Simulation Flow

A Toy Example

Outline

- P(HCC) General Equation
- Explanation:
  - Initial Panel Module
  - Policy Module
  - Imaging Module
  - Patient Exit Module
- Toy Example
  - Simulation at epoch t = 0
  - Simulation at epoch t = 1
  - Simulation at epoch t = 2
  - Simulation at epoch t = 3
  - Termination
  - Performance Measure

P(HCC) Equation

Each patient i's risk of developing HCC can be measured by the following equation:

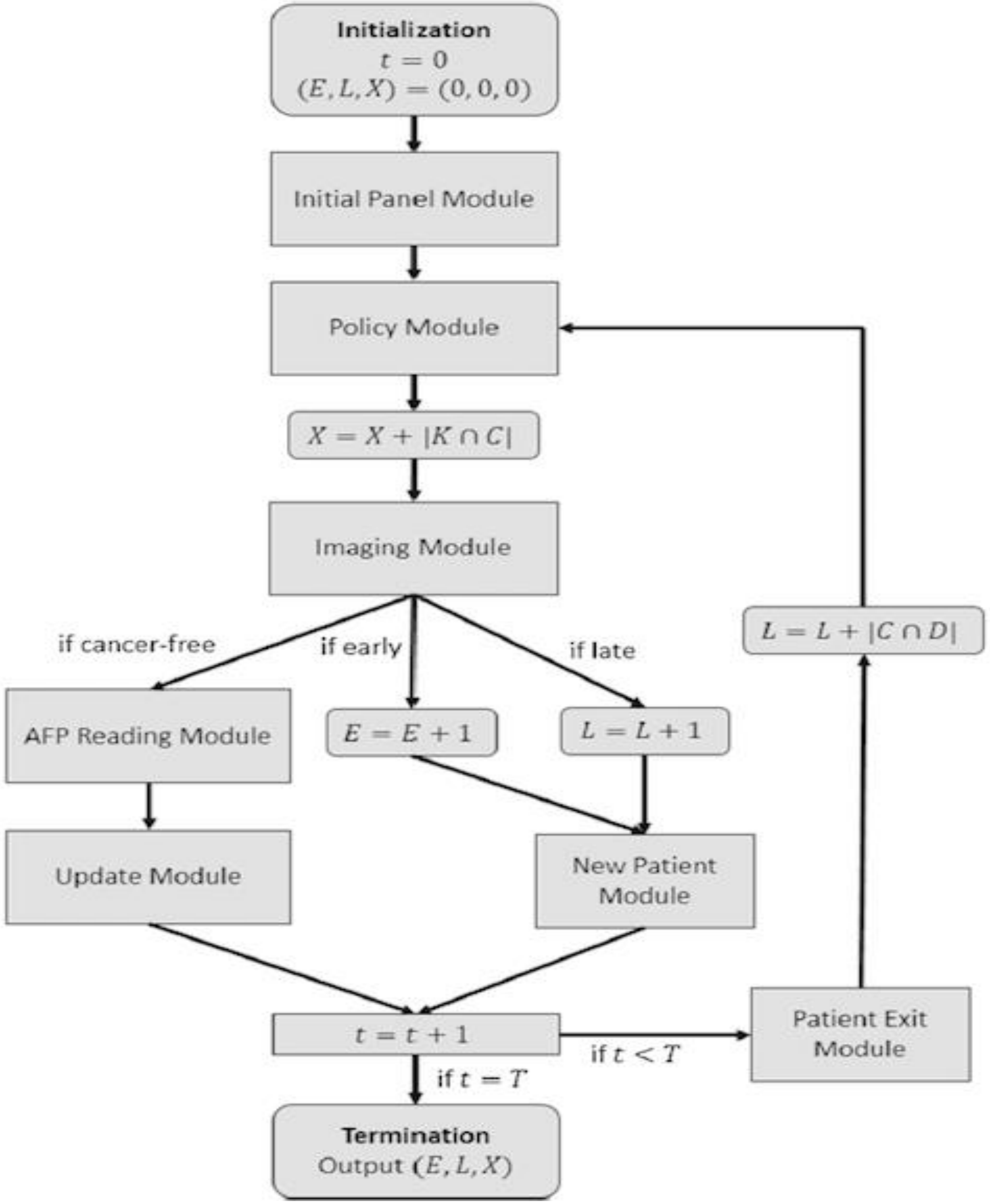
$$\boxed{P(\mathrm{HCC})_i = [1 + exp(-c_1 B_i - c_2 SD_i - c_3 RR_i)]^{-1} \qquad (1)}$$

- $P(\mathrm{HCC})_i$ is the patient's lifetime cumulative probability of developing HCC,
- B_i is a vector of all static risk cofactors measured upon enrollment into surveillance (age, ethnicity, smoker, alkaline phosphatase, blood platelets, and esophageal varices),
- SD_i is the standard deviation amongst a patient's recorded AFP readings,
- RR_i is the least squares estimate for the rate of AFP rise over time amongst a patient's recorded AFP readings,
- c_1 is a vector of the corresponding regression coefficients for all static risk factors, and
- c_2 and c_3 are regression coefficients for the AFP standard deviation and the rate of AFP rise over time.

Initial Panel Module

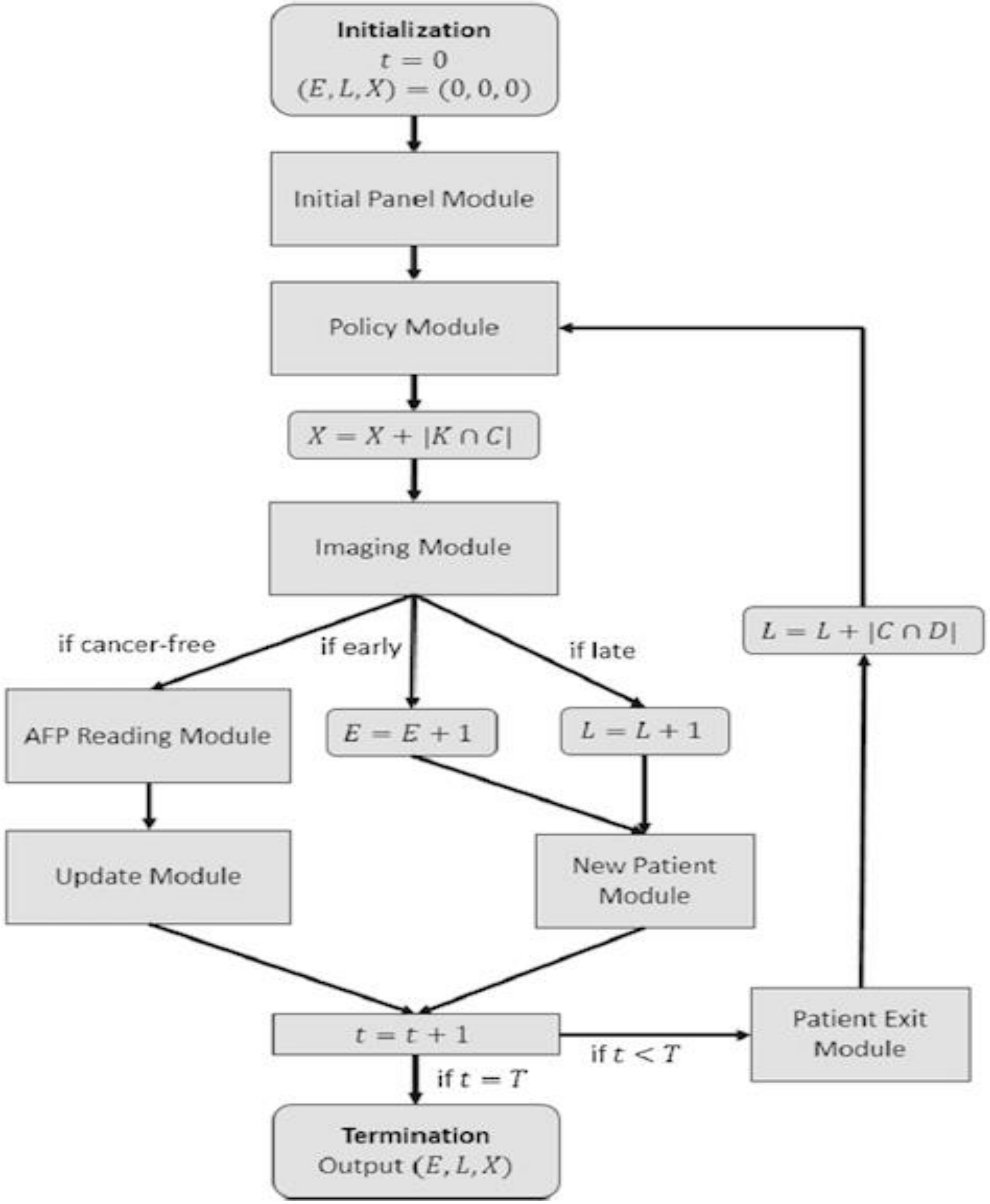
Simulation randomly draws, with replacement, a patients’ history from the dataset.

The result will be the creation of C, the set of patients who will develop cancer, and N, the set of patients who will not develop cancer in their lifetime.



Policy Module

1. Receives knowledge of N patients as input
2. Chooses subset K based on Policy Module
3. X increments by number of screenings which were spent on |K^N|



