing improvement. They found that there is a long learning curve to become expert and fully effective based on 100's of cases to 1,000 or more cases. Typically, these pioneering academic/research centers tend to charge the highest price.

Range of Quality and Price

Fortunately, a range of quality and price are becoming available from a growing number of competing suppliers in the US with quality improving with experience. For example, one private center with extensive experience started by a pioneering urologist at a leading academic center charged only $600 for a screening MRI. If price matters to you, we encourage you to research your options locally, nationally and even internationally.

Reimbursement Varies

Reimbursement (or not) by health insurers greatly affects your cost of an MRI. Research by you is required because reimbursement varies greatly, as does price. MRI for targeted biopsies and screening MRI was often reimbursed early in its development but is increasingly resisted by health insurers. Possible reimbursement policies include:

- MRI reimbursed for both biopsy and screening
- MRI reimbursed for biopsy but not for screening
- MRI not reimbursed for either biopsy or screening

Some insurance carriers will automatically refuse to reimburse a screening MRI, and others will consider it only if a strong case is made on your behalf. Consider using ultra-sound imaging prior to a screening MRI if your insurance carrier is resistant to reimbursing a screening MRI. Ultra-sound may be reimbursed and provides valuable results that will inform your MRI decision and may help make the case for reimbursement of a screening MRI.

See Our Website for Physicians Who Are Teaching MRI to Other Physicians

It is difficult to obtain information about MRI suppliers. One place to start is our website where we identify some physicians who have been teaching MRI to other physicians through continuing medical education (CME) courses. Presumably, these teachers are knowledgeable and might be willing to provide information about other physicians who supply MRI closer to your home.

5. MRI Targeted Biopsy

After using all informative screening actions, the next step is to consider one of three alternatives:

- Conventional pattern biopsy (section 3),
- MRI targeted biopsy (this section) or
- Screening MRI (section 6).

An MRI targeted biopsy offers substantial benefits compared to a conventional pattern biopsy. If you plan to choose an MRI targeted biopsy rather than a pattern biopsy, then it makes sense to consider using the MR images for screening prior to making a biopsy decision, as discussed in section *6. Screening MRI*.

Conventional Pattern Biopsy

A conventional pattern biopsy uses a template for up to 12 or more needles to sample your prostate. Prostate cancer is detected if one or more of the needles happens to pass through a tumor.

MRI Targeted Biopsy

Many leading medical centers have adopted MRI targeted biopsies as their apparent standard of care. Real-time ultra-sound images are “fused” (combined) with MR images to guide biopsy needles. A targeted biopsy typically directs fewer needles at a high suspicion tumor target or targets visible on MRI and does not sample the rest of the prostate. Some centers add a pattern biopsy to a MRI targeted biopsy, but this approach increases the risk of over-diagnosis and over-treatment for relatively little additional benefit.

Benefits of an MRI Targeted Biopsy

There are four potential benefits of an MRI targeted biopsy compared to a conventional pattern biopsy:

Misses Fewer Large Deadly Cancers

An increasing number of studies are showing that MRI targeted biopsies are superior to conventional pattern biopsies. Large, aggressive (high-grade) tumors are deadliest with their diagnosis the primary goal of screening and biopsy. MR imaging does a good job of identifying them for targeting by biopsy. Men can take emotional comfort if an MRI targeted biopsy does not find cancer because a deadly large, aggressive tumor is unlikely to have been missed. A conventional pattern biopsy can miss cancers that fall between the needles or grow in areas not always sampled, such as the anterior region of the prostate.

Better Defines Diagnosed Cancers

It is increasingly important to define diagnosed prostate cancers well for subsequent treatment decisions. MRI targeted biopsies can put several needles through the target tumor to define the extent and pathology of the tumor, which can be combined with the MR image to create a reasonably complete picture of the tumor. In contrast, a conventional pattern biopsy has no image of a tumor and a single needle may pass through the “edge” of the tumor rather than the center, where the most aggressive cancer cells may exist. A tumor that is well-defined by an MRI targeted biopsy allows better decisions about: 1) active surveillance if the cancer is small and not very aggressive, 2) the potential for focal therapy and 3) more aggressive treatment if it looks like the tumor extends beyond the prostate capsule.

Reduces the Need for Repeat Biopsies

MRI targeted biopsies reduce the need for repeat biopsies because large, aggressive (high-grade) tumors are less likely to be missed by the first biopsy. Many men with elevated risks of prostate cancer that is not found by the first conventional pattern biopsy undergo one or more repeat biopsies looking for tumors that might have been missed the first time.

Potential to Reduce Over-Diagnosis

MRI targeted biopsies often find high-risk prostate cancers while reducing the chance of finding low-risk cancers that lead to over-diagnosis and over-treatment.

6. Screening MRI

After using all informative screening actions, the next step is to consider one of three alternatives:

- Conventional pattern biopsy (section 3),
- MRI targeted biopsy (section 5) or
- Screening MRI (this section).

The case for an MRI targeted biopsy was presented in section *5. MRI Targeted Biopsy*. If you will choose MRI for targeting your biopsy, it makes sense to consider using the MR images for screening to inform the decision to biopsy.

Screening MRI or Biopsy Next

The primary reasons to choose a screening MRI next rather than a biopsy are:

- Increase the chance of finding the largest and most aggressive cancers that are deadliest.
- Reduce the chances of:
    - Needing a biopsy and
    - Subsequent cancer diagnosis and possible treatment,
    - While maintaining the relatively high probability of finding the largest and most aggressive cancers that are deadliest.
- Strengthen the case for a biopsy if a tumor is visible on MR images with high MRI Suspicion Score.

If you are considering a screening MRI, then read all of this section 6 before making a decision with your physicians. It is easy to get swept up by this new technology and schedule a screening MRI before it makes sense for you.

Screening MRI vs More Information

If you can't justify a screening MRI now, consider gathering more information with another PSA test or a PHI or 4Kscore blood test that includes PSA, in one year - or six months or even three months depending on your sense of urgency. Another PSA or PHI test in the future will provide new information for you to re-estimate your risks using the ERSPC risk calculator, and the additional PSA will allow better estimation of your PSA trend and its growth rate. Over time, periodic additional PSA or PHI or 4Kscore tests allow you to reassess your changing risks – which may go down or up enough to reconsider an MRI.

MRI Suspicion Scores

MR images are often evaluated on a PI-RADS™v2 score from [1] for very low suspicion to [5] for very high suspicion. https://www.acr.org/Quality-Safety/Resources/PIRADS

A high [4] or very high [5] MRI Suspicion Score means there is a relatively high probability of high-risk cancer and lower probabilities of low-risk or no cancer in the target region of the prostate. Biopsy of target regions with a 4 or 5 suspicion score is currently the best way to diagnose most high-risk cancers with decreased chance of over-diagnosis of lower-risk cancers. A biopsy of a region with a moderate suspicion score [3] may find cancer but increases the chance of over diagnosis of low-risk cancer. With a moderate suspicion score [3], a follow-up MRI in a year or two is an alternative to a targeted biopsy now. The risk of over-diagnosis of low-risk cancers increases even more for low [1] or [2] suspicion score regions.

Pioneers in multi-parametric imaging for prostate cancers often suggest:

- Targeted biopsy for high suspicion scores [4 or 5];
- No biopsy for low suspicion scores [1 or 2]; and
- Discussion with the patient based on other evidence for a moderate suspicion score [3]. Prior to choosing a screening MRI, it is worth deciding how you will respond to a moderate suspicion score [3].

Evaluating a Screening MRI Based on Your Risk Assessment

We have found that evaluating a screening MRI depends on your risk assessment for a conventional pattern biopsy in section *3. Conventional Pattern Biopsy*. Two alternative risk assessments are:

A. Prostate cancer risks **justify** a conventional pattern biopsy now.
B. Prostate cancer risks do **not justify** a conventional pattern biopsy now.

We evaluate screening MRI decisions for each of those assessments below.

