WIM VAN CRIEKINGE

deVGen

BETA MADE WITH Drupal

MDxHealth

YES WE TIMELAB

GenOhm
lab.informatics.simplified.

Reagent

NXT-DX

Wobblebase

H42

doc.ai

BioLizard

BioBix
Lab for Bioinformatics and computational genomics

15 "genome hackers"
mostly engineers (statistics)

VUmc VU University Medical Center Amsterdam

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

nxtgnt

scientists, technicians,
geneticists, clinicians

Centre for Synthetic Biology

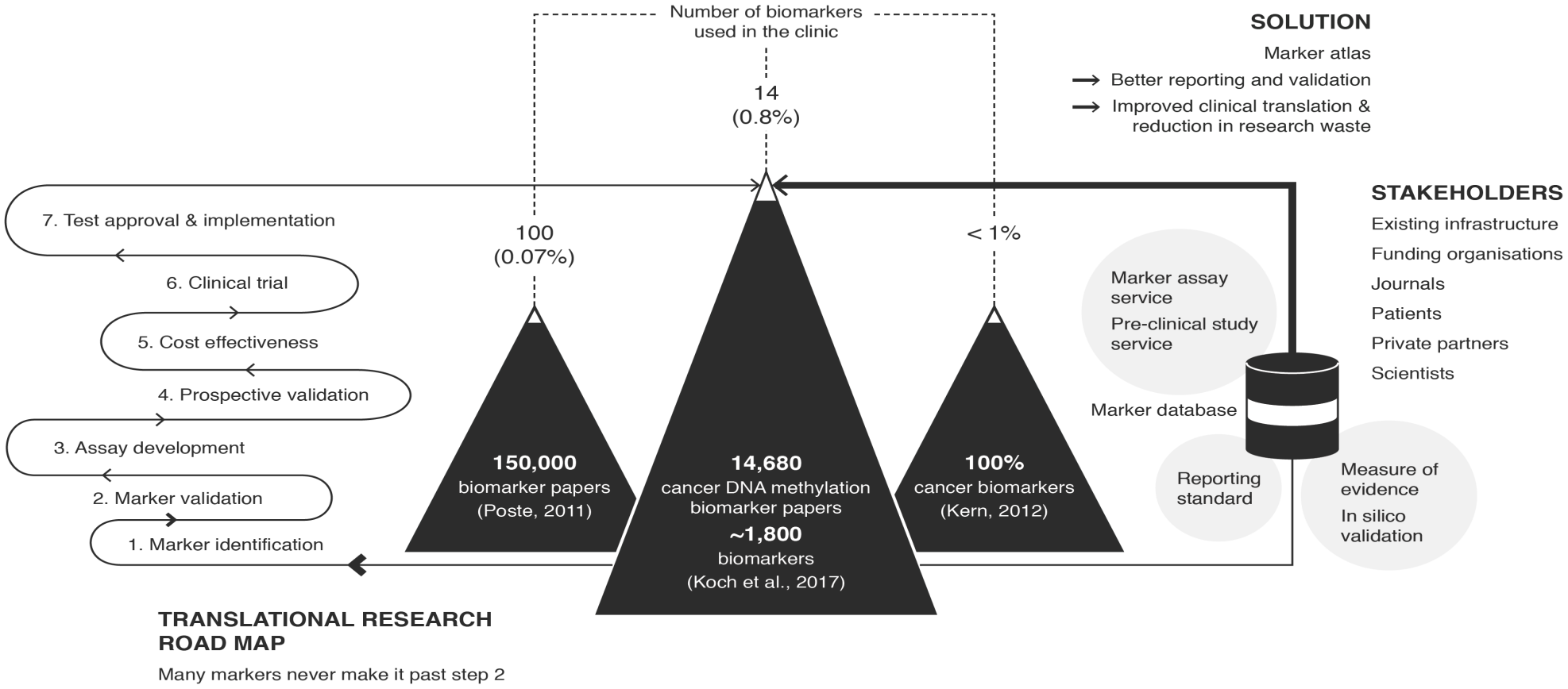
N2N

>100 people
Hardware/software engineers,
mathematicians, molecular biologists

novalis

https://noval.is

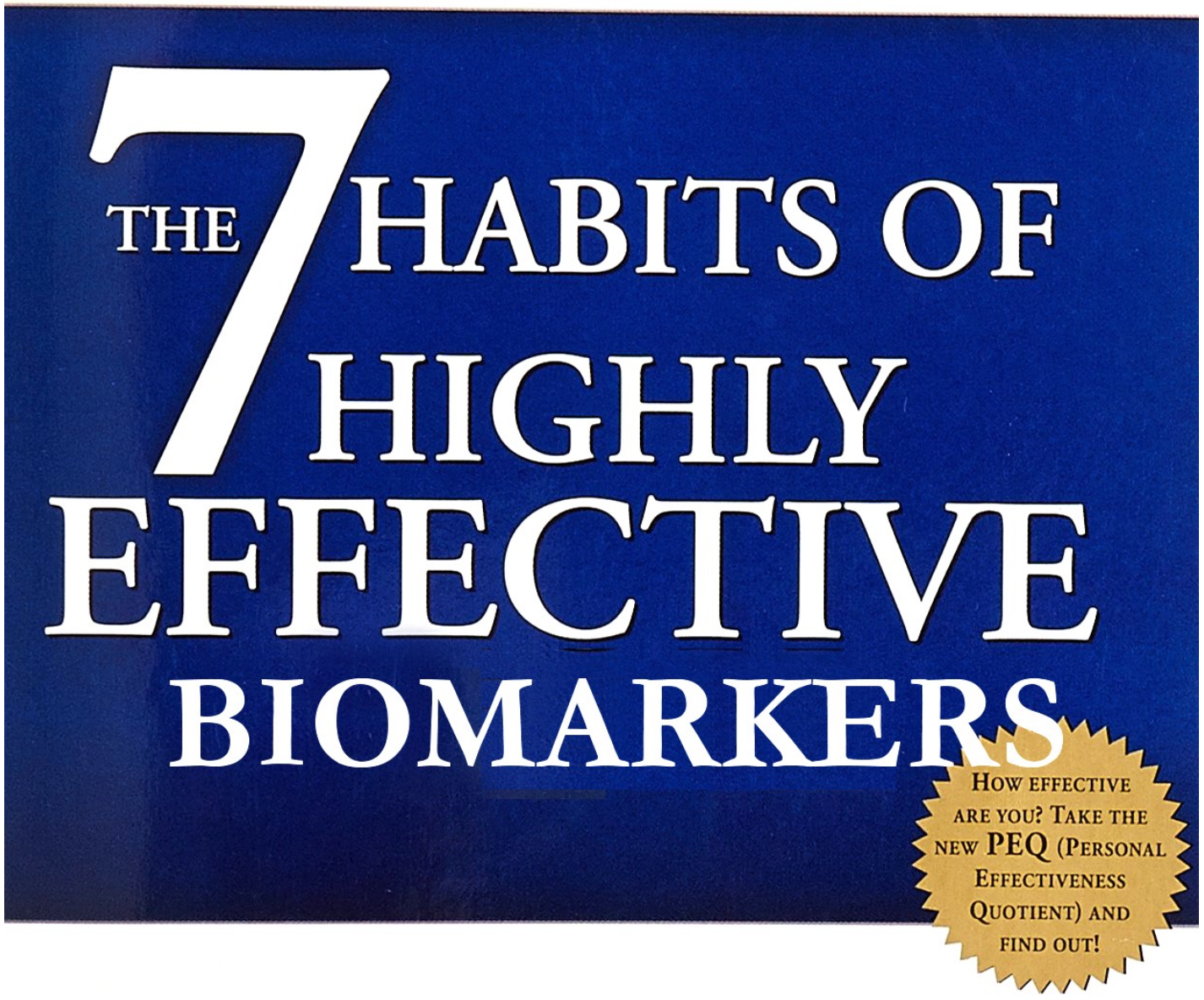
Despite mountains of marker publications, very few markers enter clinical practice ….