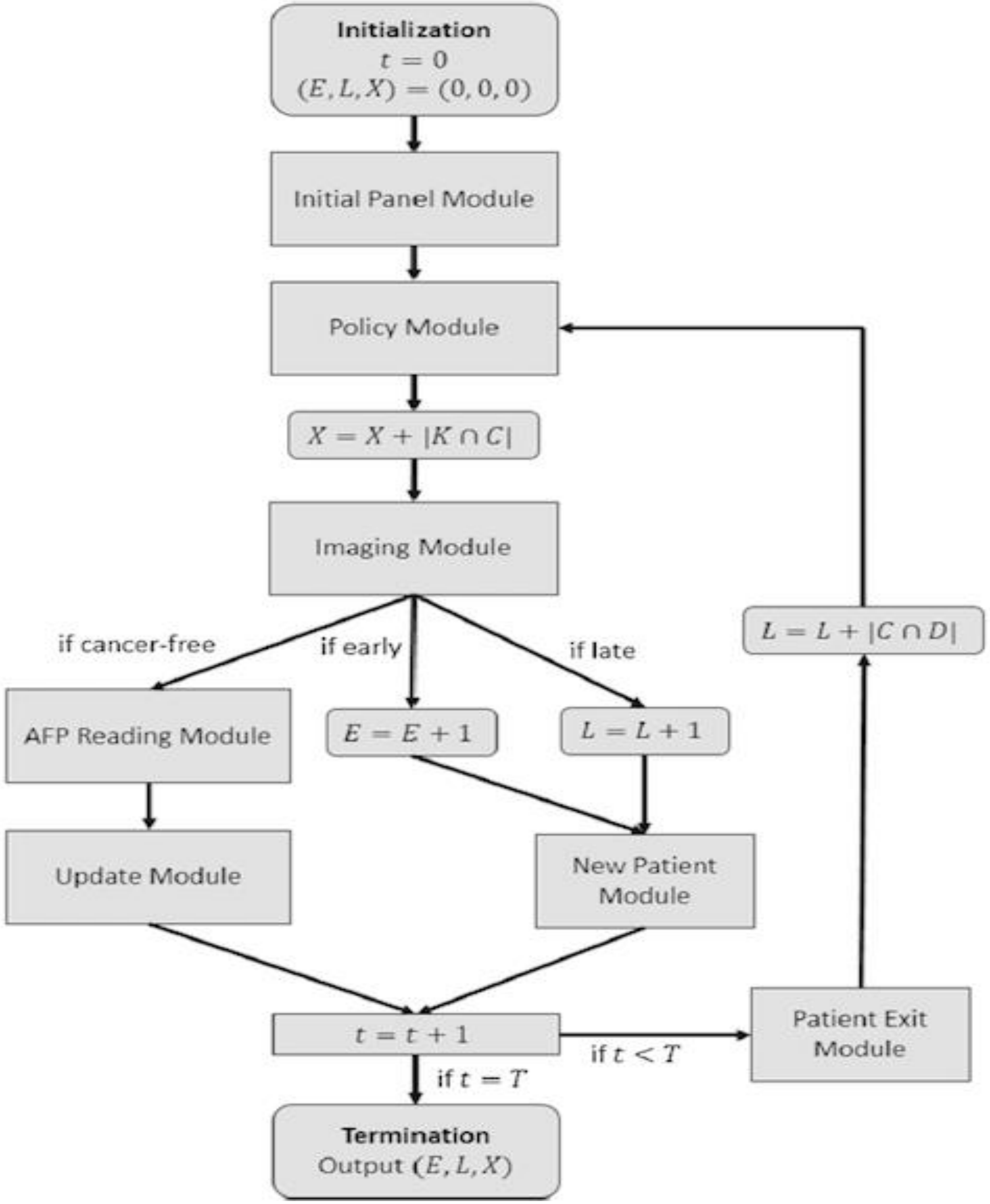
Imaging Module

- Query current cancer state:
  - If patient never developed cancer → automatically assign cancer-free
  - If patient has tumor of size s– sbar at time tbar → estimate tumor size s at time t

$$s = 2^{\frac{t-\bar{t}}{\delta}} \cdot \bar{s} \tag{4}$$

- Assign State as per:

$$\text{State} = \begin{cases} \text{Early} & \text{if } t \geq \bar{t} \text{ and } 1 \leq s \leq 5 \\ \text{Late} & \text{if } t \geq \bar{t} \text{ and } 5 < s \\ \text{Cancer-Free} & \text{if Otherwise} \end{cases} \tag{5}$$



Imaging Module Output - If:

<u>Cancer Free: AFP Module and Update Module</u>

- Query new AFP readings
- Calculate RR and SS
- Update Variables (For each Cancer Free Patient)

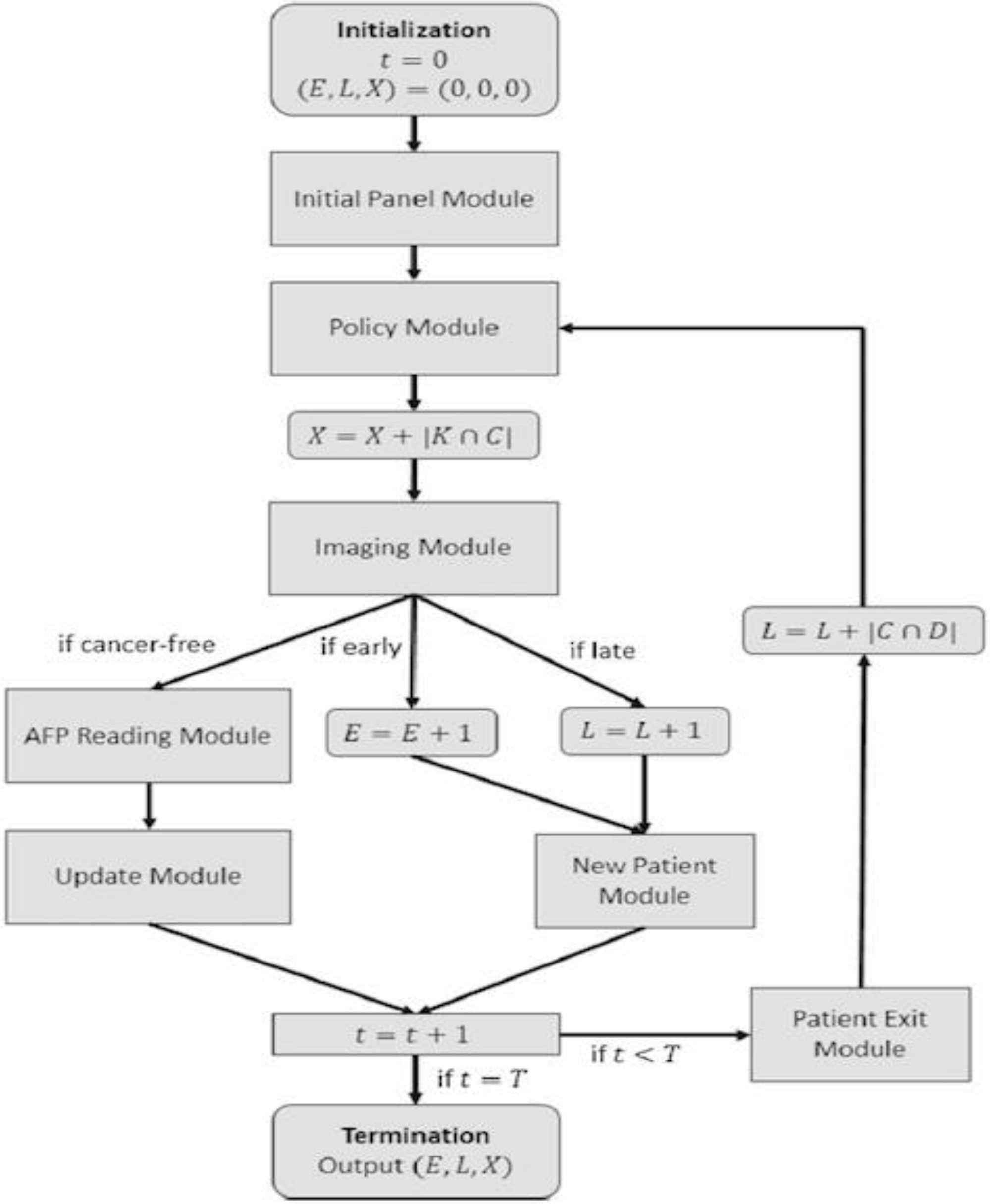
<u>Early: E and New Patient Module</u>

- E = E + 1
- Replace Patients belonging to E

<u>Late: L and New Patient Module</u>

- L = L + 1
- Replace Patients belonging to L

Advance to t+1

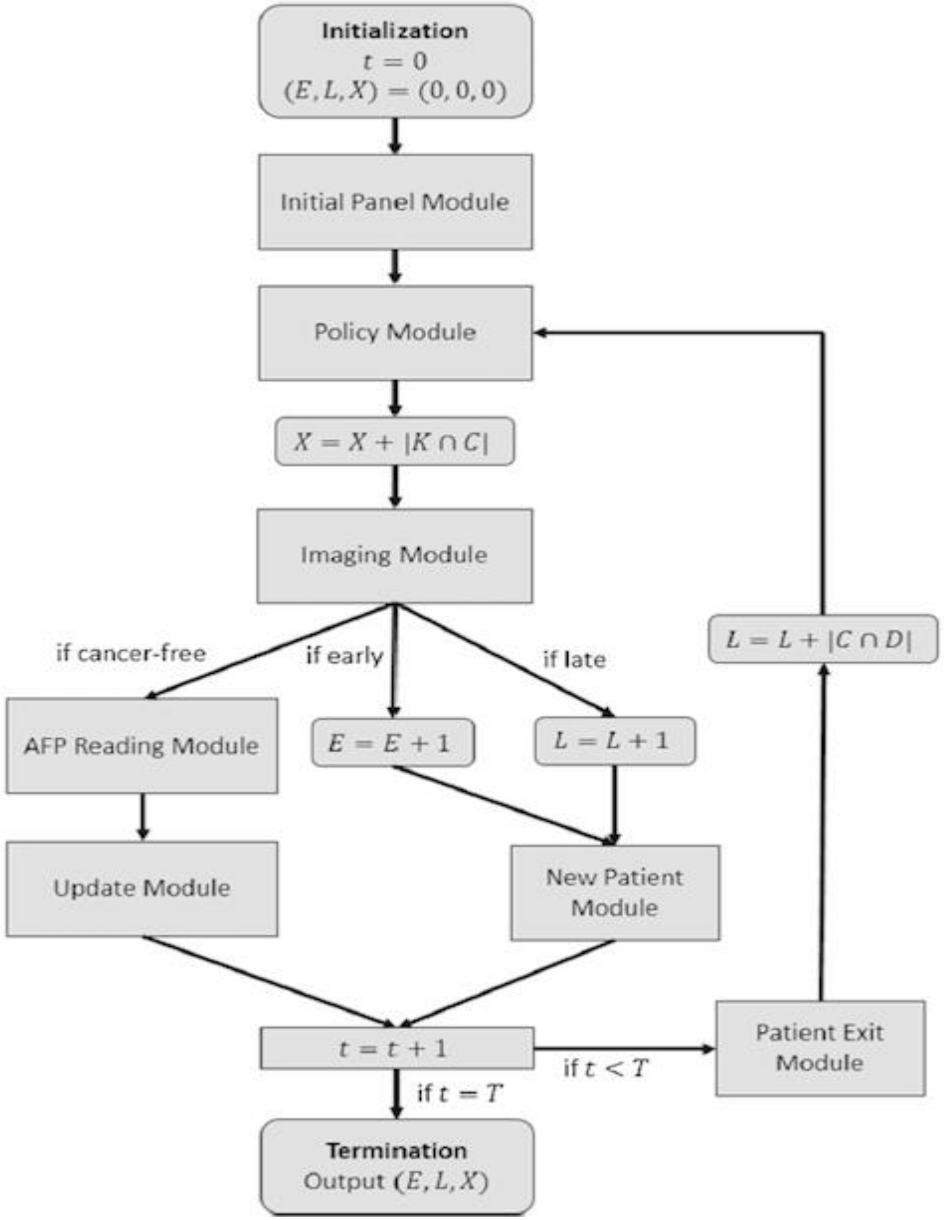


Patient Exit Module

If t < T:

- D = departing patients (subset of K)
  - Time t >= T, or death, or voluntary withdrawal
  - Patients in D eliminated and replaced

- All patients D^C increment L by 1
  - L = L + |C^D|



Time $t = 0$

$T = 4$

List of N Patients (t=0)

HCC (3)

Pid	Age	Eth	Sm	Alk	Bld	Eso	AFP	SS	RR	ciBi	S-	t
1	46	1	1	149	141	1	95	0	0	-1.1	S-	0

Pid	Age	Eth	Sm	Alk	Bld	Eso	AFP	SS	RR	ciBi	S-	t
2	59	2	0	121	99	0	88	0	0	-18	S-	0

Pid	Age	Eth	Sm	Alk	Bld	Eso	AFP	SS	RR	ciBi	S-	t
3	46	1	1	307	49	0	81	0	0	-2.7	S-	0

$C = \{P_1, P_2, P_3\}$

$D = \{P_4, P_5, P_6, P_7, P_8, P_9, P_{10}, P_{11}, P_{12}\}$

Note: s is the the size of tumor at a certain time t.