A. Prostate Cancer Risks Justify a Conventional Pattern Biopsy Now

Use this section if you have assessed the estimated reductions in life expectancy from a 1-year delay in biopsy and concluded that a conventional pattern biopsy is **justified** now. If used to inform the biopsy decision in this case, a screening MRI has two potential benefits:

- Reduce the need for biopsy
- Reduce the chance of diagnosis and potential over-treatment

The size of these benefits depends on what MRI Suspicion Scores will trigger a biopsy for you. In order to have already justified a conventional pattern biopsy now, your cancer risks are likely to be elevated and possibly high. For good reason, you may face the following coaching from your physicians:

- High MRI Suspicion Score [4 or 5]:
    - Very strong encouragement to biopsy
- Moderate MRI Suspicion Score [3]:
    - Strong encouragement to biopsy

- Low MRI Suspicion Score [1 or 2]:
    - Weak or no encouragement to biopsy

Therefore, we will compare the following two strategies with a conventional pattern biopsy now:

- Realistic Strategy - Biopsy for Moderate or High MRI Suspicion Score [3, 4 or 5]
- Aggressive Strategy - Biopsy for High MRI Suspicion Score [4 or 5]

Biopsy for moderate or high MRI Suspicion Score [3, 4 or 5] is the **realistic** strategy for most men considering a screening MRI. Faced with sufficiently high prostate cancer risks to justify a biopsy now and possibly strong encouragement from their physicians, most men are likely to biopsy at a moderate MRI Suspicion Score [3], as well as high MRI Suspicion Score [4 or 5]. In the results below, we highlight the reductions for this **realistic** strategy in **bold.** Faced with the same situation a few men may push back against their physicians and choose the aggressive strategy, where they will delay a biopsy for a moderate MRI Suspicion Score [3].

Reduce the Need for Biopsy

A screening MRI can reduce the need for biopsy with the reduction dependent on the strategy: Realistic or Aggressive.

Recall that this section applies if you have assessed that a conventional pattern biopsy is **justified** by elevated prostate cancer risks.

In the absence of MRI Screening, the probability of an already justified conventional pattern **B**iopsy {**B**} is:

{B4} **100%** chance of conventional pattern biopsy

If you choose the **R**ealistic **S**trategy, {**RS**}, and will biopsy for both moderate and high screening MRI Suspicion Scores [3, 4 or 5], then the probability of biopsy will decrease to:

{RS1} **58.3%** chance of targeted biopsy for moderate or high MRI Suspicion Score

If you choose the **A**ggressive **S**trategy, {**AS**}, and will biopsy only for a high screening MRI Suspicion Score [4 or 5], then the probability of biopsy will decrease further to:

{AS1} 21.7% chance of targeted biopsy for high MRI Suspicion Score

Reduce the Chance of Diagnosis and Potential Over-Treatment

A screening MRI can also reduce the chance of diagnosis and potential over-treatment with the reduction dependent on the strategy: Realistic or Aggressive.

Recall that this section applies if you have assessed that a conventional pattern biopsy is **justified** by elevated prostate cancer risks.

In the absence of MRI Screening, the probability of diagnosis by an already justified conventional pattern biopsy is:

{B2a} **21.0%** probability a biopsy will find cancer

If you choose the **Realistic S**trategy, {**RS**}, and will biopsy for both moderate and high screening MRI Suspicion Scores [3, 4 or 5], then the probability of diagnosis will decrease to:

{RS2} **17.7%** chance of diagnosis by targeted biopsy for moderate or high screening MRI Suspicion Score

If you choose the **A**ggressive **S**trategy, {**AS**}, and will biopsy only for a high screening MRI Suspicion Score [4 or 5], then the probability of diagnosis will decrease further to:

{AS2} 12.7% chance of diagnosis by targeted biopsy for high MRI Suspicion Score

Do the Benefits Justify a Screening MRI?

As shown above for this case *A. Justified Biopsy*, MRI Screening can both: 1) Reduce the need for biopsy and 2) Reduce the chance of diagnosis and potential over-treatment. The question is whether these benefits justify a screening MRI when a conventional pattern biopsy is **justified**. Your decision may depend on the additional financial costs of a screening MRI. There are several possibilities.

If you plan to use an MRI targeted biopsy:

- **MRI Reimbursed** - Use of the MR images for screening adds little additional cost if the MRI will be reimbursed however the images are used. In this case, why not use the MRI results for screening to inform the decision to biopsy?
- **MRI Reimbursed for Biopsy but Not for Screening** - Your health insurance provider may reimburse the MRI for a targeted biopsy but not reimburse the MRI if it is only used for screening. In this case, you should consider the potentially high additional cost of a screening MRI if you don't proceed with the biopsy. You may choose to shop for lower cost suppliers of screening MRIs in this case.
- **MRI Not Reimbursed** - Your health insurance provider may not reimburse the MRI whether used for screening or for biopsy. If you plan to pay for the additional MRI cost of a targeted biopsy then use of the MR images for screening adds little additional cost. Your overall decision is whether to pay the not reimbursed potentially high cost of an MRI for use in both screening and targeting. The alternative is a conventional pattern biopsy without MRI. In this case, you may choose to shop for lower cost suppliers of MRIs.

If you don't plan to use the MR images for a targeted biopsy, it probably does not make sense to consider a screening MRI.

B. Prostate Cancer Risks Do Not Justify a Pattern Biopsy Now

Use this section if you have assessed the estimated reductions in life expectancy from a 1-year delay in biopsy and concluded that a conventional pattern biopsy is **not justified** now. If used to inform the biopsy decision in this case, a screening MRI has a potential benefit:

- Possible justification of a targeted biopsy if the MRI results in a high MRI Suspicion Score or possibly a moderate MRI Suspicion Score

The results of a screening MRI could decrease your apparent risks if MRI Suspicion Score is low and could increase your apparent risks if MRI Suspicion Score is high. A high MRI Suspicion Score may increase your apparent risk enough to justify a targeted biopsy and, therefore, possibly justify a screening MRI to see if the images produce a high MRI Suspicion Score. The analysis in this section is designed to help you decide if the implications of a possible high MRI Suspicion Score change your analysis enough to justify a biopsy and, therefore, possibly justify a screening MRI now.

Estimated Probabilities of MRI Suspicion Scores

Analysis of the speculative scenarios for this *Example* produces the following estimates of **P**robabilities of the five MRI **S**uspicion **S**cores {**PSS**}:

{PSS5}	8.7%	chance of 5 MRI Suspicion Score
{PSS4}	13.0%	chance of 4 MRI Suspicion Score
{PSS3}	36.6%	chance of 3 MRI Suspicion Score
{PSS2}	35.7%	chance of 2 MRI Suspicion Score
{PSS1}	6.0%	chance of 1 MRI Suspicion Score

Estimated Probabilities of Cancer Found by Targeted Biopsy for Suspicion Scores

Analysis of the speculative scenarios for this *Example* produces the following estimates of probabilities of **C**ancer found by targeted biopsy for the five MRI **S**uspicion **S**cores {**CSS**}:

{CSS5}	76.5%	chance of cancer for 5 MRI Suspicion Score
{CSS4}	46.6%	chance of cancer for 4 MRI Suspicion Score
{CSS3}	13.8%	chance of cancer for 3 MRI Suspicion Score
{CSS2}	8.0%	chance of cancer for 2 MRI Suspicion Score
{CSS1}	6.4%	chance of cancer for 1 MRI Suspicion Score

This table suggests how effectively MRI screening can identify prostate cancer for high MRI Suspicion Scores [4 or 5] with the possibility of delaying a biopsy for low MRI Suspicion Scores [1 or 2] and uncertainty about a moderate MRI Suspicion Score [3]. However, a high probability of cancer alone is not sufficient to justify a biopsy and a

screening MRI. It is even more important to consider the potential reduction in life expectancy from delay, as presented in the next section.