3

2

1


THE 7 HABITS OF HIGHLY EFFECTIVE BIOMARKERS
HOW EFFECTIVE ARE YOU? TAKE THE NEW PEQ (PERSONAL EFFECTIVENESS QUOTIENT) AND FIND OUT!

Biomarker ?

Biomarker ?

EFFECT OF HOMOLOGOUS BONE MARROW INJECTIONS IN X-IRRADIATED RABBITS*

K. A. PORTER†

From the Laboratories for Surgical Research, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass.

Received for publication March 30, 1957

In this report marrow transplantation experiments with rabbits are described in which the sex difference between the heterophil nuclei of male and female is used to provide a biological "marker". It is shown that implanted female marrow cells survive, proliferate and contribute heterophils to the peripheral blood of male irradiated animals for considerable periods of time. The effect on survival of the host is not great however.

Biomarker

An objective and « predictive » measure … at the molecular level … of normal and pathogenic processes and responses to therapeutic interventions

Characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacologic response to a drug

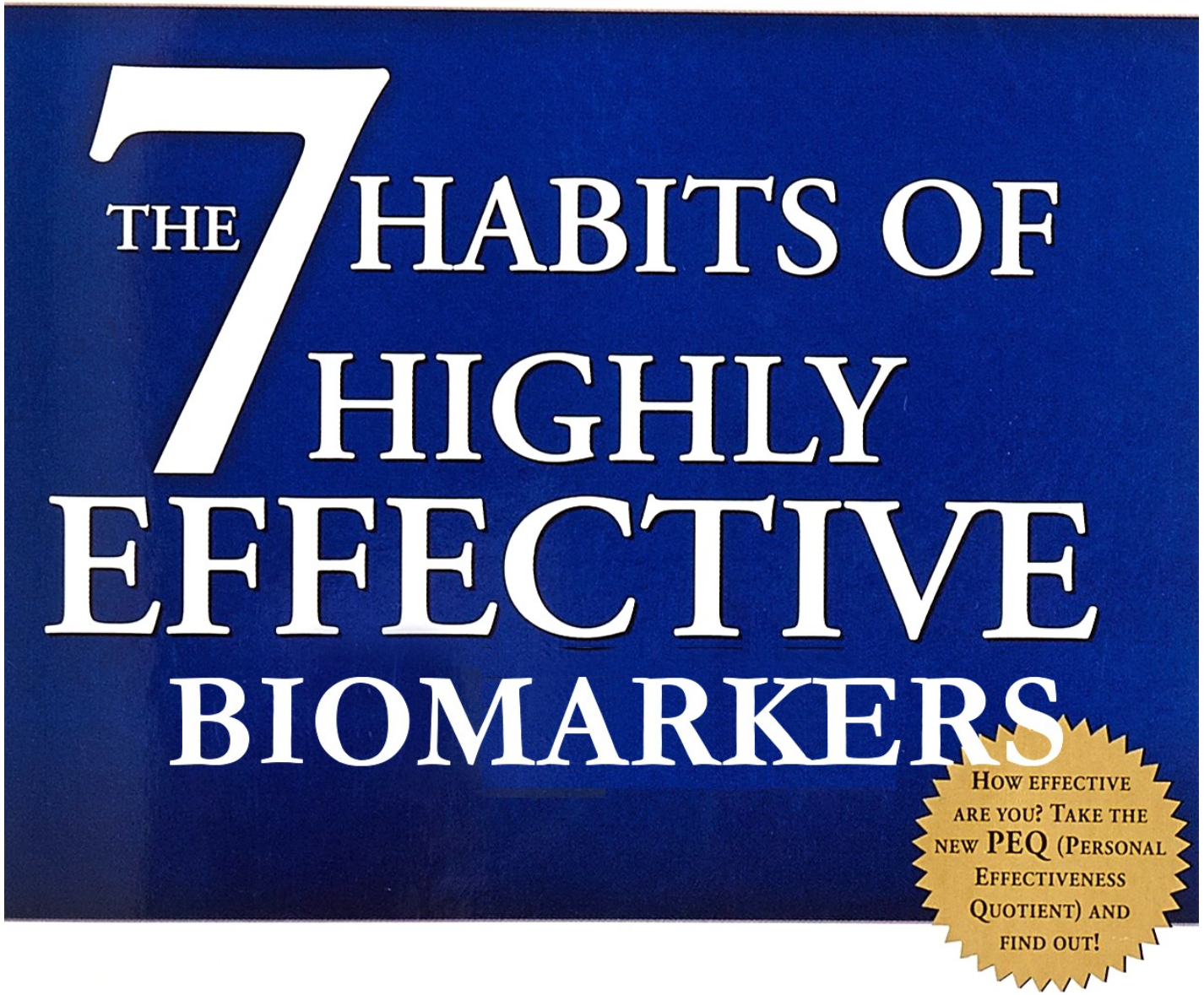
A biomarker is valid if:

- It can be measured in a test system with well established performance characteristics
- Evidence for its clinical significance has been established

3

2

1


THE 7 HABITS OF HIGHLY EFFECTIVE BIOMARKERS
HOW EFFECTIVE ARE YOU? TAKE THE NEW PEQ (PERSONAL EFFECTIVENESS QUOTIENT) AND FIND OUT!

Effective biomarker

D+ D-

THE 2 × 2 DECISION MATRIX

		Actually Abnormal	Actually Normal
T+	Diagnosed as Abnormal	True Positive (TP)	False Positive (FP)
T-	Diagnosed as Normal	False Negative (FN)	True Negative (TN)

	D +	D -
T +	a	b
T -	c	d

Validity

	Gold standard	
	Disease Present	Disease Absent
Test positive	a (TP)	b (FP)
Test negative	c (FN)	d (TN)

Validity:	Sensitivity	Specificity
	= a/(a+c)	= d/(b+d)
	= TP/Diseased	= TN/Healthy

TP = true positive; FP = false positive
TN = true negative; FN = false negative

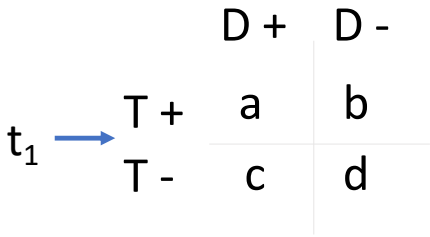
Clinical applications

	D +	D -
T +	a	b
T -	c	d

- A *specific* test can be useful to rule *in* a disease. Why?
  - Very specific tests give few false positives. So, if the result is positive, you can be sure the patient has the condition ('nothing else would give this result')