Non HCC (9)

Pid	Age	Eth	Sm	Alk	Bld	Eso	AFP	SS	RR	ciBi	t
4	46	1	1	116	54	1	94	0	0	-0.47	0

Pid	Age	Eth	Sm	Alk	Bld	Eso	AFP	SS	RR	ciBi	t
5	53	1	1	84	82	0	82	0	0	ciBi	0

Pid	Age	Eth	Sm	Alk	Bld	Eso	AFP	SS	RR	ciBi	t
6	53	1	1	127	84	0	83	0	0	ciBi	0

Pid	Age	Eth	Sm	Alk	Bld	Eso	AFP	SS	RR	ciBi	t
7	57	2	0	53	130	0	89	0	0	ciBi	0

Pid	Age	Eth	Sm	Alk	Bld	Eso	AFP	SS	RR	ciBi	t
8	53	1	1	108	90	1	89	0	0	ciBi	0

Pid	Age	Eth	Sm	Alk	Bld	Eso	AFP	SS	RR	ciBi	t
9	55	1	1	56	89	1	89	0	0	ciBi	0

List of N Patients (t=0)

HCC (3)

Pid	AFP	SS	RR	ciBi	s-	t
1	95	0	0	-1.13	s-	0

Pid	AFP	SS	RR	ciBi	s-	t
2	88	0	0	-18.6	s-	0

Pid	AFP	SS	RR	ciBi	s-	t
3	81	0	0	-2.74	s-	0

$C = \{P_1, P_2, P_3\}$

$D = \{P_4, P_5, P_6, P_7, P_8, P_9, P_{10}, P_{11}, P_{12}\}$

Note: s is the the size of tumor at a certain time t.

Non HCC (9)

Pid	AFP	SS	RR	ciBi	t
4	94	0	0	-0.47	0

Pid	AFP	SS	RR	ciBi	t
5	82	0	0		0

Pid	AFP	SS	RR	ciBi	t
6	83	0	0		0

Pid	AFP	SS	RR	ciBi	t
7	89	0	0		0

Pid	AFP	SS	RR	ciBi	t
8	89	0	0		0

Pid	AFP	SS	RR	ciBi	t
9	89	0	0		0

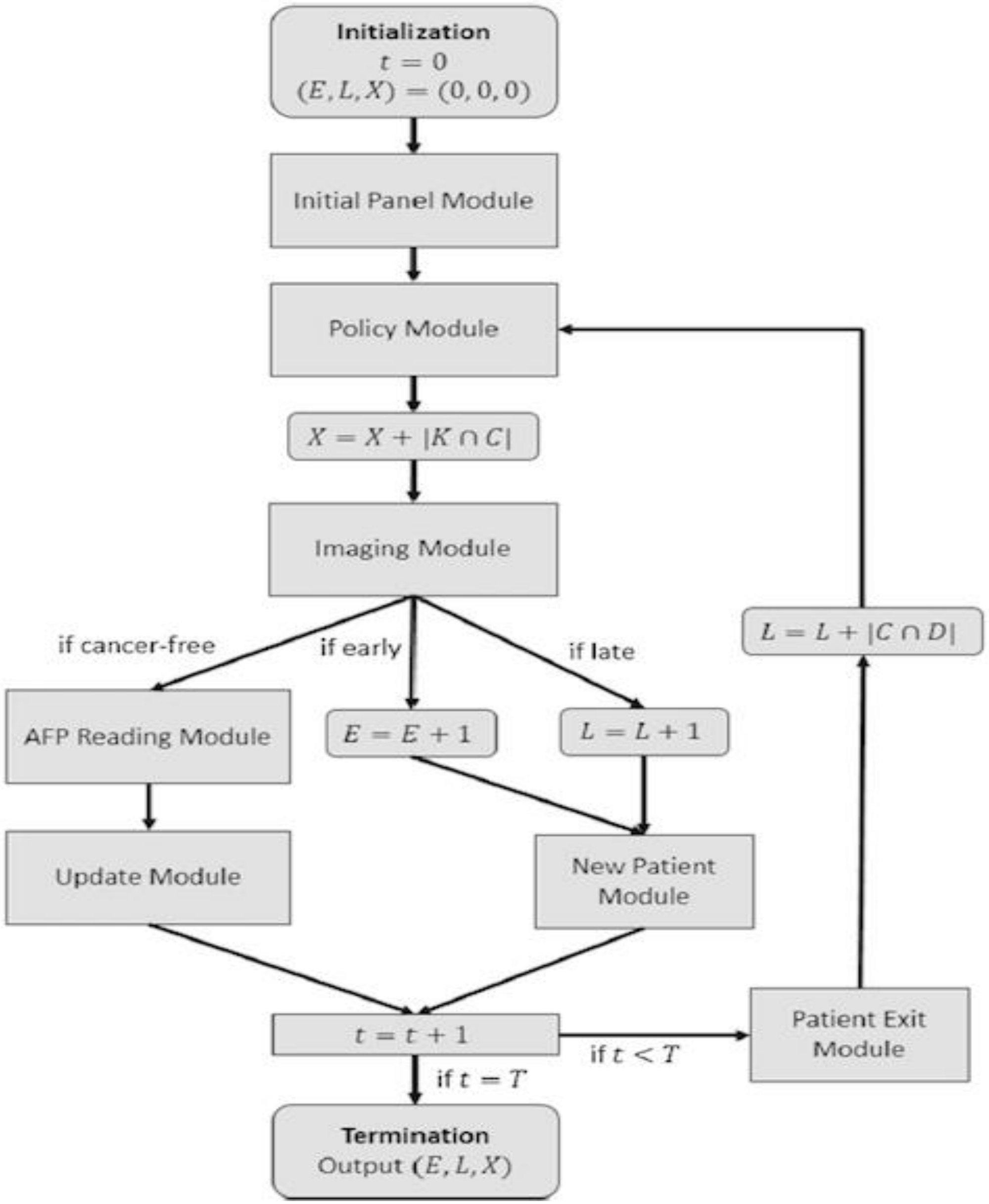
CiBi is a constant for each patient. So I calculate it at the beginning of the simulation.

Policy Module (t=0)

- Calculate P(HCC) & Rank. Then choose k=3 out of N=12
- $P_1=0.6 > P_4 = 0.55 > P_3=0.50$ $> P_1 = 0.3 > P_{10} = 0.3 > \ldots$

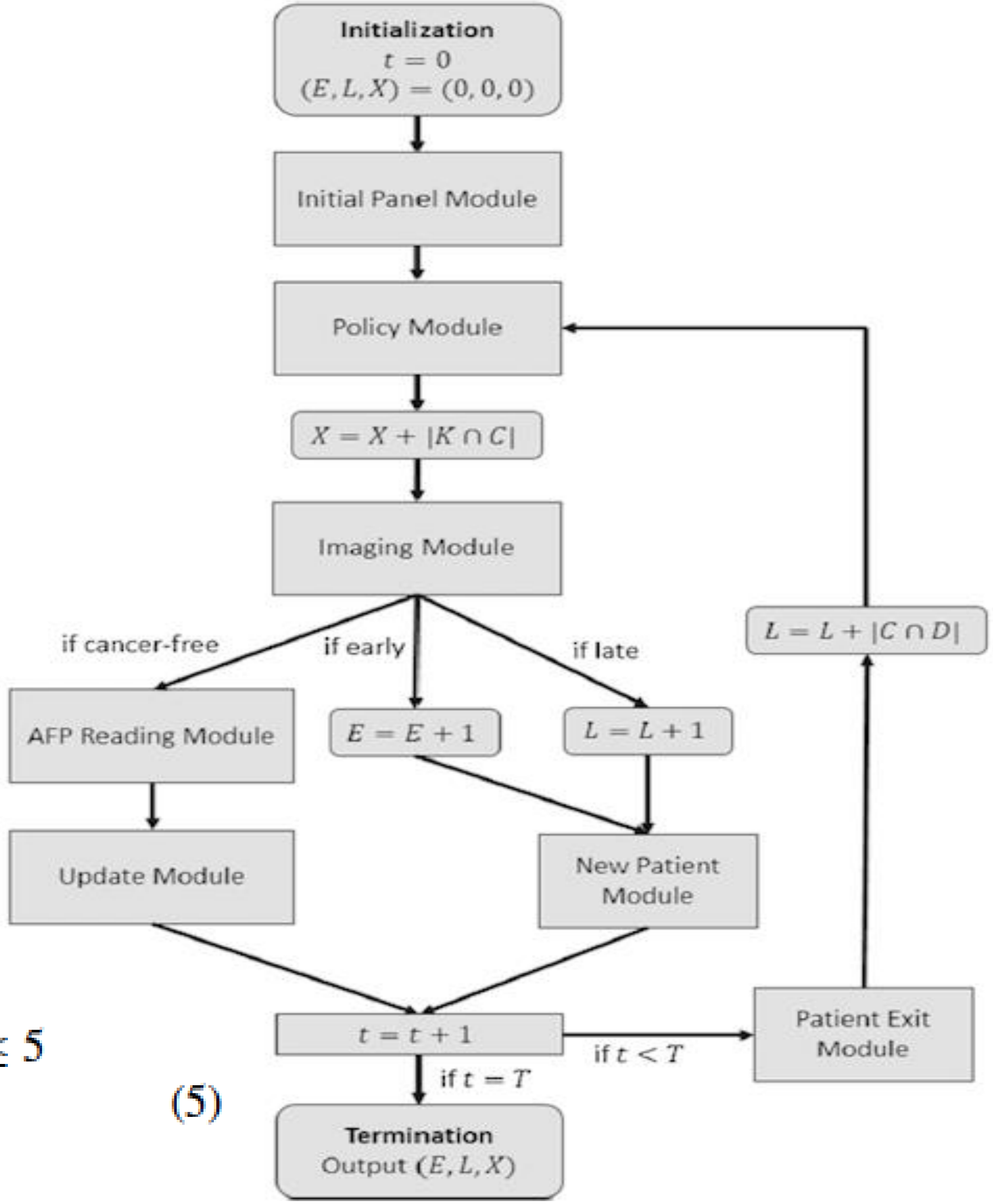
- $X = X + |K \wedge C|$
  - $X = 0$
  - $K = \{P_1, P_4, P_3\}$
  - $C = \{P_1, P_2, P_3\}$
  - $|K \wedge C| = 2$
- $X = 0 + 2 = 2$