Estimated Reduction in Life Expectancy from a 1-Year Delay for Suspicion Scores

Analysis of the speculative scenarios for this *Example* produces the following estimates of the **R**eduction in life expectancy for a 1-yer delay for the five MRI **S**uspicion **S**cores {**RSS**}:

{RSS5}	0.09	year "if-cancer" reduction in life expectancy for 5 MRI Suspicion Score
{RSS4}	0.08	year "if-cancer" reduction in life expectancy for 4 MRI Suspicion Score
{RSS3}	0.05	year "if-cancer" reduction in life expectancy for 3 MRI Suspicion Score
{RSS2}	0.05	year "if-cancer" reduction in life expectancy for 2 MRI Suspicion Score
{RSS1}	0.03	year "if-cancer" reduction in life expectancy for 1 MRI Suspicion Score

Interpretation of these results depends on what MRI Suspicion Scores will trigger a biopsy for you. You may face the following coaching from your physicians:

- High MRI Suspicion Score [4 or 5]:
  - Very strong encouragement to biopsy
- Moderate MRI Suspicion Score [3]:
  - Strong to moderate encouragement to biopsy
- Low MRI Suspicion Score [1 or 2]:
  - Weak or no encouragement to biopsy

Therefore, we will compare the following two strategies with a conventional pattern biopsy now:

- Realistic Strategy - Biopsy for Moderate or High MRI Suspicion Score [3, 4 or 5]
- Aggressive Strategy - Biopsy for High MRI Suspicion Score [4 or 5]

Biopsy for moderate or high MRI Suspicion Score [3, 4 or 5] is the **realistic** strategy for most men considering a screening MRI. Faced with possibly strong to moderate encouragement from their physicians, many men are likely to biopsy at a moderate MRI Suspicion Score [3], as well as high MRI Suspicion Score [4 or 5]. Faced with the same situation some men may push back against their physicians and choose the aggressive strategy and delay a biopsy for a moderate MRI Suspicion Score [3].

Realistic Strategy - Biopsy for Moderate Plus High MRI Suspicion Score [3, 4 or 5]

Analysis of the speculative scenarios suggests the following estimate of the reduction in life expectancy for a 1-yer delay for the **Realistic S**trategy {**RS**} of moderate or high MRI Suspicion Scores [3, 4 or 5]:

{RS3}	0.08	year "if-cancer" reduction in life expectancy for moderate or high MRI Suspicion Score

Aggressive Strategy - Biopsy for High MRI Suspicion Score [4 or 5]

Analysis of the speculative scenarios suggests the following estimate of the reduction in life expectancy for a 1-yer delay for the **A**ggressive **S**trategy of high MRI Suspicion Scores [4 or 5]:

{AS3}	0.08	year "if-cancer" reduction in life expectancy for high MRI Suspicion Score

This aggressive strategy that delays a biopsy for a moderate MRI Suspicion Score [3] may be justified by the relatively lower estimate of the reduction in life expectancy for a 1-year delay for a moderate MRI Suspicion Score [3]:

{RSS3}	0.05	year "if-cancer" reduction in life expectancy for moderate MRI Suspicion Score

Typically, the reduction in life expectancy for a moderate suspicion score [3] is less than that for a conventional pattern biopsy. Therefore, if you plan to delay a conventional pattern biopsy because the reduction in life expectancy is too low then it makes sense to plan on delaying a biopsy after a moderate MRI Suspicion Score [3] if the reduction is even lower. However, delay in that case can be difficult emotionally, especially if your physicians are encouraging you to biopsy for a moderate MRI Suspicion Score [3].

Personal Risk Assessment for the If-Cancer Cases

Next, we will follow the process of section *3. Conventional Pattern Biopsy* where you may have concluded that a conventional pattern biopsy is **not justified** now. Three cases are shown:

- Conventional pattern biopsy case
- **Realistic** strategy for screening MRI with the result in **bold**
- Aggressive strategy for screening MRI

Please look into the future and imagine that your biopsy has found prostate cancer, which we call the "if-cancer" case. If you delay a biopsy, then you will also delay possible diagnosis and treatment if warranted. In other words, a delay in biopsy will delay this "if-cancer" case, which is our focus. For this "if-cancer" case, the reduction in life expectancy from a 1-year delay in biopsy, diagnosis and treatment if warranted is:

{B3}	0.07	year reduction in life expectancy for conventional pattern biopsy
{RS3}	**0.08**	year reduction in life expectancy for the **realistic** MRI strategy
{AS3}	0.08	year reduction in life expectancy for the aggressive MRI strategy

For these "if-cancer" cases where prostate cancer has been diagnosed, delay defers two negative consequences:

- Emotional costs that accompany a possible diagnosis of cancer.
- Potential side effects of treatment if warranted, such as impotence and incontinence.

From this "if-cancer" perspective, your biopsy timing decision should be based on your assessment of these two consequences and the "if-cancer" reduction in life expectancy from the bullets above.

The assessment is very personal with wide variation among men and among physicians with potentially large differences between men and their physicians. For example, some urologists might be more concerned about the dangers of cancer while some primary care physicians might be more concerned about the side effects of biopsy, emotional costs of diagnosis and side effects of treatment. Different men seem to have highly divergent assessments of the risk tradeoffs.

Compare the reductions above for pattern biopsy and the two screening MRI strategies to your assessment of the benefits of deferring diagnosis and treatment if warranted:

- Some men might wait for a 1.0-year "if-cancer" reduction in life expectancy:
    - They place a high value on their currently high quality of life that would be disrupted by diagnosis and treatment if warranted and
    - Are much less concerned about losing life expectancy toward the end of life when they expect their quality of life may be low.
- Other men might only wait for a 0.25-year "if-cancer" reduction in life expectancy:
    - They are less concerned about disruption of their current quality of life from diagnosis and treatment if warranted and
    - Are more concerned about losing life expectancy, perhaps because they want to see their grandchildren grow up or live as long-as their spouse.

For convenience, the reductions for pattern biopsy and the two screening MRI strategies are repeated below:

{B3}	0.07	year reduction in life expectancy for conventional pattern biopsy
{RS3}	**0.08**	year reduction in life expectancy for the **realistic** MRI strategy
{AS3}	0.08	year reduction in life expectancy for the aggressive MRI strategy

Consider a biopsy when the reduction in life expectancy exceeds your assessment of the benefits, perhaps 0.25-year or 1.0-year or other benefit.

CAUTION: Don't Choose a Screening MRI Until You Are Ready to Biopsy

A screening MRI is a major step that will start a process that can't be reversed and has strong implications. Don't choose a screening MRI until you are emotionally and intellectually ready for a biopsy triggered by a high and possibly moderate MRI Suspicion Score. Your estimated probabilities of biopsy triggered by a screening MRI depend on your strategy:

Realistic Strategy - If you choose the **R**ealistic **S**trategy {**RS**} and will biopsy for both moderate and high screening MRI Suspicion Scores [3, 4 or 5], then the probability of biopsy will be:

{RS1} **58.3%** chance of targeted biopsy for moderate or high MRI Suspicion Score

Aggressive Strategy - If you choose the **A**ggressive **S**trategy {**AS**} and will biopsy only for a high screening MRI Suspicion Score [4 or 5], then the probability of biopsy will decrease further to:

{AS1} 21.7% chance of targeted biopsy for high MRI Suspicion Score

We suggest considering the following process for choosing screening MRI timing for this case B, where a conventional pattern biopsy is **not justified**:

- Choose your screening MRI strategy: Realistic or possibly Aggressive
- Choose your biopsy risk threshold using the process above with the two examples as starting points:
    - Some men might wait for a 1.0-year “if-cancer” reduction in life expectancy.
    - Other men might only wait for a 0.25-year “if-cancer” reduction in life expectancy.
- Delay your screening MRI until the “if-cancer” reduction in life expectancy for your screening MRI strategy reaches your biopsy risk threshold.

Glossary

CDR – Cancer death risk over time assuming no death from other causes.

Delay - Each screening action can be taken now (or soon) or delayed. In this report, we consider a 1-year delay that is convenient for analysis and discussion.

Conventional Pattern Biopsy uses a template for up to 12 or more needles to sample your prostate without targeting using MR images.

DRE is a digital rectal exam of your prostate for a hard lump that might suggest the possibility of cancer and to estimate the size of your prostate.

ERSPC-RC is an online calculator of prostate cancer risk based on the European Randomized Study of Screening for Prostate Cancer Risk.

4Kscore is a calculation based on a panel of four PSA-related blood tests and other information that is more effective than PSA alone for prostate cancer screening.

Free PSA % is the ratio of the free subset of PSA to PSA that is more effective than PSA alone for prostate cancer screening.

Impotence is the inability of a man to achieve an erection. Reduced potency is a side effect risk of prostate cancer treatment.

Incontinence is lack of voluntary control over urination. Reduced continence is a side effect risk of prostate cancer treatment.