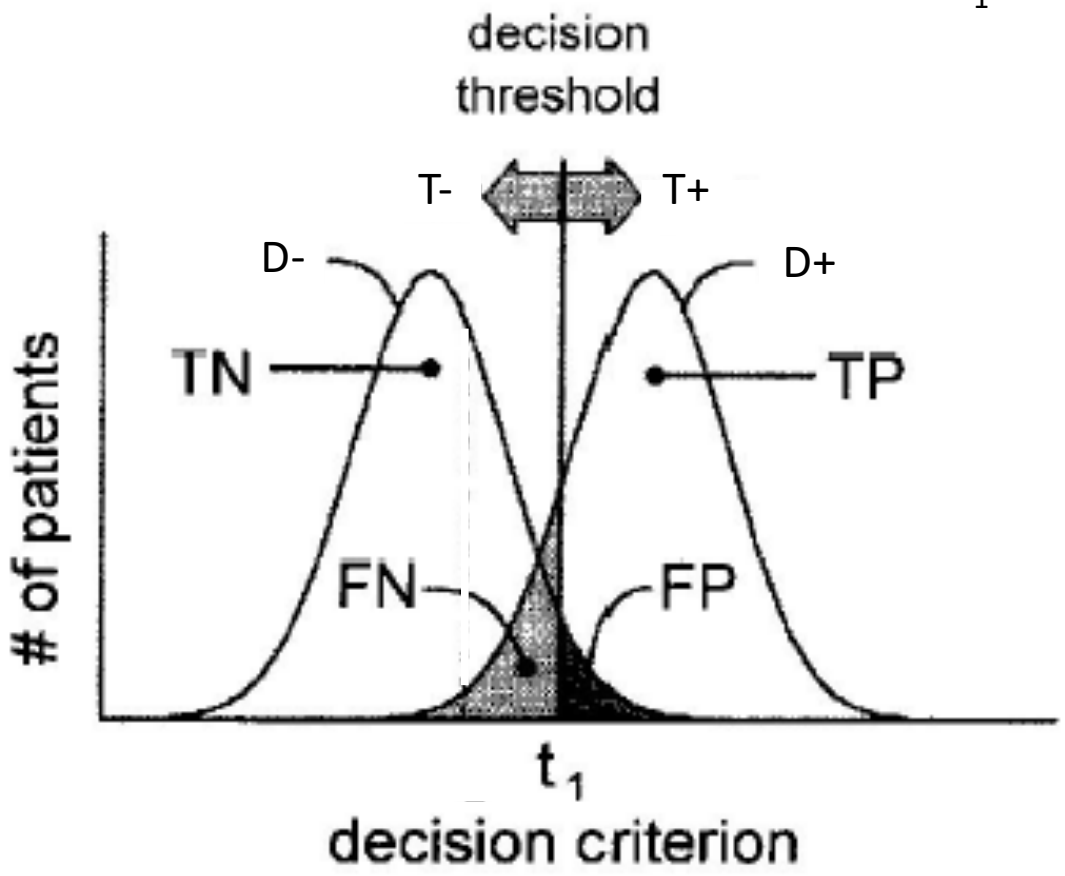
- A *sensitive* test can be useful for ruling a disease *out:*
  - A negative result on a very sensitive test (which detects all true cases) reassures you that the patient does not have the disease