- X is the number of screening spent on patients who would eventually develop cancer



Imaging Module (t=0)

- K chosen are: P_1, P_4, P_3
  - P_1 → belongs to C (tumor sbar at tbar=1)
    - Estimated tumor s = 2^(0-tbar)*sbar = 0.25
    - **<u>Cancer Free</u>**
  - P_4 → belongs to C
    - Estimate tumor s = 0.125
    - **<u>Cancer Free</u>**
  - P_3 → belongs to N
    - **<u>Cancer Free</u>**



$$\text{State} = \begin{cases} \text{Early} & \text{if } t \geq \bar{t} \text{ and } 1 \leq s \leq 5 \\ \text{Late} & \text{if } t \geq \bar{t} \text{ and } 5 < s \\ \text{Cancer-Free} & \text{if Otherwise} \end{cases} \quad (5)$$

Note: $s = 2^{\frac{t-\bar{t}}{\bar{s}}} \cdot \bar{s}$

Imaging Module Output (t=0)

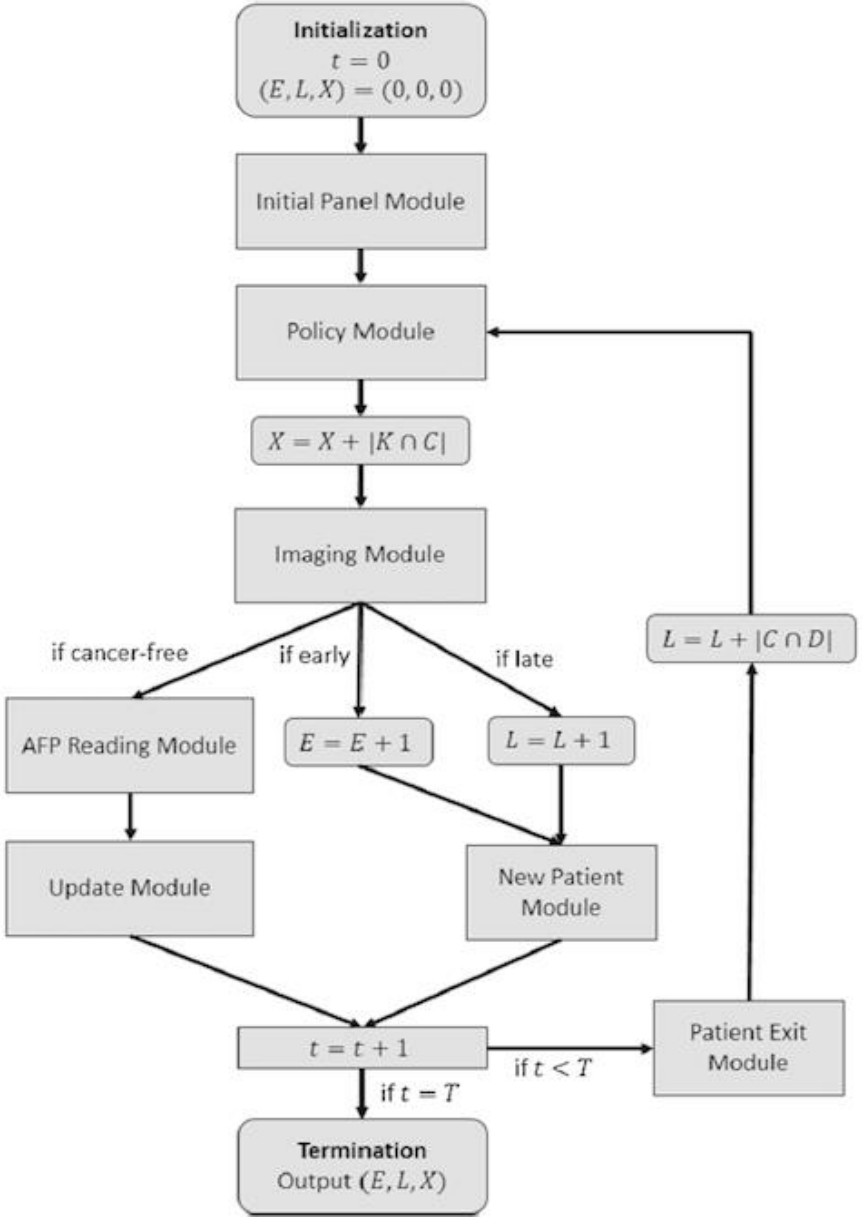
P_1, P_4, P_3 → Cancer Free

Cancer Free: AFP Module and Update Module

- Query new AFP readings
- Calculate RR and SS
- Update Variables (For each Cancer Free Patient)

Pid	ciBi	AFP	SS	RR	sbar at tbar	t
1	-1.13	95	0	0	sbar	0
1	-1.13	200	74	105	sbar	1

- Advance to **t+1**

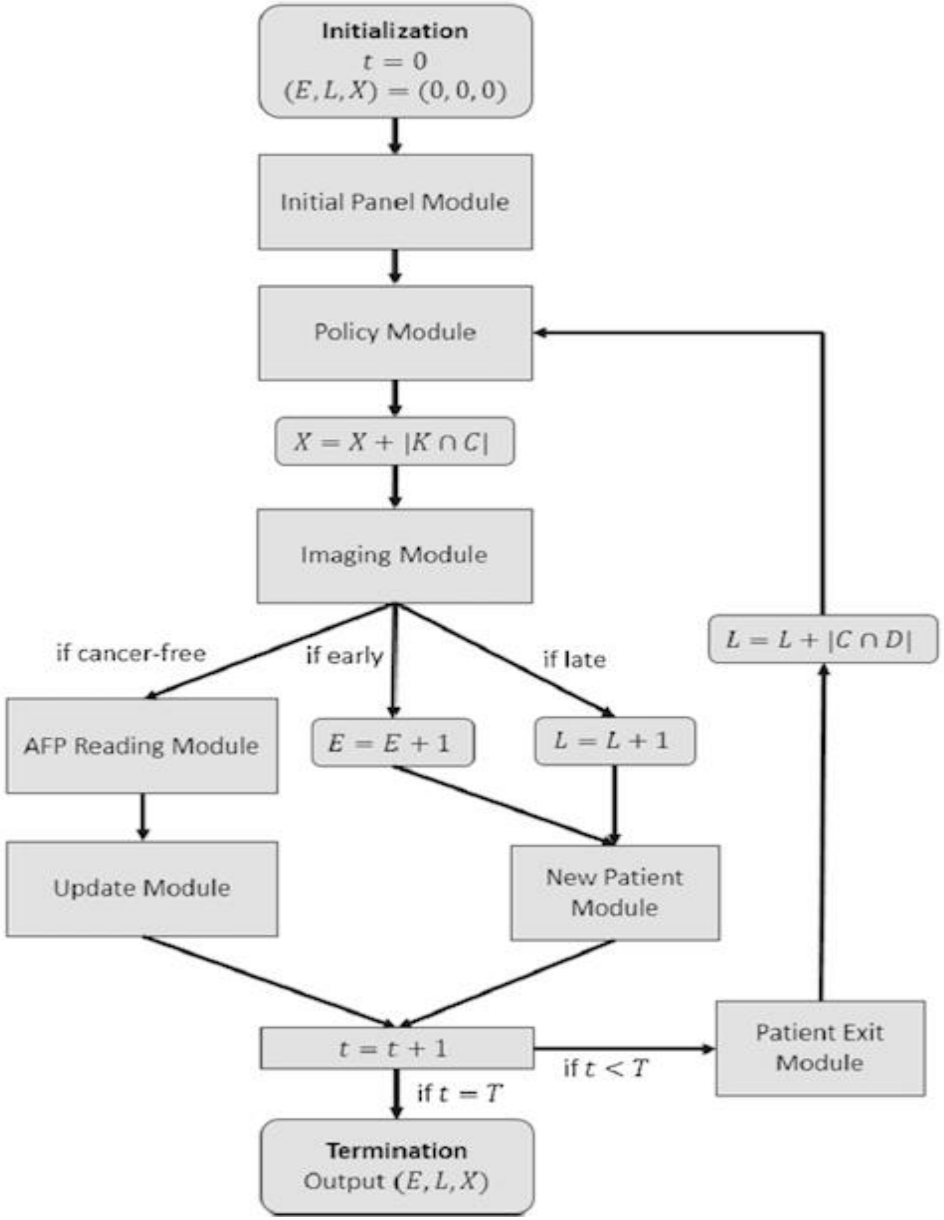


Time $t = 1$

$T = 4$

Patient Exit Module (t=1)

- D = departing patients (subset of K)
  - Time t >= T, or death, or voluntary withdrawal
  - Patients in D eliminated and replaced
- All patients D^C increment L by 1
  - D = 0
  - D^C = 0
  - L = L + |C^D|



List of N Patients (t=1)

HCC (3)

Pid	c1Bi	AFP	SS	RR	s	t
1	-1.13	95	0	0	s	0
1	-1.13	200	74	105	s	1

Pid	c1Bi	AFP	SS	RR	s	t
2	-18.6	88	0	0	s	0

Pid	c1Bi	AFP	SS	RR	s	t
3	-2.7	81	0	0	s	0
3	-2.7	200	84	119	s	1

Non HCC (9)