Life Expectancy is the number of years you expect to live on average that determines your exposure to prostate cancer risk.

MRI (magnetic resonance imaging) offers an improved way to screen for large aggressive prostate cancers that are deadliest while reducing over-diagnosis.

MRI Suspicion Score - MR images of the prostate are often evaluated on a score from [1] for very low suspicion to [5] for very high suspicion of prostate cancer.

MRI Targeted Biopsy typically directs a few needles at a high suspicion tumor target(s) visible on MR images and does not sample the rest of the prostate.

Multi-Parametric MRI is a sophisticated MR imaging method used to identify possible prostate cancer tumors.

PCA3 is a genetic urine test used for prostate cancer screening.

PCPT-RC is an online calculator of prostate cancer risk based on the Prostate Cancer Prevention Trial.

PHI (Prostate Health Index) is a calculation based on a panel of three PSA-related blood tests that is more effective than PSA alone for prostate cancer screening.

PSA (prostate-specific antigen) blood test is the foundation of prostate cancer screening.

PSA Calibration - Two very different calibrations are used for PSA with WHO calibration about 20% below Hybritech calibration. Multiply all WHO calibrated PSA values by 1.25 for Hybritech calibration.

PSA Adjustment for BPH Treatment - Proscar (finasteride) or Avodart (dutasteride) treatment for BPH (prostate enlargement) reduces PSA by about 50% on average. PSA test levels should be doubled for use in risk calculators

PSA Trend Analysis of PSA tests may provide insights about how fast PSA from cancer is growing and how fast cancer risks may be growing.

Reduction in Life Expectancy can be the result of prostate cancer with further reductions from delay in biopsy, diagnosis and treatment

Risk Calculator is an online service that calculates prostate cancer risks based on input.

Screening MRI is used to assess prostate cancer risk prior to making a biopsy decision.

Sepsis is a severe infection that can occur after biopsy and can be life threatening.

Speculative Strategy Analysis is speculative because medical studies are available to inform only parts of the analysis and assumptions must be made to complete the analysis.

Speculative Scenarios - For this report, 100 equally likely speculative scenarios for prostate cancer have been estimated.

TRUS (transrectal ultra-sound) imaging supports estimation of prostate volume and can help identify regions of increased cancer risk.

Appendix A. Speculative Prostate Cancer Scenarios

This appendix provides optional background information for men who want a deeper understanding of the analysis. Speculative scenarios are used to estimate results that can usefully inform discussions. For this *Example* report, we have estimated 100 equally likely speculative prostate cancer scenarios based on the *Example* personal information and studies of prostate cancer. The scenarios are speculative because medical studies are available to inform only parts of the analysis and assumptions must be made to fully develop the scenarios, such as the growth rate in prostate cancer risk. Our focus is on the reduction in life expectancy from a 1-year delay.

- Speculative Scenario Generation Process
- Table of 100 Speculative Cancer Scenarios
- Chart of 100 Speculative Cancer Scenarios
- Cancer Death Risk Over Time

Speculative Scenario Generation Process

In this section, we introduce seven major steps in the process used to generate 100 equally likely speculative prostate cancer scenarios:

- Prostate Cancer Death Risk
- Adjusted Cancer Death Risk
- Life Expectancy with Prostate Cancer
- Delay Increase in Cancer Death Risk
- Distributions of Cancer Death Risk
- Tumor Volume Distributions Corresponding to Cancer Death Risk Distributions
- MRI Performance vs Tumor Volume

See *ProstateSmart.info* to learn more,

Prostate Cancer Death Risk

Estimates of prostate cancer death risk (CDR) provide the foundation of our analysis. We start with a large, validated study of surgery treatment at prominent medical centers: Cleveland Clinic, Memorial Sloan Kettering and Baylor. This study provides estimates of CDR ten and fifteen years after surgery as a function of PSA and clinical variables, such as clinical Gleason score from biopsy. The clinical variables allow us to estimate distributions of CDR as a function of PSA and allow us to adjust CDR for the Gleason score output of risk calculators. The CDR results for these centers is consistent with results for Johns Hopkins and the University of Michigan, which were added for a subsequent study of CDR for PSA and pathological variables.

Adjusted Cancer Death Risk

The PCPT risk calculator produces estimates of probabilities of high and low-grade prostate cancer based on clinical Gleason score. The ERSPC risk calculator provides similar results that include large tumors in the high-risk category. We use the relationships of CDR to clinical grade from the previous section to adjust the CDR associated with various risk calculator results.

Life Expectancy with Prostate Cancer

Life expectancy is a useful way to summarize your lifetime. Many medical studies of prostate cancer death report survival over-time after diagnosis and possible treatment. Prostate cancer survival has a corresponding probability of cancer death over-time assuming no other cause of death, which is called the cancer-specific death probability (or CDR in this report). Many men find it easier to think in terms of life expectancy and the years that cancer death might reduce it rather than the often-small corresponding probabilities of cancer death. Therefore, we use standard methods to translate risk of cancer death into reductions in life expectancy.

Delay Increase in Cancer Death Risk

As with other cancers, prostate cancer appears to progress and become deadlier over time. The rate that deadliness increases is a key determinant of the consequences of delay in terms of death risk and reduced life expectancy. The Cleveland Clinic article shows that CDR increases with increasing PSA, which suggests that PSA may reflect how fast cancer is progressing and increasing in deadliness. The reported increase in CDR is not quite proportional to PSA with some diminishing returns. Conservatively, we assume CDR increases proportionally to estimated PSA from cancer. Using PSA trend analysis, the growth rate in estimated PSA from cancer (PSAgr) may suggest growth rate in CDR. We use that growth rate to inform the choice of growth rate in CDR used in the scenarios.

Distributions of Cancer Death Risk

In our analysis, we use the distribution of CDR to create a range of scenarios, including rare deadly cancers. The Cleveland Clinic article shows reasonably consistent distributions of CDR for three different risk assessment methods. We use these to estimated distributions of CDR at 10 and 15 years for the overall study. Then we use the PSA groups to estimate CDR distributions for each PSA range. These distributions are then scaled based on PSA and cancer grade.

Tumor Volume Distributions Corresponding to Cancer Death Risk Distributions

We are interested in the performance of MRI. As a first step, we use a Mayo Clinic article on the influence of tumor volume on CDR to translate the distribution of CDR from the Cleveland Clinic article into the corresponding tumor volume distribution.

MRI Performance vs Tumor Volume

Articles from NIH, NYU, UCLA, Mayo Clinic, UC London and others show the encouraging performance of multi-parametric MR imaging and MRI targeted biopsies for identifying prostate cancer with performance improving for more aggressive cancers and for larger tumors. We use results of the PROMIS and Template Mapping Biopsy studies by UC London to estimate MRI performance as a function of tumor volume.

Table of 100 Speculative Cancer Scenarios

Scenarios are descriptions of a range of possible outcomes. We estimate 100 equally likely speculative prostate cancer scenarios based on the *Example* information. Equally likely means that each scenario has an estimated 1 out of 100 chance of being true, or a 1% probability of each scenario. Scenarios are a useful way to put the range of possible outcomes in perspective, including the low probabilities of the most alarming outcomes. The summary table below shows overall average results for the scenarios.

Averages of 100 Equally Likely Speculative Prostate Cancer Scenarios

	Reduction in Life Expectancy				Life Expectancy		
	Delay	**Current**	**Total**		**Delay**	**Current**	**No Ca**
Overall	**0.01**	0.11	0.13	**Overall**	83.87	83.89	84.00
If Cancer	**0.07**	0.55	0.62	**If Cancer**	83.38	83.45	84.00

The two-page table following shows all 100 scenarios: 1 through 50 on the first page, where scenario 1 is the deadliest; and 51 through 100 on the second page, where scenario 100 and other scenarios are not deadly because no prostate cancer is found by biopsy.

Reduction in Life Expectancy on the Left Side of the Tables

On the left side of the tables, three kinds of reductions in life expectancy from prostate cancer are considered for each scenario: Delay, Current and Total.