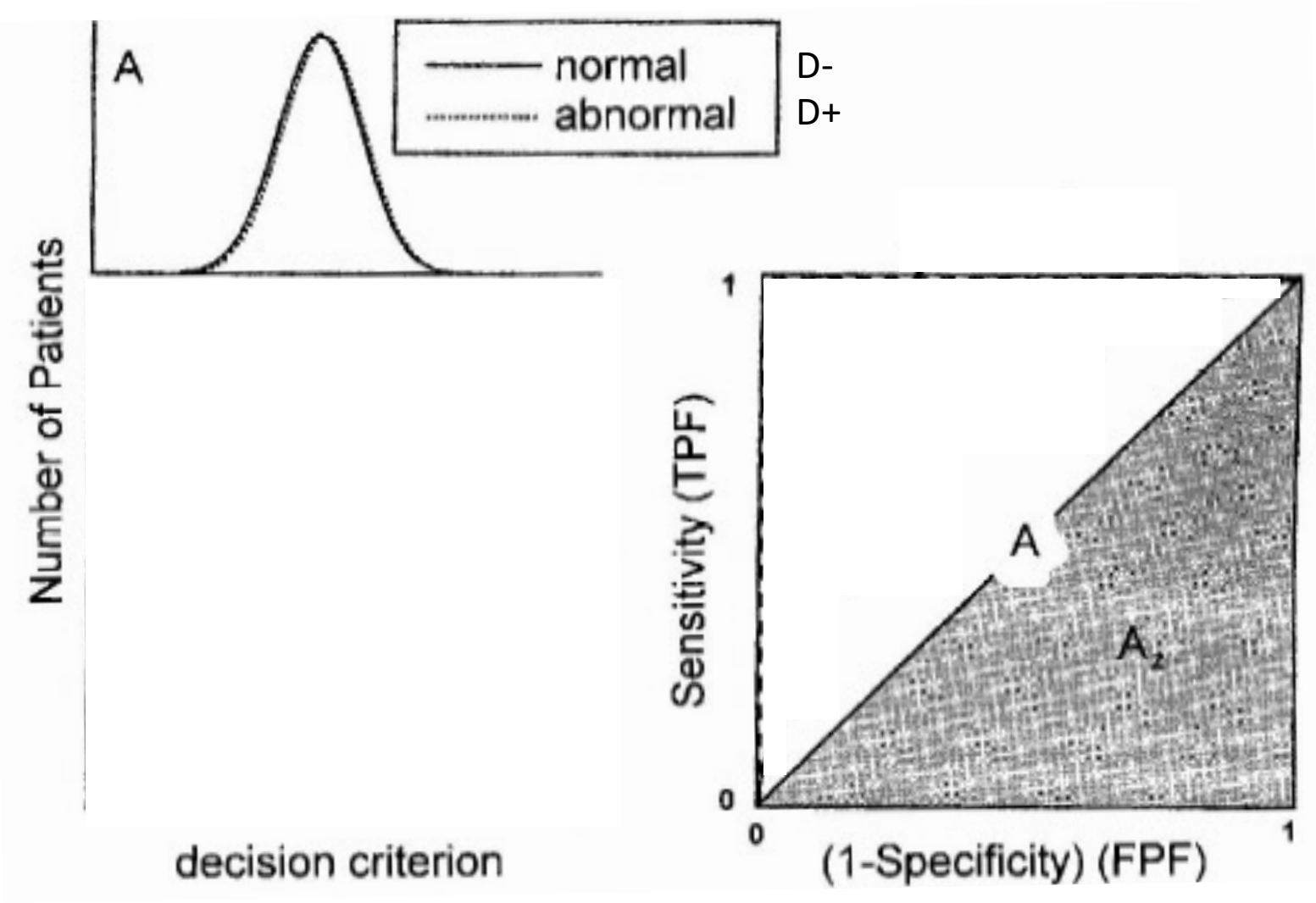
(highly) Effective biomarker



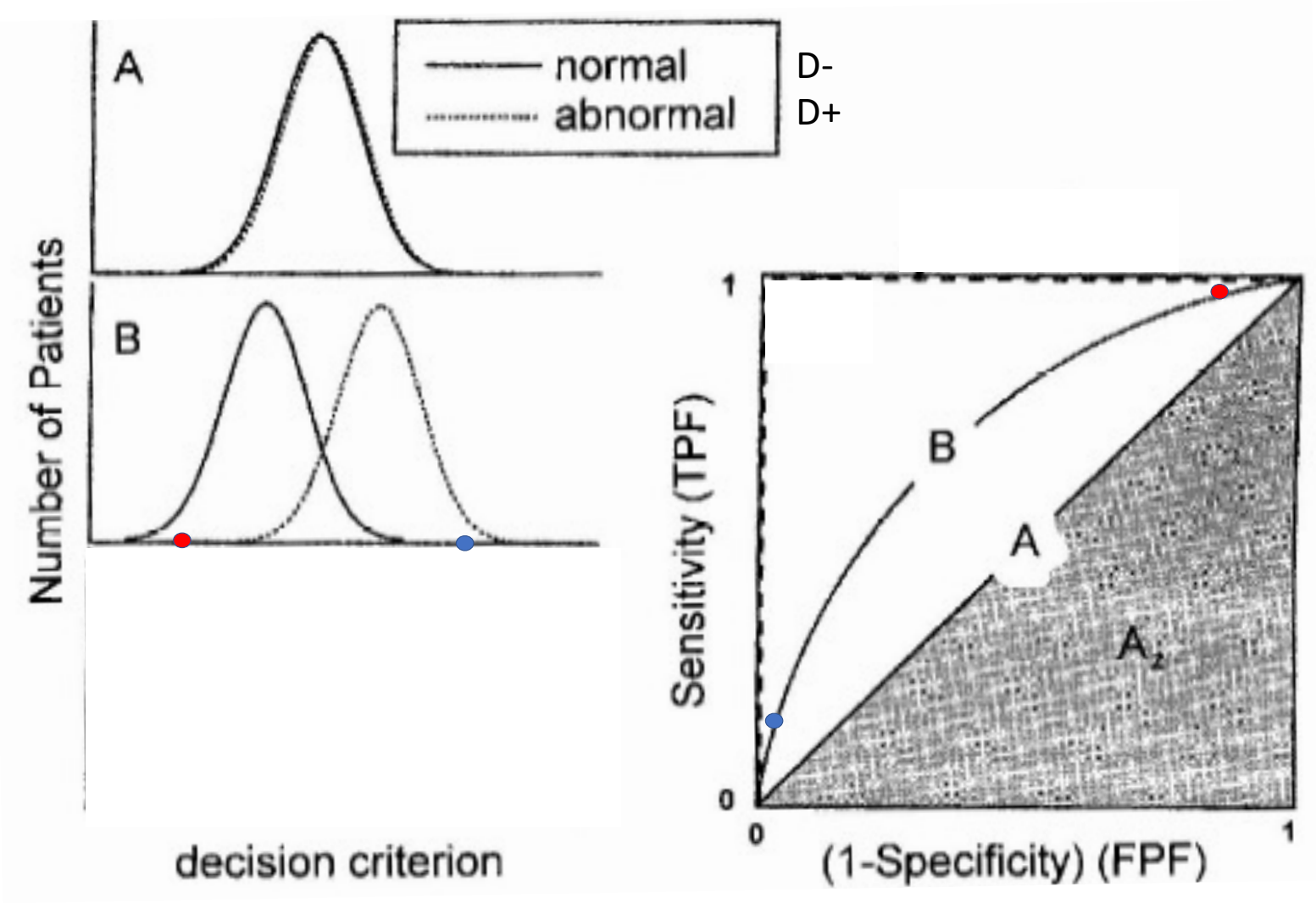
Effective biomarker

		D +	D -
t_1 →	T +	a	b
	T -	c	d

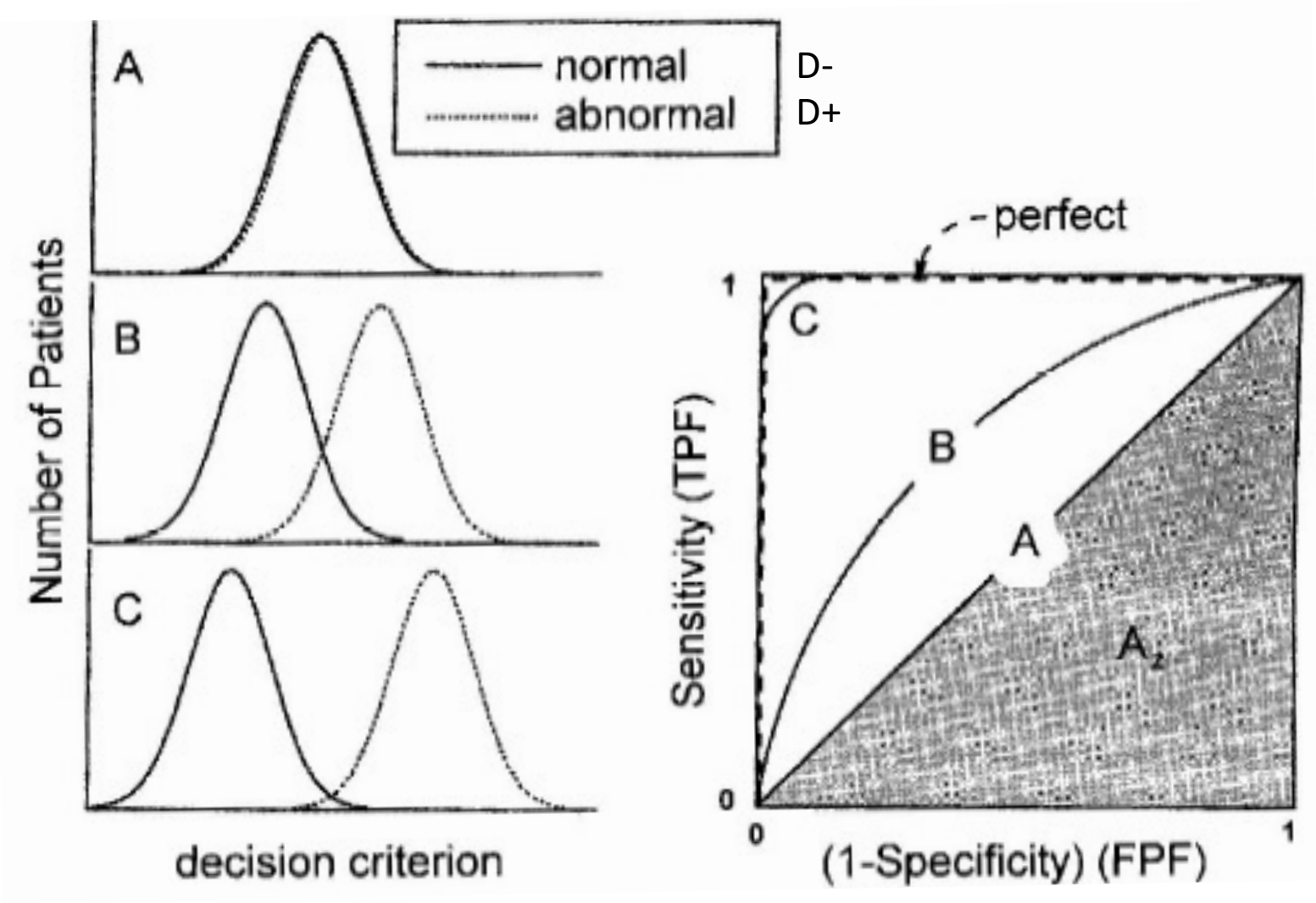



A
normal
abnormal
D-
D+
Number of Patients
decision criterion
Sensitivity (TPF)
(1-Specificity) (FPF)
1
0
0
1
A
A_z

AUC=0.5


A
B
normal
abnormal
D-
D+
Number of Patients
decision criterion
Sensitivity (TPF)
(1-Specificity) (FPF)
1
0
0
1
A
B
A_z

AUC=0.7


A
B
C
normal
abnormal
D-
D+
Number of Patients
decision criterion
perfect
1
0
C
B
A
A_z
Sensitivity (TPF)
0
1
(1-Specificity) (FPF)

AUC=0.97

(Highly) Effective biomarker ?

Sensitivity & specificity are cutoff specific

Therefore use AUC (cutoff agnostic) as measure for how effective a biomarker is

Patient's Question:

"Doctor, how likely am I to have this disease?"

- Sensitivity, specificity and AUCs don't answer this, because they work from the gold standard. **This introduces Predictive Values**
- Now you need to work from the *test result,* but you won't know whether this person is a true positive or a false positive (or a true or false negative)
- Before you do any test, the best guide you have to a diagnosis is based on prevalence !