Pid	c1Bi	AFP	SS	RR	t
4	-0.47	94	0	0	0
4	-0.47	96	1.4	2	1

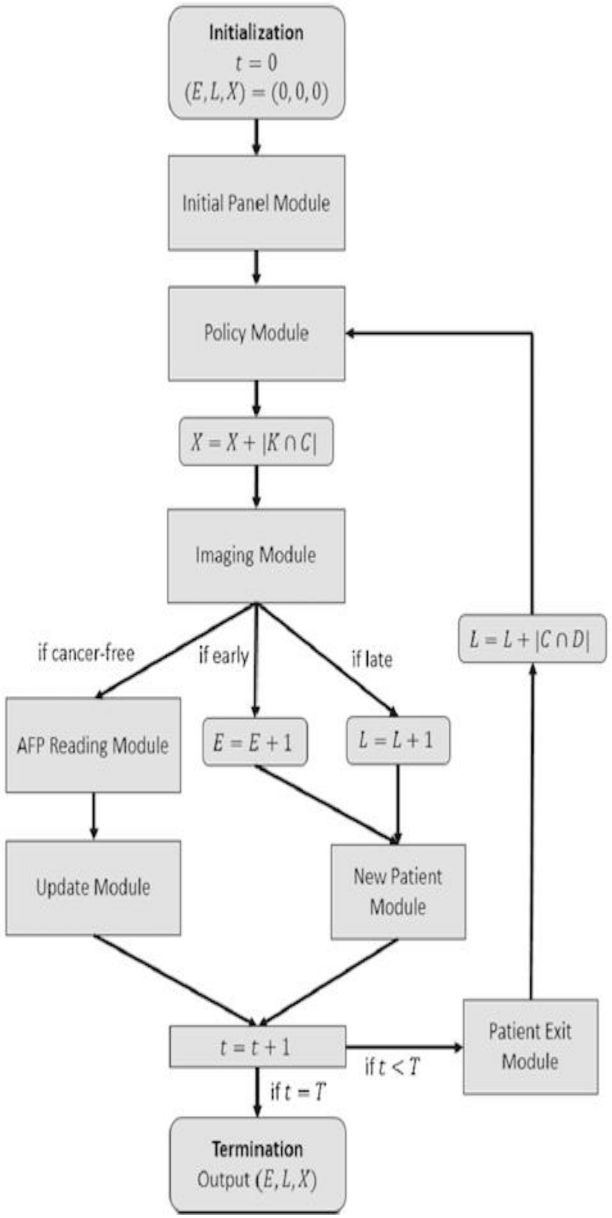
Pid	ciBi	AFP	SS	RR	t
5	c1B5	82	0	0	0

Pid	c1Bi	AFP	SS	RR	t
6	c1B6	82	0	0	0

Pid	c1Bi	AFP	SS	RR	t
7	c1B7	89	0	0	0

Pid	c1Bi	AFP	SS	RR	t
8	c1B8	89	0	0	0

Pid	c1Bi	AFP	SS	RR	t
9	c1B9	89	0	0	0



$C = \{P_1, P_2, P_3\}$

$D = \{P_4, P_5, P_6, P_7, P_8, P_9, P_{10}, P_{11}, P_{12}\}$

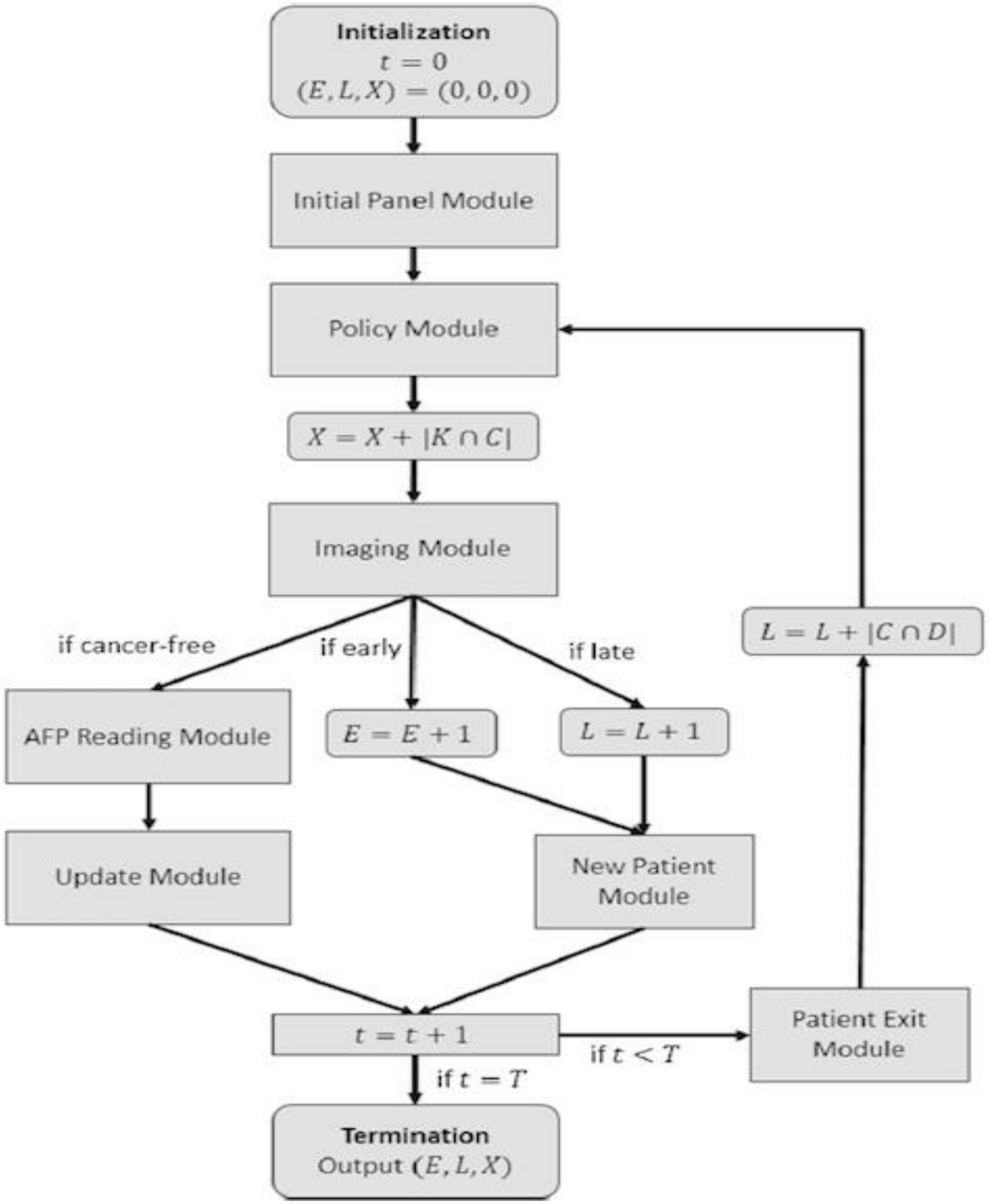
Note: P1, P3 and P4 are now updated.

Policy Module (t=1)

- Calculate P(HCC) & Rank. Then choose k=3 out of N=12
- P_1=0.67> P_4 = 0.55 > P_3=0.50 > P_1 = 0.3 > P_{10} = 0.3 > ...

- X = X + |K ^ C|
  - X = 2
  - K = {P_1, P_4, P_3}
  - C = {P_1, P_2, P_3}
  - |K ^ C| = 2
- X =2 + 2 = 4

- X is the number of screening spent on patients who would eventually develop cancer

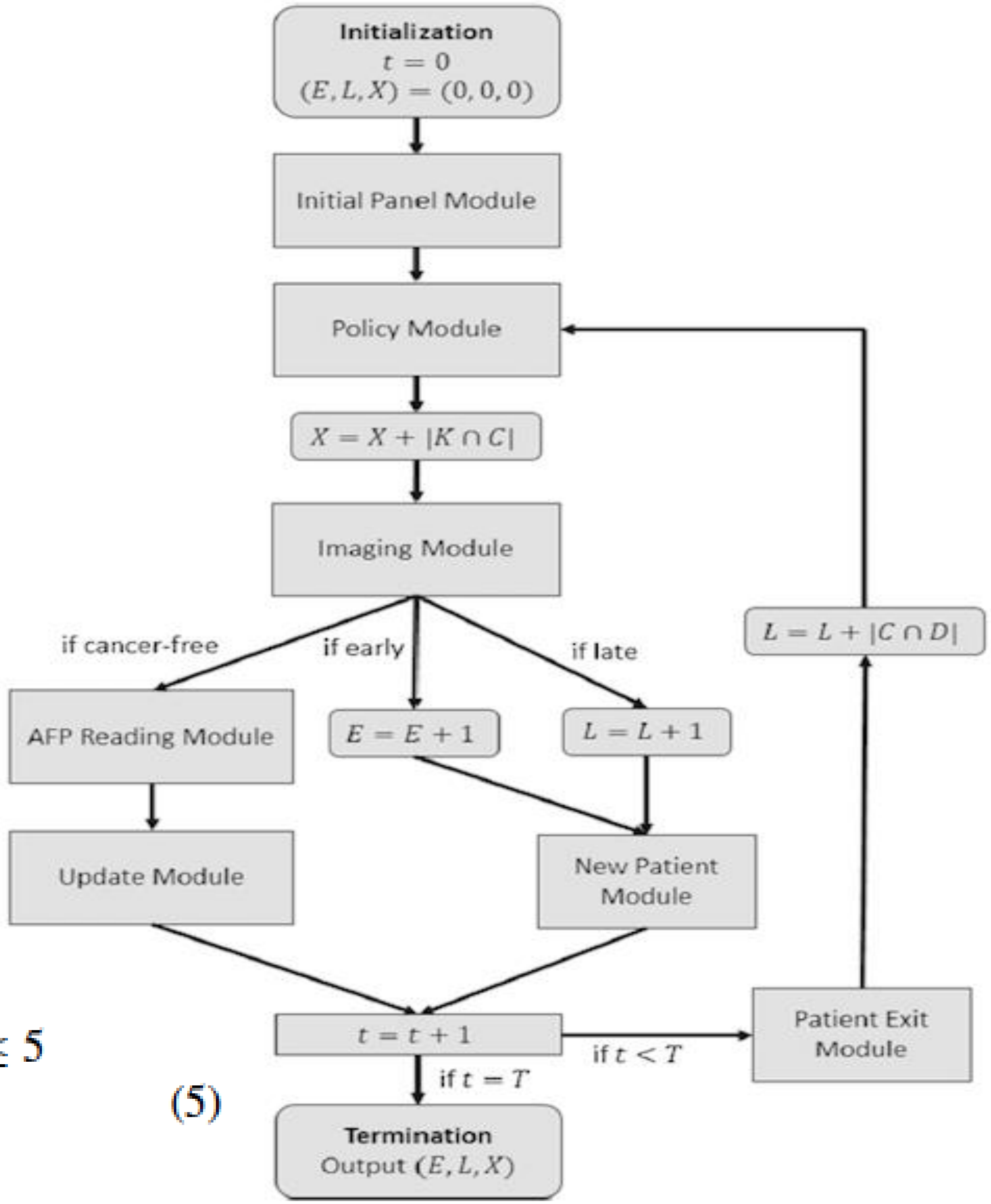


Imaging Module (t=1)

- P_1, P_3, P_4
  - P_1 → belongs to C (tumor sbar at tbar=1)
    - Estimated tumor s = 2^(1-tbar)*sbar = 1
    - (1<=s<=5 & t>=tbar) == TRUE
    - **Early**
  - P_3 → belongs to C
    - Estimate tumor s = 0.125
    - **Cancer Free**
  - P_4 → belongs to N
    - **Cancer Free**

Note: $s = 2^{\frac{t-\bar{t}}{\bar{\delta}}} \cdot \bar{s}$

$$\text{State} = \begin{cases} \text{Early} & \text{if } t \geq \bar{t} \text{ and } 1 \leq s \leq 5 \\ \text{Late} & \text{if } t \geq \bar{t} \text{ and } 5 < s \\ \text{Cancer-Free} & \text{if Otherwise} \end{cases} \qquad (5)$$