- **Delay** Reduction in Life Expectancy with Prostate Cancer Treated in 1-Year is an estimate of your reduction in life expectancy if a diagnosis of prostate cancer and subsequent treatment is delayed 1-year. Delay reductions in life expectancies are shown in the third column from the left.
- **Current** Reduction in Life Expectancy with Prostate Cancer Treated Now is an estimate of your reduction in life expectancy if prostate cancer is diagnosed now and treated if warranted. Current reductions in life expectancies are shown in the fourth column from the left.
- **Total** Reduction in Life Expectancy from Delayed Treatment of Prostate Cancer is the sum of the current reduction and the further reduction from delay. It is shown in the fifth column from the left.

Life Expectancy on the Right Side of the Tables

On the right side of the tables, three kinds of life expectancy are considered for each scenario: No Cancer, Current and Delay.

- **No Cancer** Life Expectancy without Prostate Cancer Considered is your current estimate of life expectancy prior to considering any elevated risk of death from prostate cancer. No Cancer life expectancies are shown in the first column from the right.
- **Current** Life Expectancy with Prostate Cancer Treated Now is an estimate of your reduced life expectancy if prostate cancer is diagnosed now and treated if warranted. Your life expectancy will be reduced if prostate cancer death occurs before you die of other causes. Current life expectancies are shown in the second column from the right.
- **Delay** Life Expectancy with Prostate Cancer Treated in 1-Year is an estimate of your reduced life expectancy if a diagnosis of prostate cancer and subsequent treatment is delayed 1-year. Delay life expectancies are shown in the third column from the right.

100 Equally Likely Speculative Prostate Cancer Scenarios

		Reduction in Life Expectancy					Life Expectancy		
Sc	Prob	Delay	Current	Total	Sc	Prob	Delay	Current	No Ca
1	1%	**0.17**	1.27	1.44	1	1%	82.56	82.73	84.00
2	1%	**0.14**	1.08	1.22	2	1%	82.78	82.92	84.00
3	1%	**0.13**	0.96	1.09	3	1%	82.91	83.04	84.00
4	1%	**0.12**	0.88	1.00	4	1%	83.00	83.12	84.00
5	1%	**0.11**	0.81	0.92	5	1%	83.08	83.19	84.00
6	1%	**0.10**	0.76	0.86	6	1%	83.14	83.24	84.00
7	1%	**0.09**	0.70	0.80	7	1%	83.20	83.30	84.00
8	1%	**0.08**	0.65	0.74	8	1%	83.26	83.35	84.00
9	1%	**0.08**	0.60	0.68	9	1%	83.32	83.40	84.00
10	1%	**0.07**	0.55	0.62	10	1%	83.38	83.45	84.00
11	1%	**0.06**	0.50	0.56	11	1%	83.44	83.50	84.00
12	1%	**0.06**	0.45	0.51	12	1%	83.49	83.55	84.00
13	1%	**0.05**	0.40	0.45	13	1%	83.55	83.60	84.00
14	1%	**0.05**	0.36	0.40	14	1%	83.60	83.64	84.00
15	1%	**0.04**	0.32	0.36	15	1%	83.64	83.68	84.00
16	1%	**0.03**	0.28	0.31	16	1%	83.69	83.72	84.00
17	1%	**0.03**	0.24	0.27	17	1%	83.73	83.76	84.00
18	1%	**0.03**	0.21	0.23	18	1%	83.77	83.79	84.00
19	1%	**0.02**	0.18	0.20	19	1%	83.80	83.82	84.00
20	1%	**0.02**	0.15	0.16	20	1%	83.84	83.85	84.00
21	1%	**0.01**	0.12	0.13	21	1%	83.87	83.88	84.00
22	1%	**0.00**	0.00	0.00	22	1%	84.00	84.00	84.00
23	1%	**0.00**	0.00	0.00	23	1%	84.00	84.00	84.00
24	1%	**0.00**	0.00	0.00	24	1%	84.00	84.00	84.00
25	1%	**0.00**	0.00	0.00	25	1%	84.00	84.00	84.00
26	1%	**0.00**	0.00	0.00	26	1%	84.00	84.00	84.00
27	1%	**0.00**	0.00	0.00	27	1%	84.00	84.00	84.00
28	1%	**0.00**	0.00	0.00	28	1%	84.00	84.00	84.00
29	1%	**0.00**	0.00	0.00	29	1%	84.00	84.00	84.00
30	1%	**0.00**	0.00	0.00	30	1%	84.00	84.00	84.00
31	1%	**0.00**	0.00	0.00	31	1%	84.00	84.00	84.00
32	1%	**0.00**	0.00	0.00	32	1%	84.00	84.00	84.00
33	1%	**0.00**	0.00	0.00	33	1%	84.00	84.00	84.00
34	1%	**0.00**	0.00	0.00	34	1%	84.00	84.00	84.00
35	1%	**0.00**	0.00	0.00	35	1%	84.00	84.00	84.00
36	1%	**0.00**	0.00	0.00	36	1%	84.00	84.00	84.00
37	1%	**0.00**	0.00	0.00	37	1%	84.00	84.00	84.00
38	1%	**0.00**	0.00	0.00	38	1%	84.00	84.00	84.00
39	1%	**0.00**	0.00	0.00	39	1%	84.00	84.00	84.00
40	1%	**0.00**	0.00	0.00	40	1%	84.00	84.00	84.00
41	1%	**0.00**	0.00	0.00	41	1%	84.00	84.00	84.00
42	1%	**0.00**	0.00	0.00	42	1%	84.00	84.00	84.00
43	1%	**0.00**	0.00	0.00	43	1%	84.00	84.00	84.00
44	1%	**0.00**	0.00	0.00	44	1%	84.00	84.00	84.00
45	1%	**0.00**	0.00	0.00	45	1%	84.00	84.00	84.00
46	1%	**0.00**	0.00	0.00	46	1%	84.00	84.00	84.00
47	1%	**0.00**	0.00	0.00	47	1%	84.00	84.00	84.00
48	1%	**0.00**	0.00	0.00	48	1%	84.00	84.00	84.00
49	1%	**0.00**	0.00	0.00	49	1%	84.00	84.00	84.00
50	1%	**0.00**	0.00	0.00	50	1%	84.00	84.00	84.00

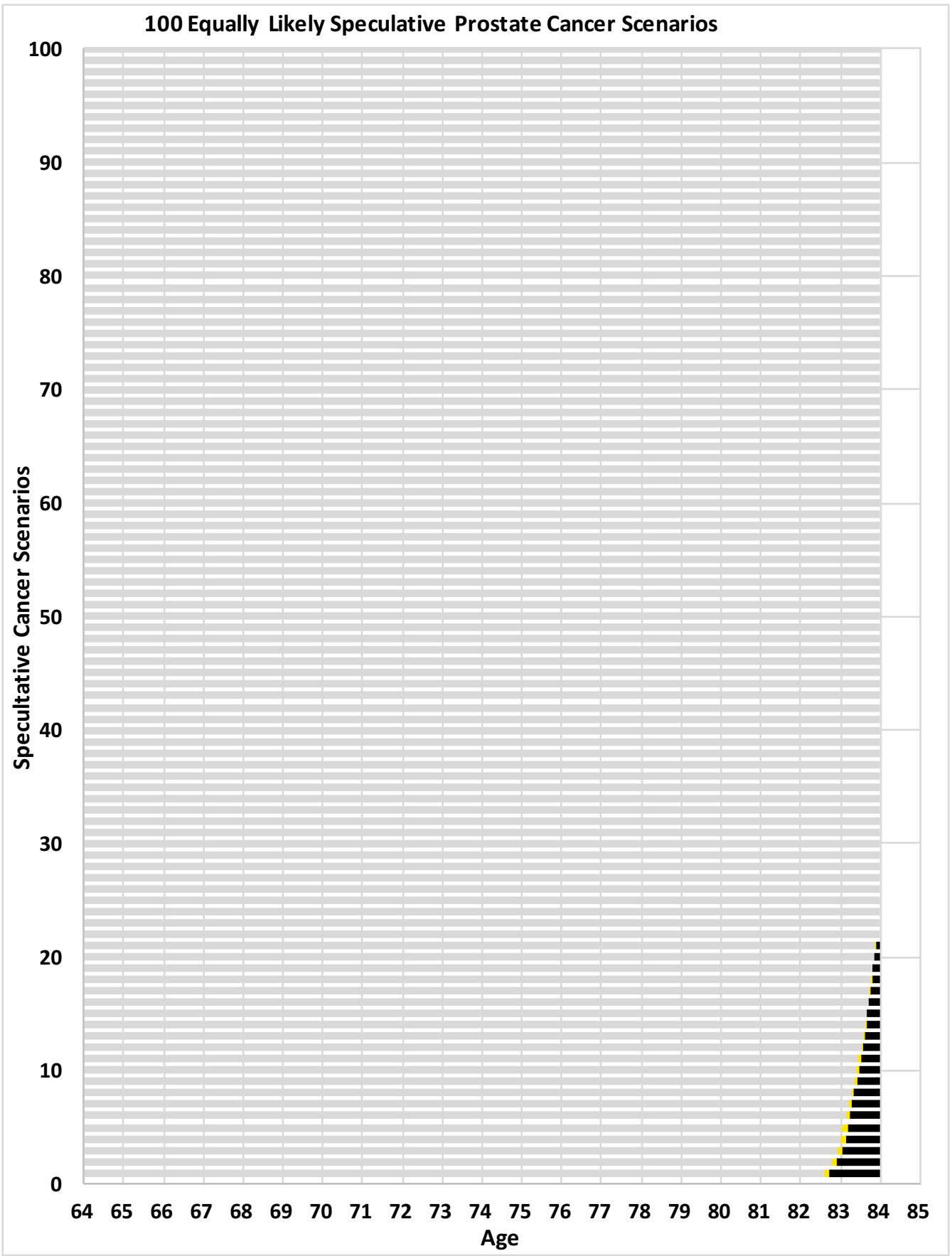
100 Equally Likely Speculative Prostate Cancer Scenarios (continued)