- Prevalence indicates the 'pre-test probability of disease'

2 x 2 table: Prevalence (a+c / N)

	Disease present (D+)	Disease absent (D-)	Total
Test positive (T+)	a	b	a+b
Test negative (T-)	c	d	c+d
Total	a+c	b+d	N

Positive and Negative Predictive Values

- Based on rows, not columns
  - Positive Predictive Value (PPV) = a/(a+b)
    = Probability that a positive score is a true positive
  - NPV = d/(c+d); same for a negative test result
  - BUT… there's a big catch:

	D +	D –
T +	a	b
T –	c	d

- We are now working across the columns, so PPV & NPV depend on how many cases of disease there are (**prevalence**).
- As prevalence goes down, PPV goes down (it's harder to find the smaller number of cases) and NPV rises.
- So, PPV and NPV must be determined for each clinical setting,
- But they are immediately useful to clinician: they reflect this *population,* so tell us about *this patient*

Prevalence and Predictive Values

A. Specialist referral hospital

	D +	D -
T +	50	10
T -	5	100

Sensitivity = 50/55 = 91%
Specificity = 100/110 = 91%

Prevalence = 55/165 = 33%

PPV = 50/60 = 83%
NPV = 100/105 = 95%

Prevalence and Predictive Values

A. Specialist referral hospital

	D +	D -
T +	50	10
T -	5	100

Sensitivity = 50/55 = 91%
Specificity = 100/110 = 91%

Prevalence = 55/165 = 33%

PPV = 50/60 = 83%
NPV = 100/105 = 95%

B. Primary care

	D +	D -
T +	50	100
T -	5	1000

Sensitivity = 50/55 = 91%
Specificity = 1000/1100 = 91%

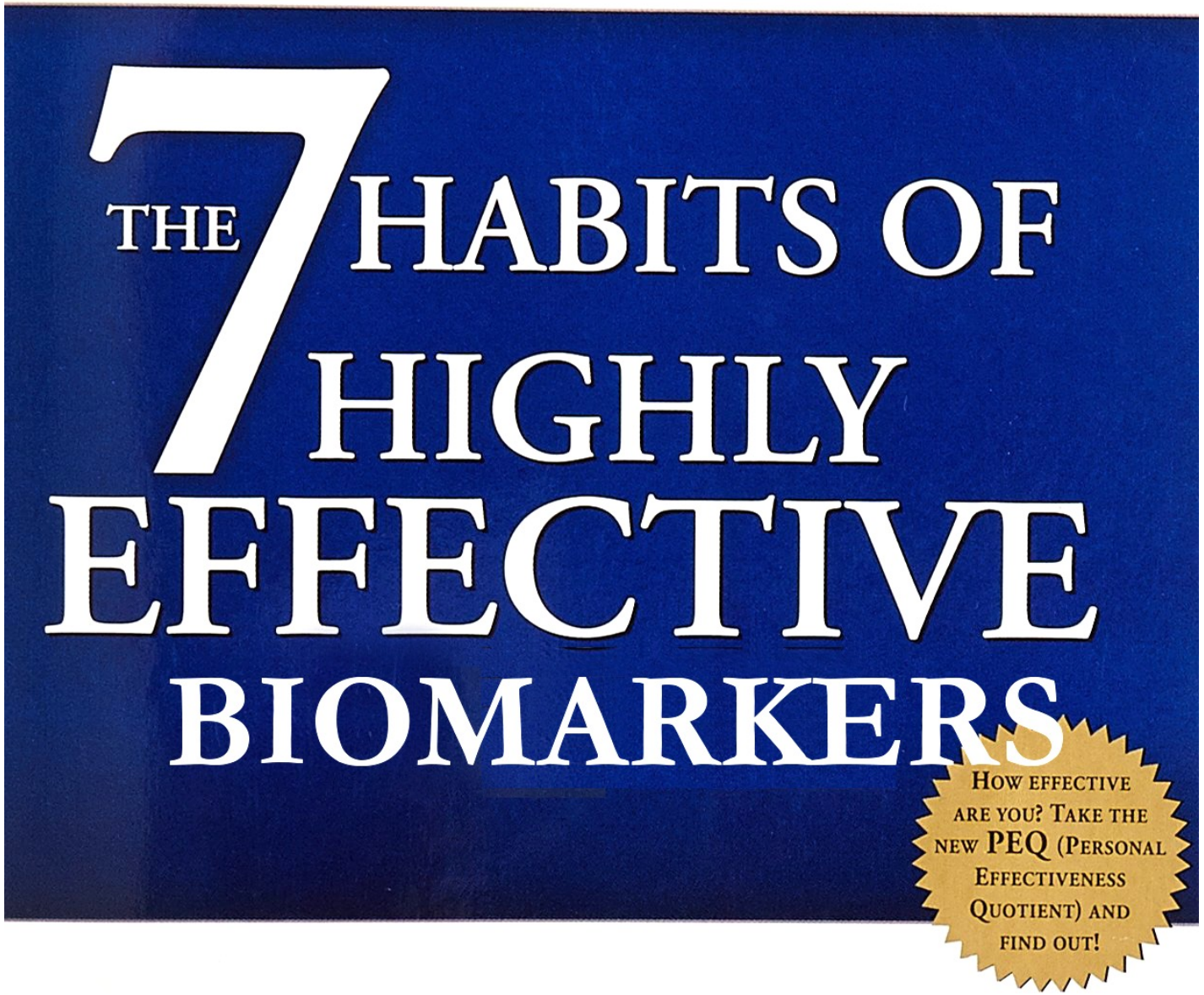
Prevalence = 55/1155 = 3%

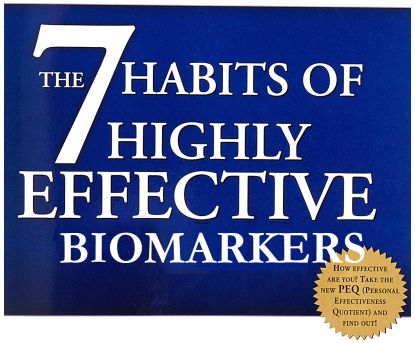
PPV = 50/150 = 33%
NPV = 1000/1005 = 99.5%

3

2

1


THE 7 HABITS OF
HIGHLY
EFFECTIVE
BIOMARKERS
HOW EFFECTIVE ARE YOU? TAKE THE NEW PEQ (PERSONAL EFFECTIVENESS QUOTIENT) AND FIND OUT!



The Marker (yourself)

1. Be proactive
2. Begin with the end in mind
3. Put first things first

The Environment

4. Seek first to understand, then to be understood
5. Think win-win
6. Synergize

The Marker & Environment

7. Sharpen the Saw

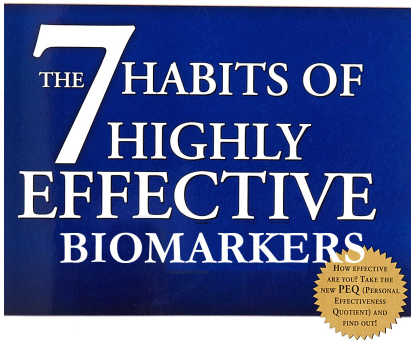
Table 1

Patents and research investments: Evidence from Mansfield (1986) survey

***Percent of Developed or Commercially Introduced Inventions That Would Not Have Been Developed or Commercially Introduced if Patent Protection Could Not Have Been Obtained, Twelve Industries*, 1981–83.[a]**

Industry	Percent That Would Not Have Been Introduced	Percent That Would Not Have Been Developed
Pharmaceuticals	65	60
Chemicals	30	38
Petroleum	18	25
Machinery	15	17
Fabricated metal products	12	12
Primary metals	8	1
Electrical equipment	4	11
Instruments	1	1
Office equipment	0	0
Motor vehicles	0	0
Rubber	0	0
Textiles	0	0

Source: Mansfield (1986) Table 1.