Imaging Module Output (t=1)

P_3, P_4 → Cancer Free; P_1 → Early

Cancer Free: AFP Module and Update Module (P_3, P_4)

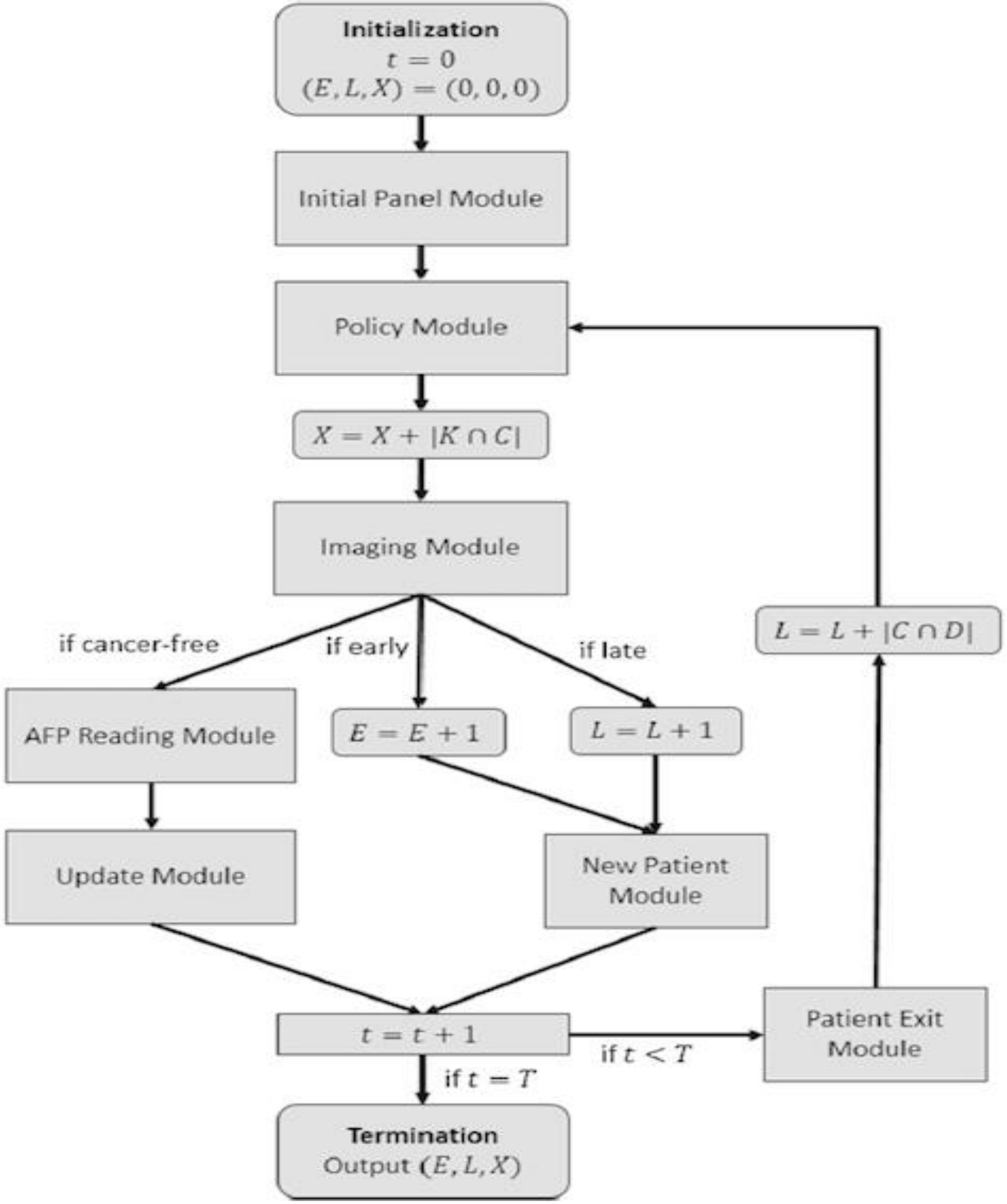
Pid	c1Bi	AFP	SS	RR	Sbar at tbar	t
3	-2.7	81	0	0	sbar	0
3	-2.7	200	84	119	sbar	1
3	-2.7	100	64	-100	sbar	2

Early: E and New Patient Module (P_1)

- P_1 → Early → E = 0 + 1 = 1
- Replace P_1

Pid	c1Bi	AFP	SS	RR	Sbar at tbar	t
new	-2	99	0	0	sbar	0

- Advance to **t+1**

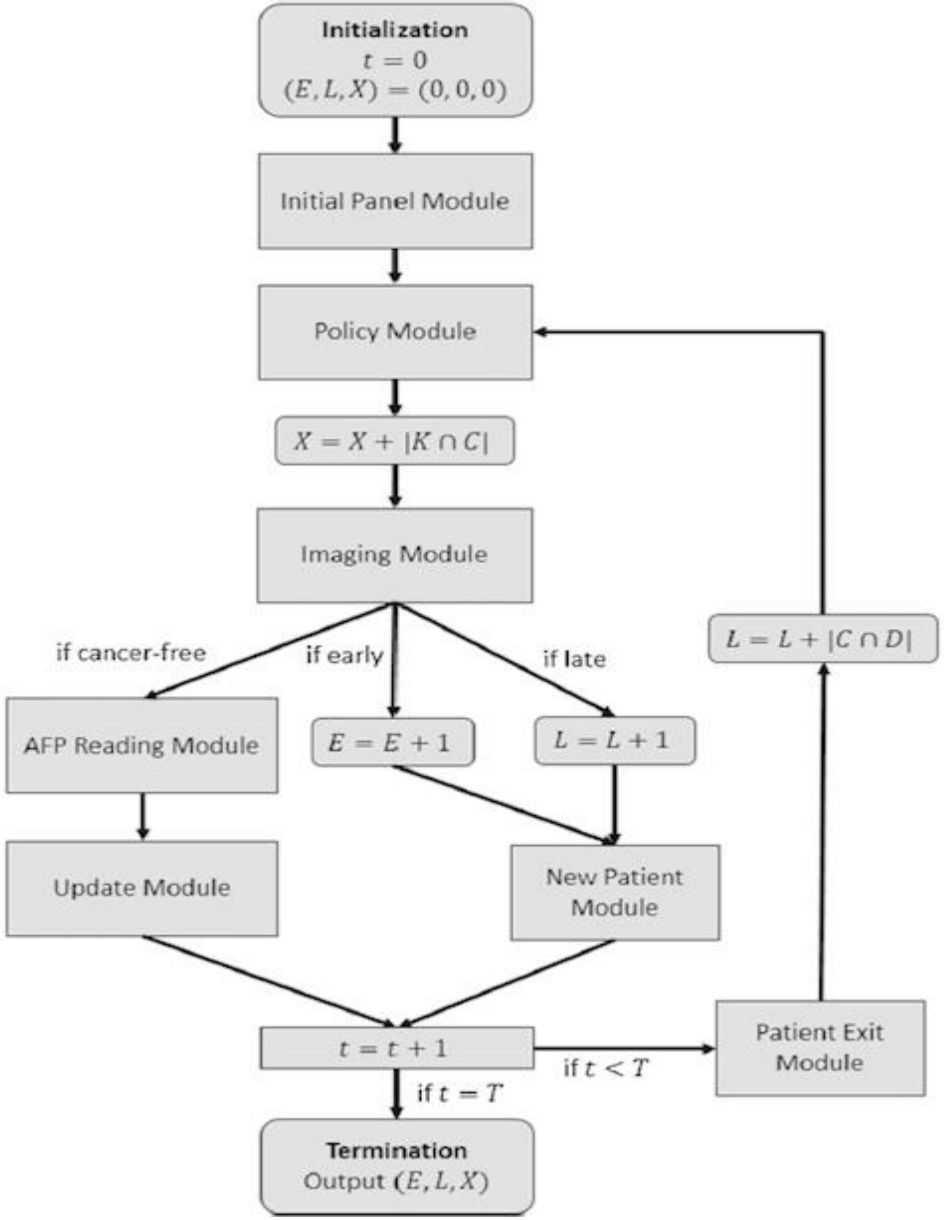


Time $t = 2$

$T = 4$

Patient Exit Module (t=2)

- D = departing patients (subset of K)
  - Time t >= T, or death, or voluntary withdrawal
  - Patients in D eliminated and replaced
- All patients D^C increment L by 1
  - D = 0
  - D^C = 0
  - L = L + |C^D|



List of N Patients (t=2)

HCC (3)

Pid	c1Bi	AFP	SS	RR	s	t
1	-1.13	95	0	0	8	0
1	-1.13	200	74	105	8	1

Pid	c1Bi	AFP	SS	RR	s	t
new	-2	99	0	0	3	0

Pid	c1Bi	AFP	SS	RR	s	t
2	-18.6	88	0	0	8	0

Pid	c1Bi	AFP	SS	RR	s	t
3	-2.7	81	0	0	8	0
3	-2.7	200	84	119	8	1

Non HCC (9)

Pid	c1Bi	AFP	SS	RR	s	t
4	-0.47	94	0	0	0	0
4	-0.47	96	1.4	2	0	1

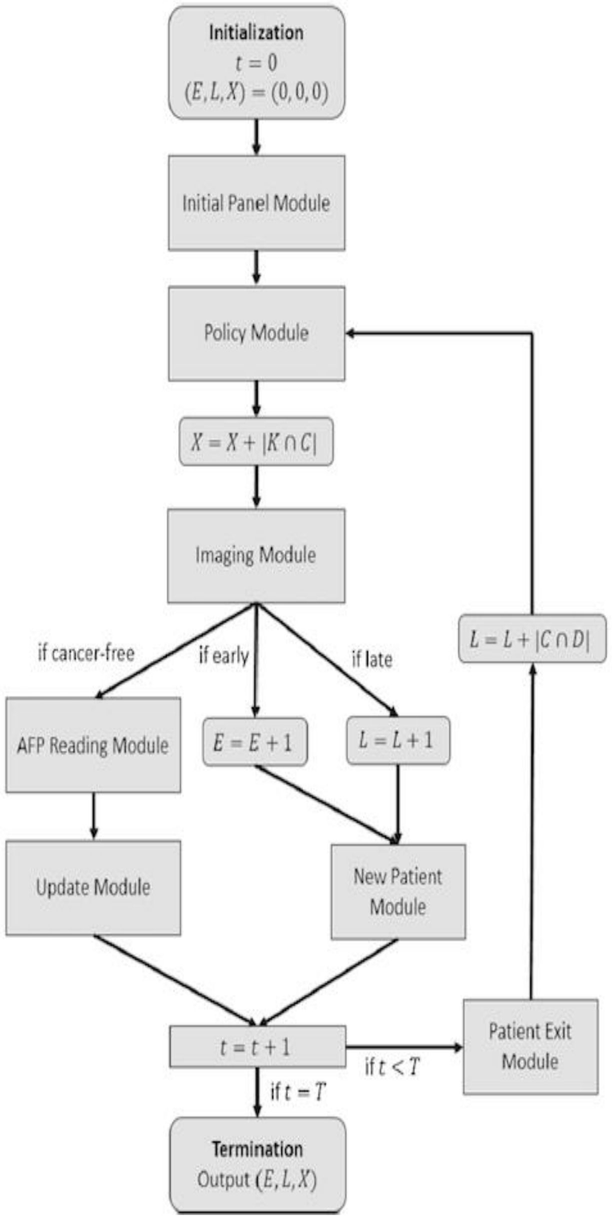
Pid	ciBi	AFP	SS	RR	s	t
5	c1B5	82	0	0	0	0