		Reduction in Life Expectancy					Life Expectancy		
Sc	**Prob**	**Delay**	**Current**	**Total**	**Sc**	**Prob**	**Delay**	**Current**	**No Ca**
51	1%	**0.00**	0.00	0.00	51	1%	84.00	84.00	84.00
52	1%	**0.00**	0.00	0.00	52	1%	84.00	84.00	84.00
53	1%	**0.00**	0.00	0.00	53	1%	84.00	84.00	84.00
54	1%	**0.00**	0.00	0.00	54	1%	84.00	84.00	84.00
55	1%	**0.00**	0.00	0.00	55	1%	84.00	84.00	84.00
56	1%	**0.00**	0.00	0.00	56	1%	84.00	84.00	84.00
57	1%	**0.00**	0.00	0.00	57	1%	84.00	84.00	84.00
58	1%	**0.00**	0.00	0.00	58	1%	84.00	84.00	84.00
59	1%	**0.00**	0.00	0.00	59	1%	84.00	84.00	84.00
60	1%	**0.00**	0.00	0.00	60	1%	84.00	84.00	84.00
61	1%	**0.00**	0.00	0.00	61	1%	84.00	84.00	84.00
62	1%	**0.00**	0.00	0.00	62	1%	84.00	84.00	84.00
63	1%	**0.00**	0.00	0.00	63	1%	84.00	84.00	84.00
64	1%	**0.00**	0.00	0.00	64	1%	84.00	84.00	84.00
65	1%	**0.00**	0.00	0.00	65	1%	84.00	84.00	84.00
66	1%	**0.00**	0.00	0.00	66	1%	84.00	84.00	84.00
67	1%	**0.00**	0.00	0.00	67	1%	84.00	84.00	84.00
68	1%	**0.00**	0.00	0.00	68	1%	84.00	84.00	84.00
69	1%	**0.00**	0.00	0.00	69	1%	84.00	84.00	84.00
70	1%	**0.00**	0.00	0.00	70	1%	84.00	84.00	84.00
71	1%	**0.00**	0.00	0.00	71	1%	84.00	84.00	84.00
72	1%	**0.00**	0.00	0.00	72	1%	84.00	84.00	84.00
73	1%	**0.00**	0.00	0.00	73	1%	84.00	84.00	84.00
74	1%	**0.00**	0.00	0.00	74	1%	84.00	84.00	84.00
75	1%	**0.00**	0.00	0.00	75	1%	84.00	84.00	84.00
76	1%	**0.00**	0.00	0.00	76	1%	84.00	84.00	84.00
77	1%	**0.00**	0.00	0.00	77	1%	84.00	84.00	84.00
78	1%	**0.00**	0.00	0.00	78	1%	84.00	84.00	84.00
79	1%	**0.00**	0.00	0.00	79	1%	84.00	84.00	84.00
80	1%	**0.00**	0.00	0.00	80	1%	84.00	84.00	84.00
81	1%	**0.00**	0.00	0.00	81	1%	84.00	84.00	84.00
82	1%	**0.00**	0.00	0.00	82	1%	84.00	84.00	84.00
83	1%	**0.00**	0.00	0.00	83	1%	84.00	84.00	84.00
84	1%	**0.00**	0.00	0.00	84	1%	84.00	84.00	84.00
85	1%	**0.00**	0.00	0.00	85	1%	84.00	84.00	84.00
86	1%	**0.00**	0.00	0.00	86	1%	84.00	84.00	84.00
87	1%	**0.00**	0.00	0.00	87	1%	84.00	84.00	84.00
88	1%	**0.00**	0.00	0.00	88	1%	84.00	84.00	84.00
89	1%	**0.00**	0.00	0.00	89	1%	84.00	84.00	84.00
90	1%	**0.00**	0.00	0.00	90	1%	84.00	84.00	84.00
91	1%	**0.00**	0.00	0.00	91	1%	84.00	84.00	84.00
92	1%	**0.00**	0.00	0.00	92	1%	84.00	84.00	84.00
93	1%	**0.00**	0.00	0.00	93	1%	84.00	84.00	84.00
94	1%	**0.00**	0.00	0.00	94	1%	84.00	84.00	84.00
95	1%	**0.00**	0.00	0.00	95	1%	84.00	84.00	84.00
96	1%	**0.00**	0.00	0.00	96	1%	84.00	84.00	84.00
97	1%	**0.00**	0.00	0.00	97	1%	84.00	84.00	84.00
98	1%	**0.00**	0.00	0.00	98	1%	84.00	84.00	84.00
99	1%	**0.00**	0.00	0.00	99	1%	84.00	84.00	84.00
100	1%	**0.00**	0.00	0.00	100	1%	84.00	84.00	84.00

Chart of 100 Speculative Cancer Scenarios

For the 100 speculative cancer scenarios, life expectancies and their reductions from the table above are presented on the chart below. On the left axis, scenarios start with the deadliest number 1 at the bottom and increase to a no cancer number 100 at the top. On the bottom axis, current age starts at the left and increases to base life expectancy toward the right. There are three horizontal bar components for each scenario:

- **Current** reductions in life expectancies for cancer scenarios are shown by the black bars on the right with the widest at the bottom. No black bars are shown for no cancer found scenarios.
- **Delay** reductions in life expectancies for cancer scenarios are shown by the yellow bars to the left of the black bars. Yellow bars can be avoided by a biopsy now with possible diagnosis and treatment if warranted. No yellow bars are shown for no cancer found scenarios.
- **Remaining** life expectancies are shown by the long gray bars that extend from the current age at the left to the yellow bars for cancer scenarios or to the base life expectancy on the right for no cancer found scenarios.