The Marker (yourself)

1. Be proactive
2. Begin with the end in mind
3. Put first things first

The Environment

4. Seek first to understand, then to be understood
5. Think win-win
6. Synergize

The Marker & Environment

7. Sharpen the Saw

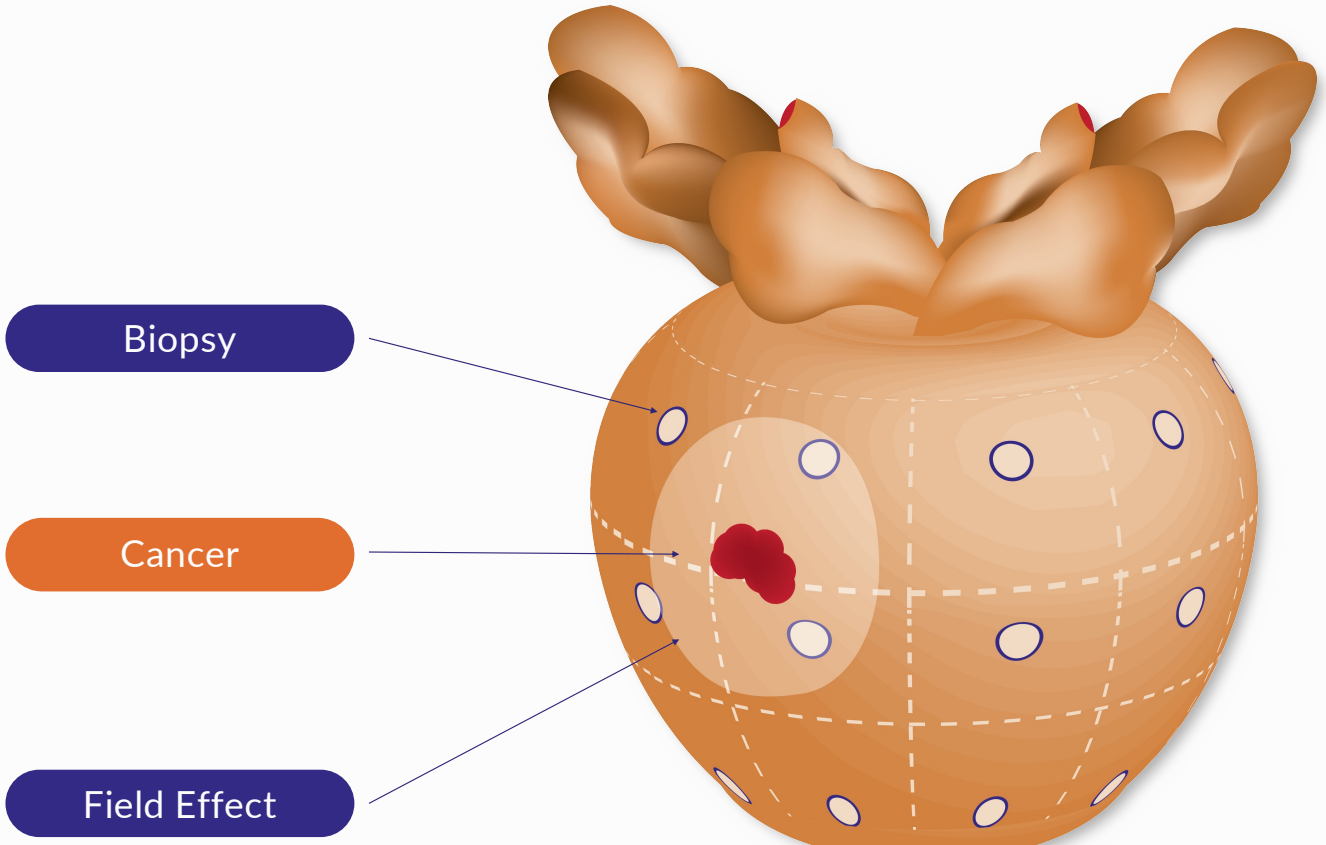
Begin with the end in mind

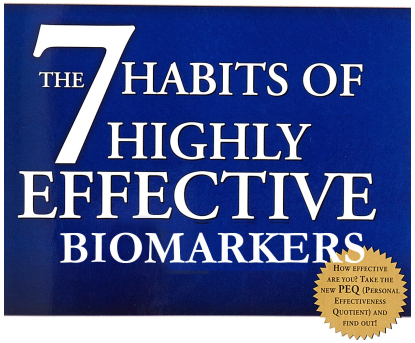
- D+: Gold standard

  The criterion that your clinical observation or simple test is judged against:

  - more definitive (but expensive or invasive) tests, such as a complete work-up, or
  - the clinical outcome (for screening tests, when workup of well patients is unethical).

  Sensitivity and specificity are calculated from a research study comparing the test to a gold standard.


Biopsy
Cancer
Field Effect



The Marker (yourself)