Pid	c1Bi	AFP	SS	RR	s	t
6	c1B6	82	0	0	0	0

Pid	c1Bi	AFP	SS	RR	s	t
7	c1B7	89	0	0	0	0

Pid	c1Bi	AFP	SS	RR	s	t
8	c1B8	89	0	0	0	0

Pid	c1Bi	AFP	SS	RR	s	t
9	c1B9	89	0	0	0	0



$C = \{\cancel{P_1}, P_2, P_3, P_{new}\}$

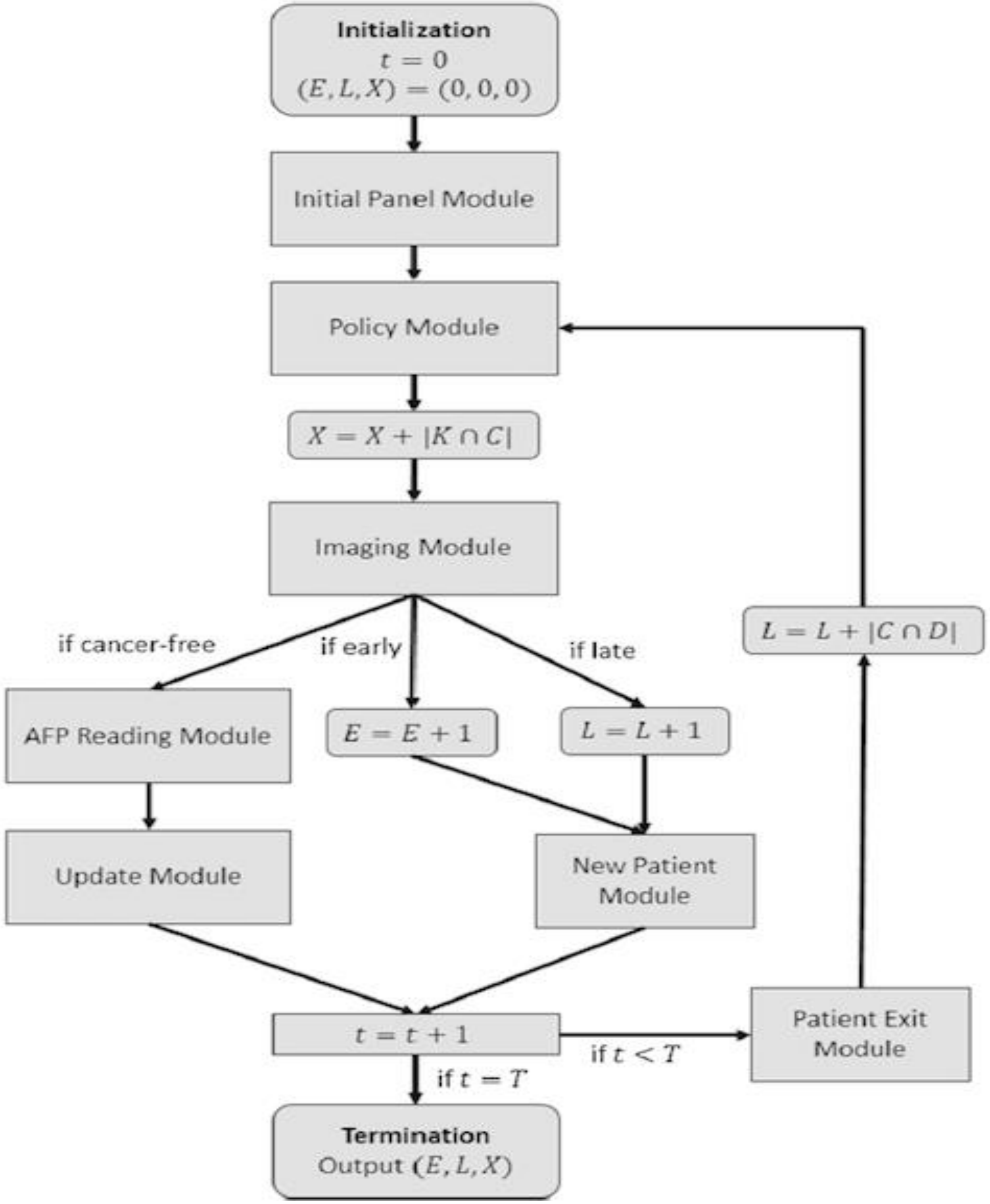
$D = \{P_4, P_5, P_6, P_7, P_8, P_9, P_{10}, P_{11}, P_{12}\}$

Policy Module (t=2)

- Calculate P(HCC) & Rank. Then choose k=3 out of N=12
- P_3=0.67> P_4 = 0.55 > P_{new}=0.50 > P_1 = 0.3 > P_8 = 0.3 > …

- X = X + |K ^ C|
  - X = 2
  - K = {P_1, P_4, P_3}
  - C = {P_1, P_2, P_3}
  - |K ^ C| = 4
- X =2 + 4 = 6

- X is the number of screening spent on patients who would eventually develop cancer



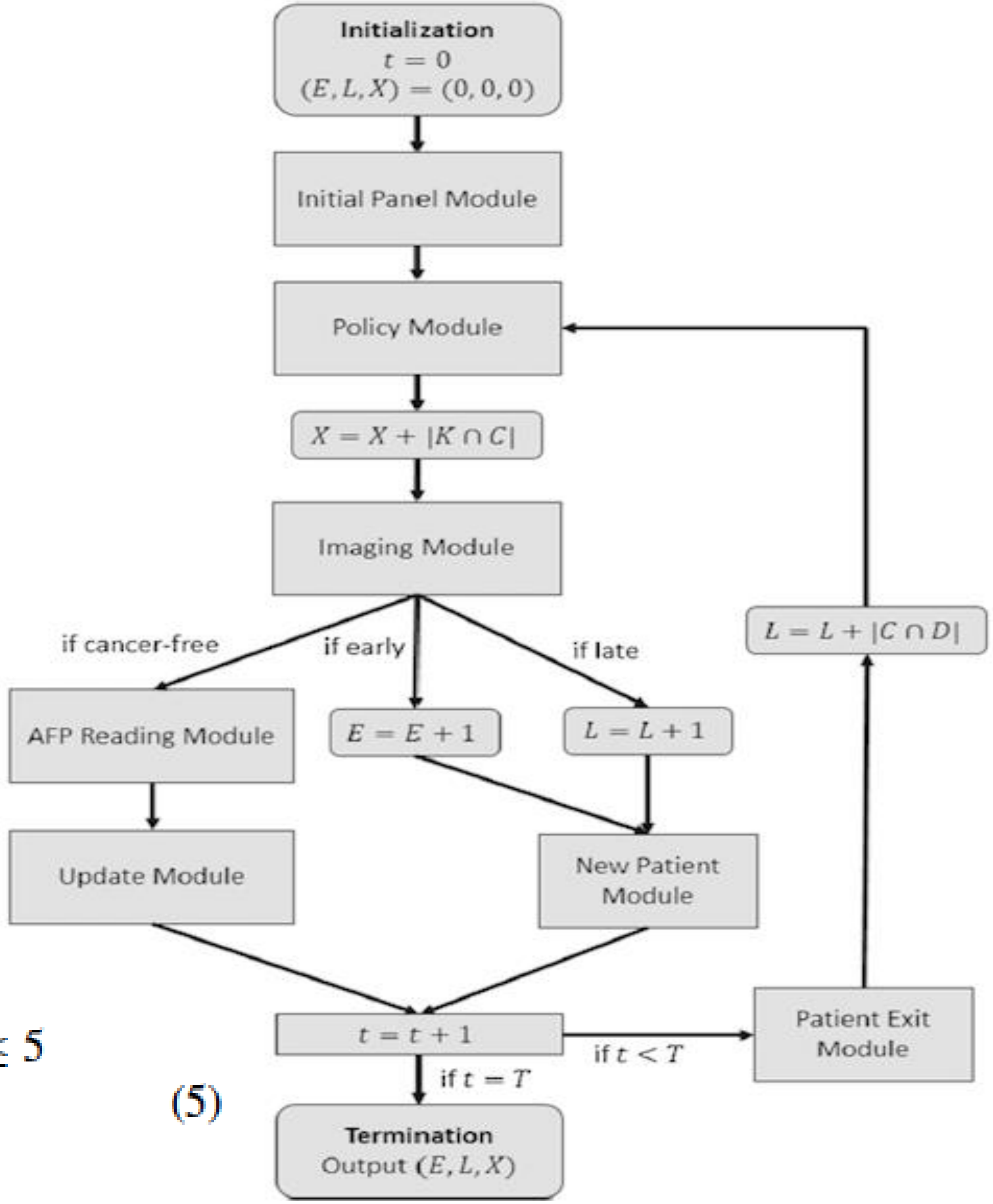
Imaging Module (t=2)

- P_3, P_{new}, P_4

  - P_3 → belongs to C
    - Estimated tumor s = 0.4
    - **Cancer Free**

  - P_{new} → belongs to C
    - Estimate tumor s = 2
    - **Early**

  - P_4 → belongs to N
    - **Cancer Free**



$$\text{State} = \begin{cases} \text{Early} & \text{if } t \geq \bar{t} \text{ and } 1 \leq s \leq 5 \\ \text{Late} & \text{if } t \geq \bar{t} \text{ and } 5 < s \\ \text{Cancer-Free} & \text{if Otherwise} \end{cases} \qquad (5)$$

Note: $s = 2^{\frac{t-\bar{t}}{\delta}} \cdot \bar{s}$

Imaging Module Output (t=2)

P_3, P_4 → Cancer Free; P_{new} → Early

Cancer Free: AFP Module and Update Module (P_3, P_4)