100 Equally Likely Speculative Prostate Cancer Scenarios
Specultative Cancer Scenarios
100
90
80
70
60
50
40
30
20
10
0
64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85
Age

Cancer Death Risk Over Time

Many men find that reduction in life expectancy is the easiest way to understand and process prostate cancer death risk. However, it can be helpful to understand how death risk increases over time after diagnosis and treatment if warranted. On average, the **deadliest other** cancers can lead to death in months or a few years after diagnosis. In contrast, prostate cancer progresses much slower with much less short-term risk of death. Overall cancer death risk over time is presented below for:

- Increase in Cancer Death Risk from Delay
- Current Cancer Death Risk with Prostate Cancer Treated Now
- Delay Cancer Death Risk with Prostate Cancer Treated in 1-Year

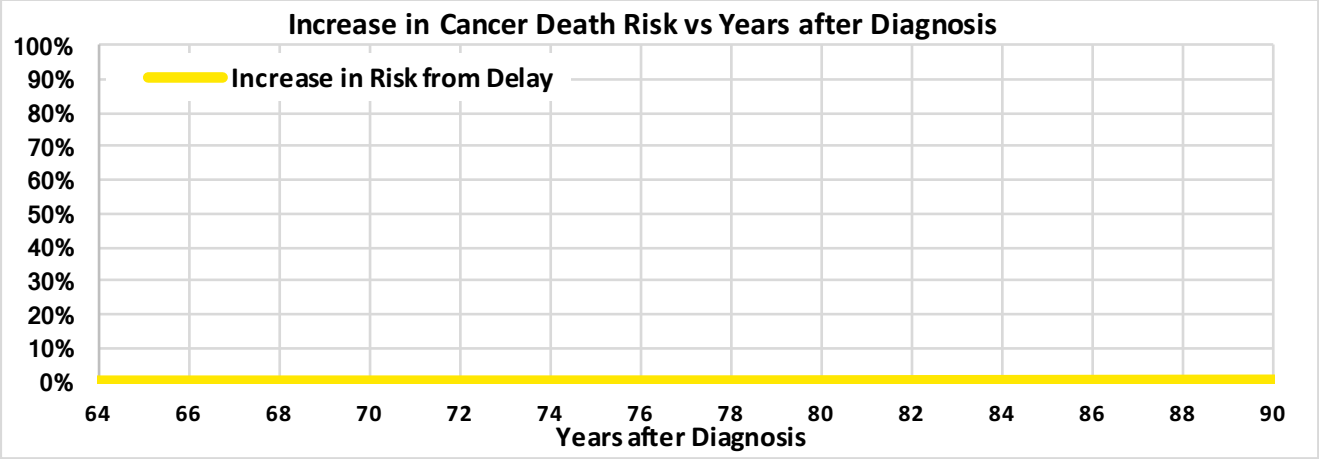
Overall results are averages of all 100 scenarios, including no cancer found scenarios. Prostate cancer death risk over time is typically presented as the probability of cancer death up to that time. In the medical literature, it is often labeled prostate cancer-specific mortality and is equivalent to one minus cancer-specific survival where death from other causes is not considered.

Increase in Cancer Death Risk from Delay

If prostate cancer treatment is delayed 1-year (the Delay case), the **Increase** in overall prostate cancer death risk is:

{CDI05}	0.00%	5-years after diagnosis and treatment if warranted
{CDI10}	0.01%	10-years after diagnosis and treatment if warranted
{CDI15}	0.05%	15-years after diagnosis and treatment if warranted
{CDI20}	0.15%	20-years after diagnosis and treatment if warranted

The yellow curve on the graph below shows the **Increase** from delay in overall prostate cancer death risk vs years after diagnosis and treatment if warranted.

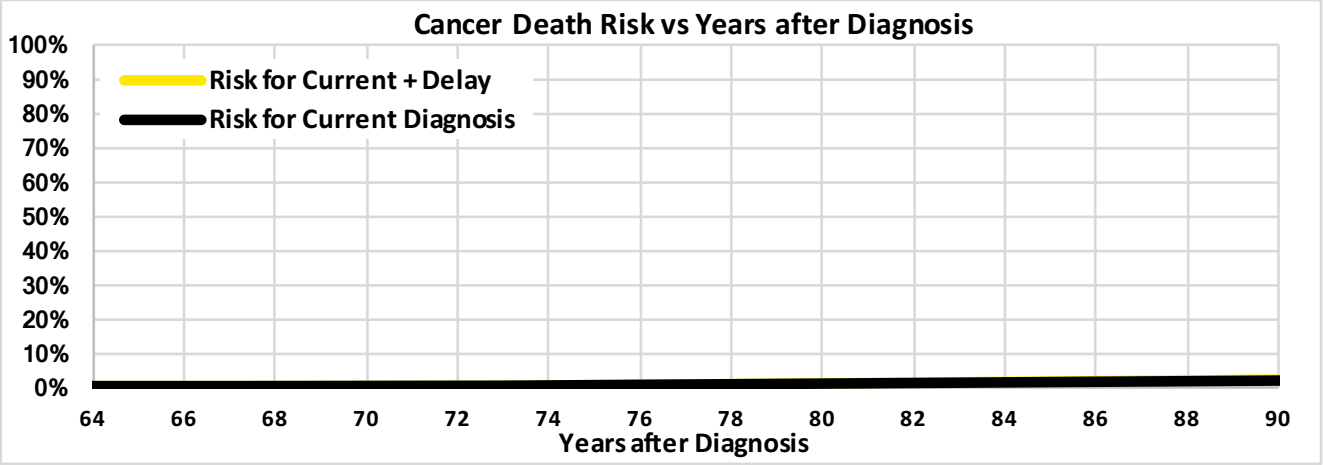


Current Cancer Death Risk with Prostate Cancer Treated Now

If prostate cancer is treated now (the Current case), overall prostate cancer death risk is:

{CDC05}	0.03%	5-years after diagnosis and treatment if warranted
{CDC10}	0.21%	10-years after diagnosis and treatment if warranted
{CDC15}	0.69%	15-years after diagnosis and treatment if warranted
{CDC20}	1.16%	20-years after diagnosis and treatment if warranted

The black curve on the graph below shows overall Current cancer death risk vs years after diagnosis and treatment if warranted.



Delay Cancer Death Risk with Prostate Cancer Treated in 1-Year

If prostate cancer treatment is delayed 1-year (the Delay case), overall prostate cancer death risk increases to:

{CDD05}	0.04%	5-years after diagnosis and treatment if warranted
{CDD10}	0.22%	10-years after diagnosis and treatment if warranted
{CDD15}	0.74%	15-years after diagnosis and treatment if warranted
{CDD20}	1.32%	20-years after diagnosis and treatment if warranted

The yellow curve on the graph above shows overall Current **plus** Delay cancer death risk vs years after diagnosis and treatment if warranted. For very low risks, the yellow curve may be hidden behind the black curve or may be partially visible.

Appendix B:
Biopsy and Treatment Risk Assessment Adjustments

For completeness, you might adjust your "if-cancer" risk assessment for two factors:

1. Consequences of a biopsy to find the prostate cancer, and
2. Consequences of possible treatment strategies to reduce the risk of side effects, including active surveillance or even focal therapy.

However, these adjustments work in opposite directions and tend to offset each other – often leading to small net adjustments.

Therefore, we **suggest skipping** this *Appendix B* unless you are very interested in the risk assessment adjustment process and are determined to fine-tune your assessment.

Personal Risk Assessment for the If-Cancer Case

In section *3. Conventional Pattern Biopsy*, you explored the following risk assessment process to determine if a conventional pattern biopsy is justified now:

Look into the future and imagine that your biopsy has found prostate cancer, which we call the "if-cancer" case. If you delay a biopsy, then you will also delay possible diagnosis and treatment if warranted. In other words, a delay in biopsy will delay this "if-cancer" case, which is our focus. For this case, the reduction in life expectancy from a 1-year delay in biopsy, diagnosis and treatment if warranted is:

{B3} 0.07 year if-cancer reduction in life expectancy from delay

For this "if-cancer" case where prostate cancer has been diagnosed, delay defers two negative consequences:

- Emotional costs that accompany a possible diagnosis of cancer.
- Potential side effects of treatment if warranted, such as impotence and incontinence.

From this "if-cancer" perspective, your biopsy timing decision should be based on your assessment of these two consequences and the "if-cancer" reduction in life expectancy {B3}.

The assessment is very personal with wide variation among men and among physicians with potentially large differences between men and their physicians. For example, some urologists might be more concerned about the dangers of cancer while some primary care physicians might be more concerned about the side effects of biopsy, emotional costs of diagnosis and side effects of treatment. Different men seem to have highly divergent assessments of the risk tradeoffs.

Compare this reduction:

{B3} 0.07 year if-cancer reduction in life expectancy from delay

to your assessment of the benefits of delaying diagnosis and treatment if warranted:

- Some men might wait for a 1.0-year “if-cancer” reduction in life expectancy:
  - They place a high value on their currently high quality of life that would be disrupted by diagnosis and treatment if warranted and
  - Are much less concerned about losing life expectancy toward the end of life when they expect their quality of life may be low.
- Other men might only wait for a 0.25-year “if-cancer” reduction in life expectancy:
  - They are less concerned about disruption of their current quality of life from diagnosis and treatment if warranted and
  - Are more concerned about losing life expectancy, perhaps because they want to see their grandchildren grow up or live as long-as their spouse.