1. Be proactive
2. Begin with the end in mind
3. Put first things first

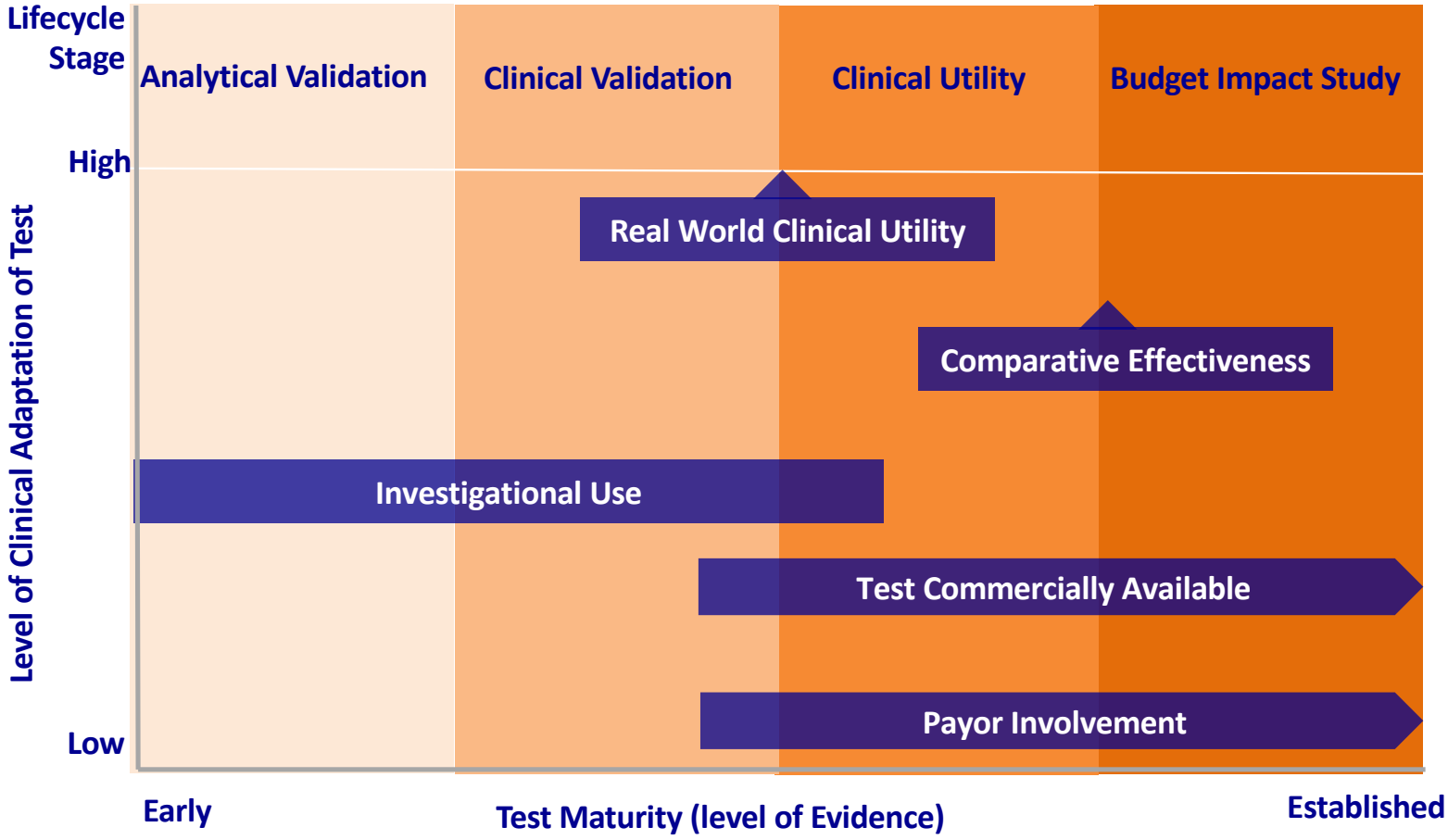
The Environment

4. Seek first to understand, then to be understood
5. Think win-win
6. Synergize

The Marker & Environment

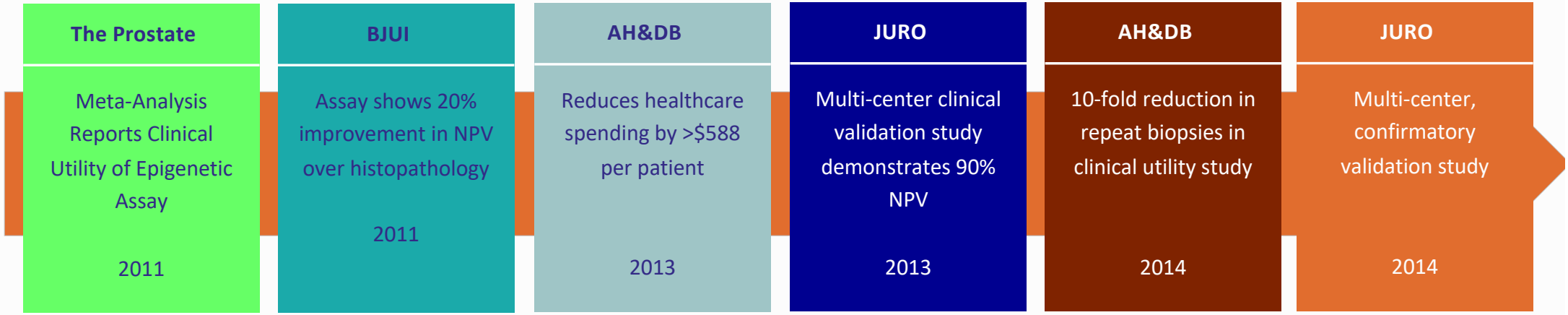
7. Sharpen the Saw

Put first things first



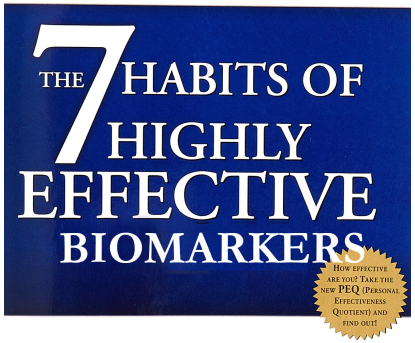
Source: Adapted from Personalized Medicine (2012) 9(1), 73-84

Put first things first



Presented at 2015 AUA

Meta-analysis MATLOC & DOCUMENT
96% NPV for Clinically Significant Cancer
90% NPV for all Cancers



The Marker (yourself)

1. Be proactive
2. Begin with the end in mind
3. Put first things first

The Environment

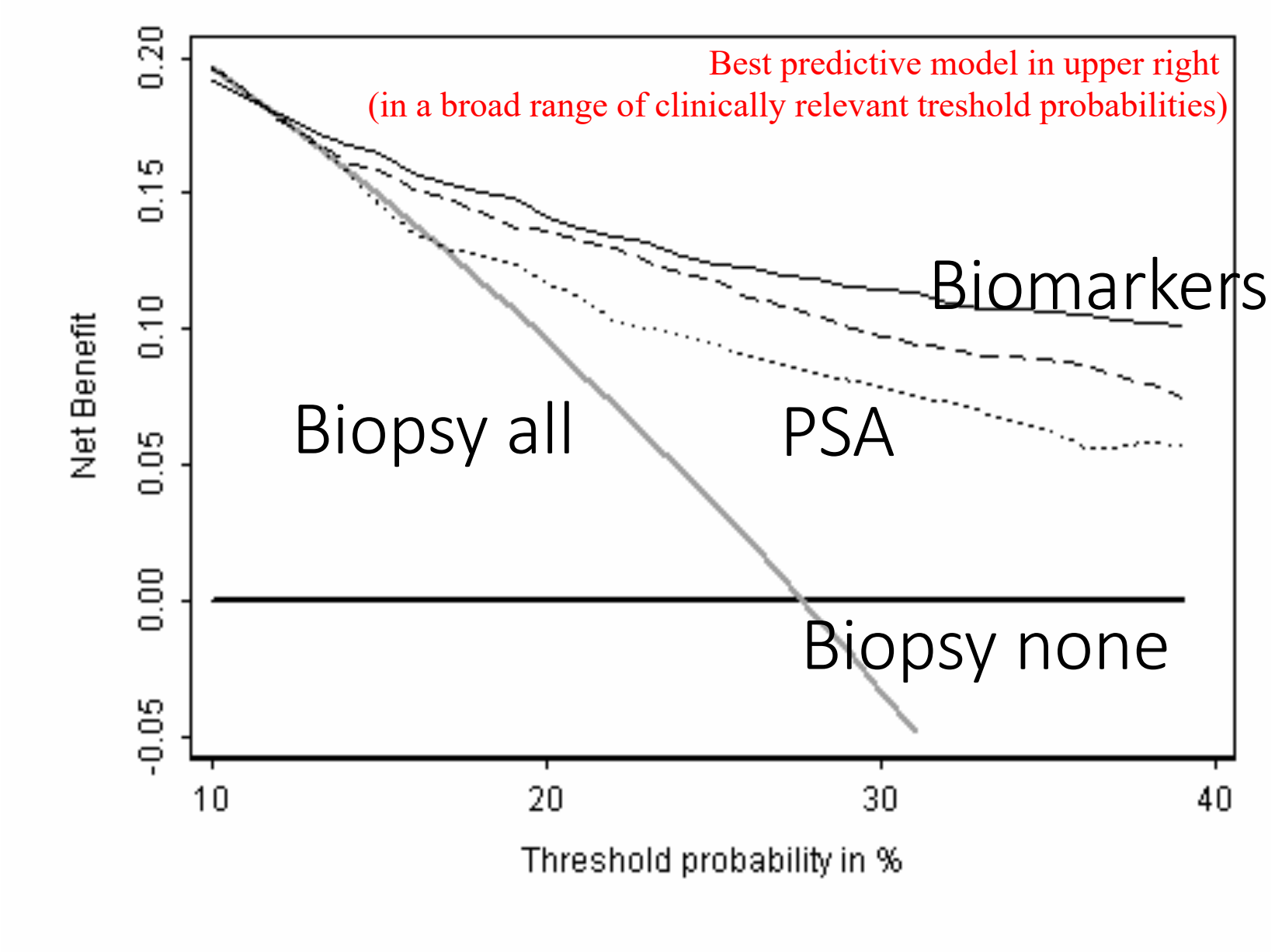
4. Seek first to understand, then to be understood
5. Think win-win
6. Synergize