Consider a biopsy when the reduction, {B3}, exceeds your assessment of the benefits, perhaps 0.25-year or 1.0-year or other benefit.

Net Biopsy and Treatment Risk Assessment Adjustments

You might adjust your “if-cancer” risk assessment for two related factors:

1. Biopsy Adjustment - Consequences of a biopsy to find the prostate cancer, and
2. Treatment Adjustment - Consequences of possible treatment strategies to reduce the risk of side effects, including active surveillance or even focal therapy.

They are discussed in the next two sections, where *examples* are shown in *Italic* font. Finally, the net effect is calculated for the *examples*.

1. Biopsy Risk Assessment Adjustment

Deferring emotional costs that accompany a possible diagnosis and potential side effects of treatment are the **primary** benefits of a 1-year delay in biopsy, diagnosis and treatment if warranted.

Deferring the discomfort of a biopsy and the risk of potentially life-threatening sepsis (infection) is the **additional** benefit of a 1-year delay. Adjusting the “if-cancer” risk assessment for a biopsy is the focus of this section. It is done in five steps:

Calculate Biopsies Needed for Each Diagnosis

Recall that the probability that a biopsy **will** find cancer is:

{B2b} 21% probability a biopsy will find cancer

This probability, {B2b}, implies that the number of biopsies needed for each diagnosis are:

{B4}	*4.8*	*biopsies needed for each diagnosis and treatment if warranted*

Where the {B4} biopsies needed is calculated by dividing 1 by the probability of diagnosis, {B2b} using the equation: {B4} = 1 / {B2b}.

Assess the Benefit of Delaying a Biopsy

Assess the benefit of delaying a biopsy as a percentage of the consequences of diagnosis and potential treatment side effects.

For example, you might assess the long-lasting negative consequences of diagnosis and treatment to be 10 times greater than the shorter-term negative consequences of a biopsy. Equivalently, the benefit of biopsy delay is one-tenth (10%) of the benefit of delaying diagnosis and treatment if warranted.

BD%	*10%*	*benefit of biopsy deferral as a percentage of diagnosis and treatment*

Calculate the Probability Adjusted Benefit Percentage

Estimate the probability adjusted benefit percentage of delaying a biopsy, {ABb%}, by multiplying that benefit percentage BD% by the number of biopsies needed for each diagnosis {B4} using the equation: ABb% = 100% + BD% x {B4}.

ABb%	=	Probability adjusted benefit percentage for biopsy delay

For the example:

BD%	*10%*	*Benefit of biopsy deferral as a percentage of diagnosis and treatment*
{B4}	*4.8*	*biopsies needed for each diagnosis and treatment if warranted*
IABb%	*48%*	*Increase in probability adjusted benefit percentage for biopsy delay*
ABb%	*148%*	*Probability adjusted benefit percentage for biopsy delay*

Assess the "If-Cancer" Benefit of Delay of Diagnosis and Treatment

For the example, you might assess the "if-cancer" benefit of delay of diagnosis and treatment to be 0.5-year reduction in life expectancy:

{B5}	*0.5*	*year benefit of delay of diagnosis and treatment*

Scale Up the Benefit of Delay

Then, scale up your "if-cancer" benefit of delay of diagnosis and treatment by the probability adjusted for **b**iopsy benefit percentage for biopsy.

ABb	=	Adjusted for biopsy benefit of delay of diagnosis and treatment
ABb	=	ABb% x {B5}

For the example:

ABb	*0.74*	*year adjusted benefit of delay of diagnosis and treatment*

2. Treatment Risk Assessment Adjustment

There is a chance that the prostate cancer found by biopsy is indolent and suitable for active surveillance rather than primary treatment (surgery or radiation). Active surveillance is increasingly used because it reduces the side effects of treatment. If you plan active surveillance of indolent cancer if diagnosed then you should consider reducing the diagnosis and treatment deferral benefit somewhat.

Focal therapy is a new family of treatments with reduced side effects that try to destroy tumors with little or no damage to the surrounding prostate tissue. Long term effectiveness of focal therapy has not been proven. Reduce your biopsy threshold further if you plan focal therapy for appropriate cancers.

The six-step adjustment process for active surveillance (and possibly focal therapy) is:

Separate the Consequences of Diagnosis and Treatment

Split the consequences of diagnosis into:

- Fear and other direct consequences of diagnosis (D%).
- Treatment side effects (T%).

Where, D% + T% = 100% are the probabilities conditional on diagnosis.

Example for diagnosed prostate cancer:

D%	*30%*	*Fear and repercussions of diagnosis are 30% of the consequences*
T%	*70%*	*Treatment side effects are 70% of the consequences*

Estimate the Active Surveillance Percentage of Diagnoses

Estimate the percentage of diagnoses for which you would choose **A**ctive **S**urveillance (and possibly focal therapy) – **AS%**. Many active surveillance programs are limited to very low risk prostate cancers, which reduces AS% to low levels. Many men start with active surveillance but elect primary treatment (surgery or radiation) within a few years, which further reduces the effective AS%.

Example:

AS%	*25%*	*Active surveillance is appropriate in 25% of the cases diagnosed*

Assess the Consequences of Active Surveillance as a Percentage of Treatment

Estimate how concerning the **s**ide **e**ffects (**se**) of **A**ctive **S**urveillance (**AS**) with annual or frequent biopsies (and possibly focal therapy) are compared with primary treatment, such as surgery or radiation (**ASse%**).

Example:

ASse%	*35%*	*Side effects if active surveillance with annual or frequent biopsies is 35% as concerning as primary treatment*

Calculate the Probability Adjusted Benefit of Delay Risk Percentage

The probability **A**djusted **B**enefit of delay risk percentage (**AB%**) is the new (reduced) percentage of the assessed benefit of delay:

ABas%	=	Probability adjusted benefit of delay risk percentage
ABas%	=	100% - T% x AS% x (1 – ASse%)

Example:

T%	*70%*	*Treatment side effects are 70% of the consequences*
AS%	*25%*	*Active surveillance is appropriate in 25% of the cases diagnosed*
ASse%	*35%*	*Side effects of active surveillance with annual or frequent biopsies*
ABas%	*89%*	*Probability adjusted benefit of delay risk percentage for AS*

Assess the "If-Cancer" Benefit of Delay of Diagnosis and Treatment

For the example, you might assess the "if-cancer" benefit of delay of diagnosis and treatment to be 0.5-year reduction in life expectancy:

{B5}	*0.5*	*year benefit of delay of diagnosis and treatment*

Scale Down the Benefit of Delay

Then, scale down your "if-cancer" benefit of delay of diagnosis and treatment {B8} by the probability **A**djusted **B**enefit of delay risk percentage (**AB%**) to calculate the **A**djusted **B**enefit of delay (**AB**):

ABas	=	Adjusted for surveillance benefit of delay of diagnosis and treatment
ABas	=	ABas% x {B5}

For the example:

ABas	*0.44*	*year adjusted for surveillance benefit of delay of diagnosis and treatment*

Net Adjusted Benefit of Delay

The **N**et probability **A**djusted **B**enefit of delay of diagnosis and treatment **percentage** (**NAB%**) is calculated as:

NAB%	=	Net probability adjusted benefit of delay of diagnosis and treatment %
NAB%	=	ABb% x ABas%

The **N**et probability **A**djusted **B**enefit of delay of diagnosis and treatment (**NAB**) is calculated as:

NAB	=	Net probability adjusted benefit of delay of diagnosis and treatment
NAB	=	NAB% x {B5}

Example:

ABb%	*148%*	*Probability adjusted benefit percentage for biopsy delay*
ABas%	*89%*	*Probability adjusted benefit of delay risk percentage for AS*
NAB%	*131%*	*Net probability adjusted benefit of delay of diagnosis and treatment %*
{B5}	*0.50*	*year benefit of delay of diagnosis and treatment*
NAB	*0.65*	*year net probability adjusted benefit of delay of diagnosis and treatment*