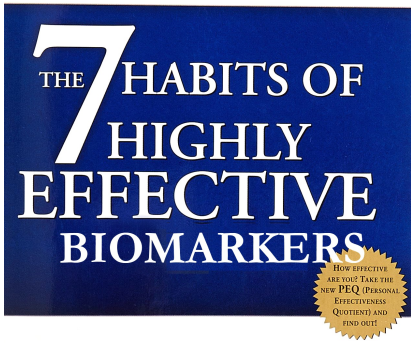
The Marker & Environment

7. Sharpen the Saw

Seek first to understand, then to be understood

- Involve all stake holders: patient & Caregiver/doctor (PCP – Specialist/Urologist)
- Traditional biostatistical techniques for evaluating models, **markers and tests do not incorporate clinical consequences**
- Sensitivity / specificity insufficient to determine which diagnostic test should be used:
  - "Depends on whether sensitivity or specificity is more important"
  - What is worse? Failing to treat a patient with residual disease (missed treatment = false negative) versus Treating a patient who is free of cancer (unnecessary treatment = false positive)
- Consider DCA (Decision Curve Analysis)


Best predictive model in upper right
(in a broad range of clinically relevant treshold probabilities)
Biomarkers
Biopsy all
PSA
Biopsy none
Net Benefit
0.20
0.15
0.10
0.05
0.00
-0.05
10
20
30
40
Threshold probability in %



The Marker (yourself)

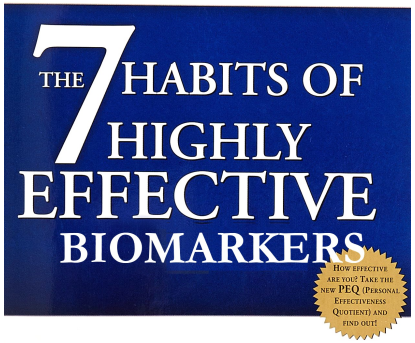
1. Be proactive
2. Begin with the end in mind
3. Put first things first

The Environment

4. Seek first to understand, then to be understood
5. Think win-win
6. Synergize

The Marker & Environment

7. Sharpen the Saw



The Marker (yourself)

1. Be proactive
2. Begin with the end in mind
3. Put first things first

The Environment

4. Seek first to understand, then to be understood
5. Think win-win

The Marker & Environment

6. Synergize
7. Sharpen the Saw

The Best of All Worlds

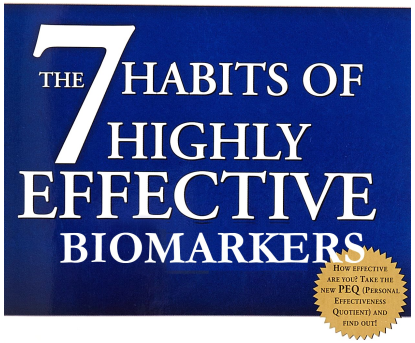
combining clinical variables

with

- molecular signatures
- imaging (eg. mpMRI)

using

- AI (machine learning)



The Marker (yourself)

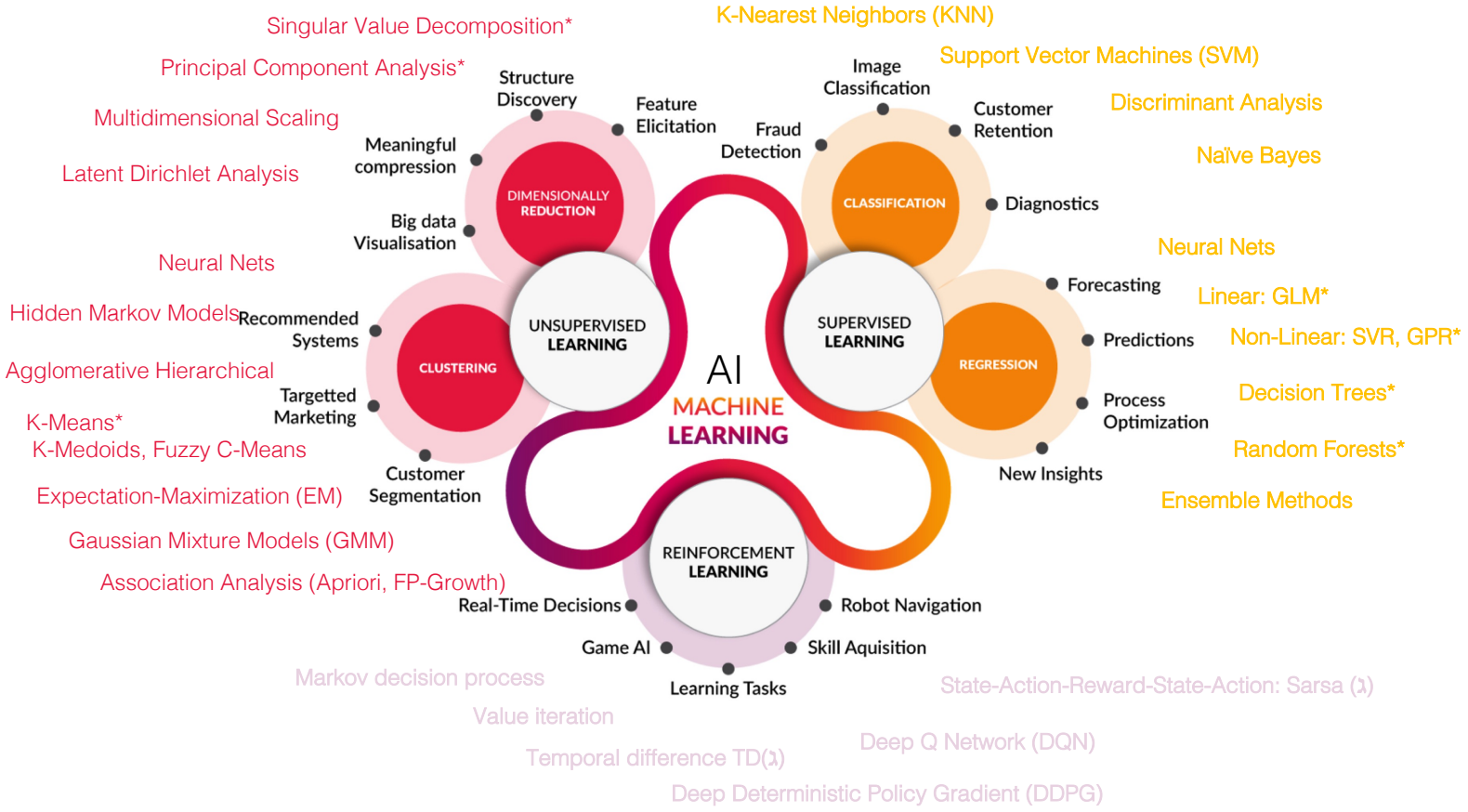
1. Be proactive
2. Begin with the end in mind
3. Put first things first

The Environment

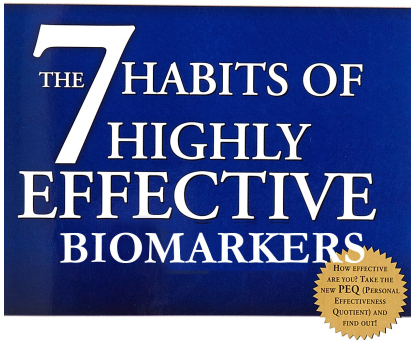
4. Seek first to understand, then to be understood
5. Think win-win
6. Synergize

The Marker & Environment

7. Sharpen the Saw



*continuous
categorical



The Marker (yourself)

1. Be proactive
2. Begin with the end in mind
3. Put first things first

The Environment

4. Seek first to understand, then to be understood
5. Think win-win
6. Synergize

The Marker & Environment

7. Sharpen the Saw