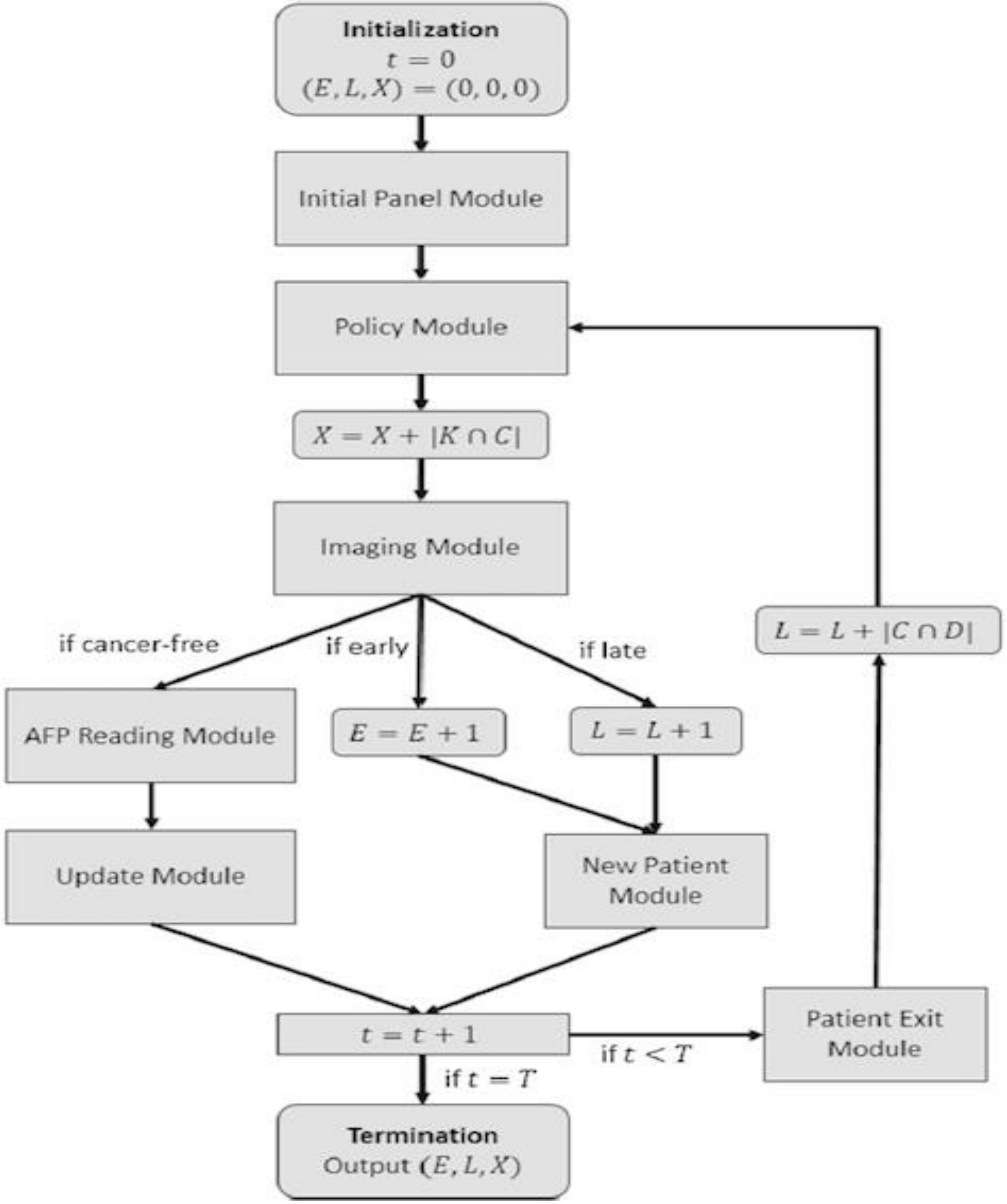
Pid	c1Bi	AFP	SS	RR	Sbar at tbar =y	t
3	-2.7	81	0	0	x	0
3	-2.7	200	84	119	x	1
3	-2.7	100	64	-100	x	2
3	-2.7	120	52	20	x	3

Early: E and New Patient Module (P_1)

- P_1 → Early → E = 0 + 1 = 1
- Replace P_1

Pid	c1Bi	AFP	SS	RR	Sbar at tbar = 1	t
New_2	-2	99	0	0	3	0

- Advance to **t+1**



Time $t = 3$

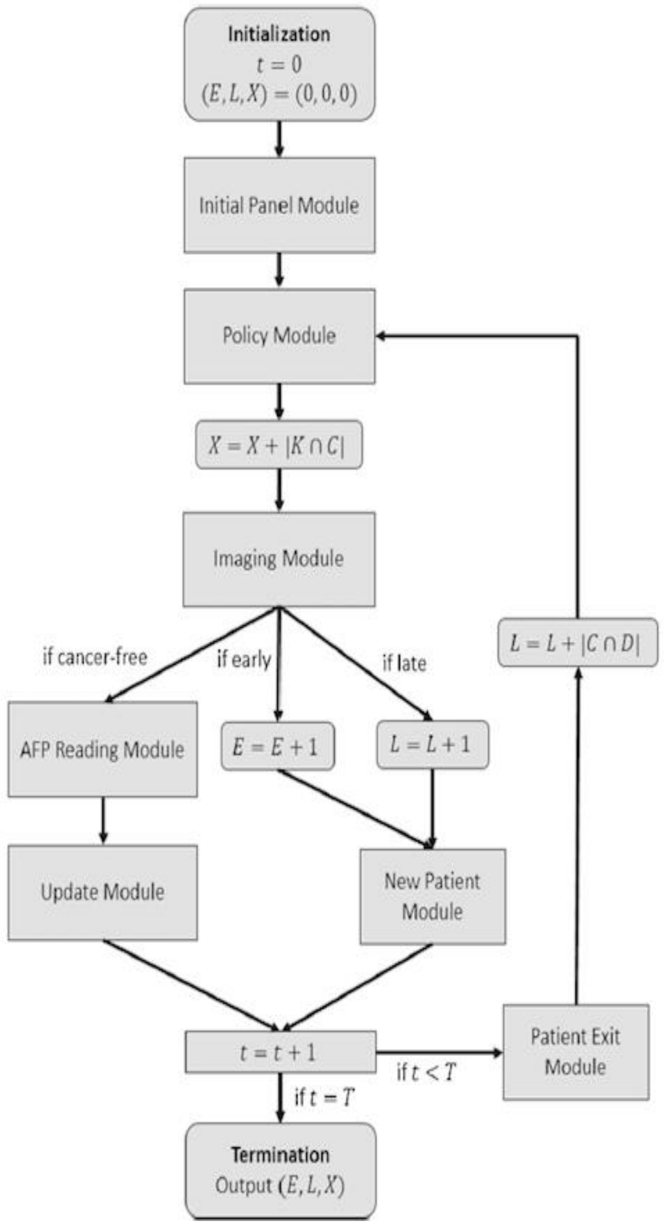
$T = 4$

Patient Exit Module (t=3)

If t < T (2 < 3):

- D = departing patients (subset of K)
  - Time t >= T, or death, or voluntary withdrawal
  - Patients in D eliminated and replaced
- P_3: (t = 3) = (T=3)
  - Patient P_3 → eliminated and replaced
- All patients D^C increment L by 1
  - D = {P_3}
  - C = {$P_{1,}$ P_3, P_{new}}
  - D^C = 1
  - L = L + |C^D|
  - **L = 0+1 = 1**

Pid	c1Bi	AFP	SS	RR	Sbar at tbar =y	t
3	-2.7	81	0	0	sbar	0
3	-2.7	200	84	119	sbar	1
3	-2.7	100	64	-100	sbar	2
3	-2.7	120	52	20	sbar	3



List of N Patients (t=3)

HCC (3)

Pid	c1Bi	AFP	SS	RR	s	t
new	-2	99	0	0	3	0

REPLACE

Pid	c1Bi	AFP	SS	RR	s	t
2	-18.6	88	0	0	8	0

Pid	c1Bi	AFP	SS	RR	s	t
3	-2.7	81	0	0	8	0
3	-2.7	200	84	119	8	1

REPLACE

$C = \{\cancel{P_1}, P_2, P_3, P_{new\_2}\}$

$D = \{P_4, P_5, P_6, P_7, P_8, P_9, P_{10}, P_{11}, P_{12}\}$

Non HCC (9)

Pid	c1Bi	AFP	SS	RR	s	t
4	-0.47	94	0	0	0	0
4	-0.47	96	1.4	2	0	1

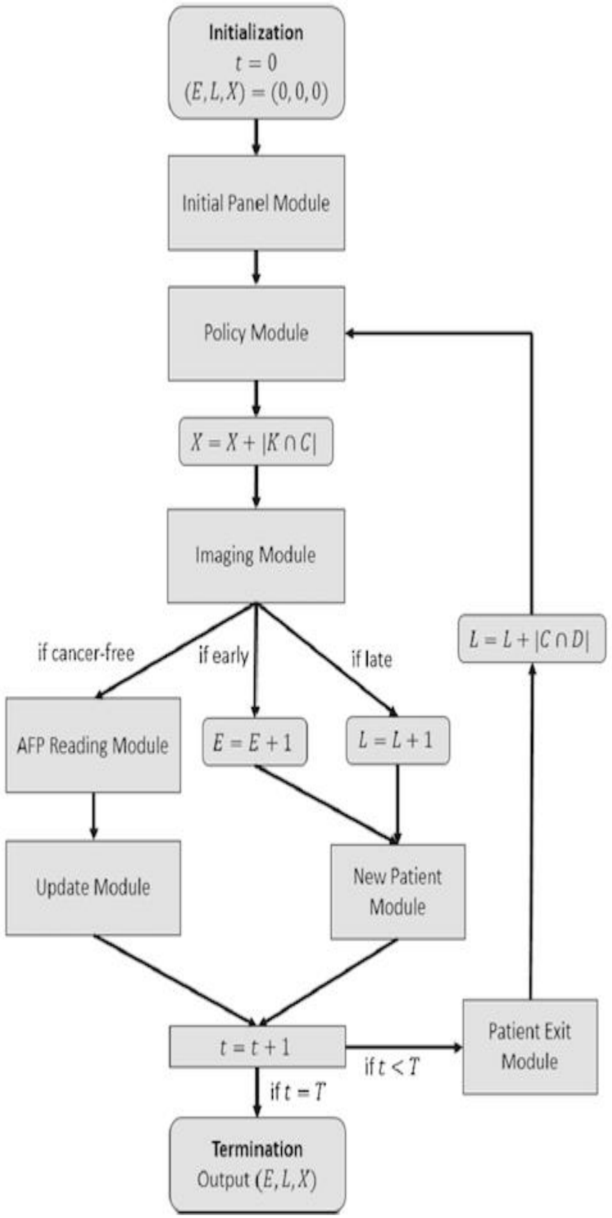
Pid	ciBi	AFP	SS	RR	s	t
5	c1B5	82	0	0	0	0

Pid	c1Bi	AFP	SS	RR	s	t
6	c1B6	82	0	0	0	0

Pid	c1Bi	AFP	SS	RR	s	t
7	c1B7	89	0	0	0	0

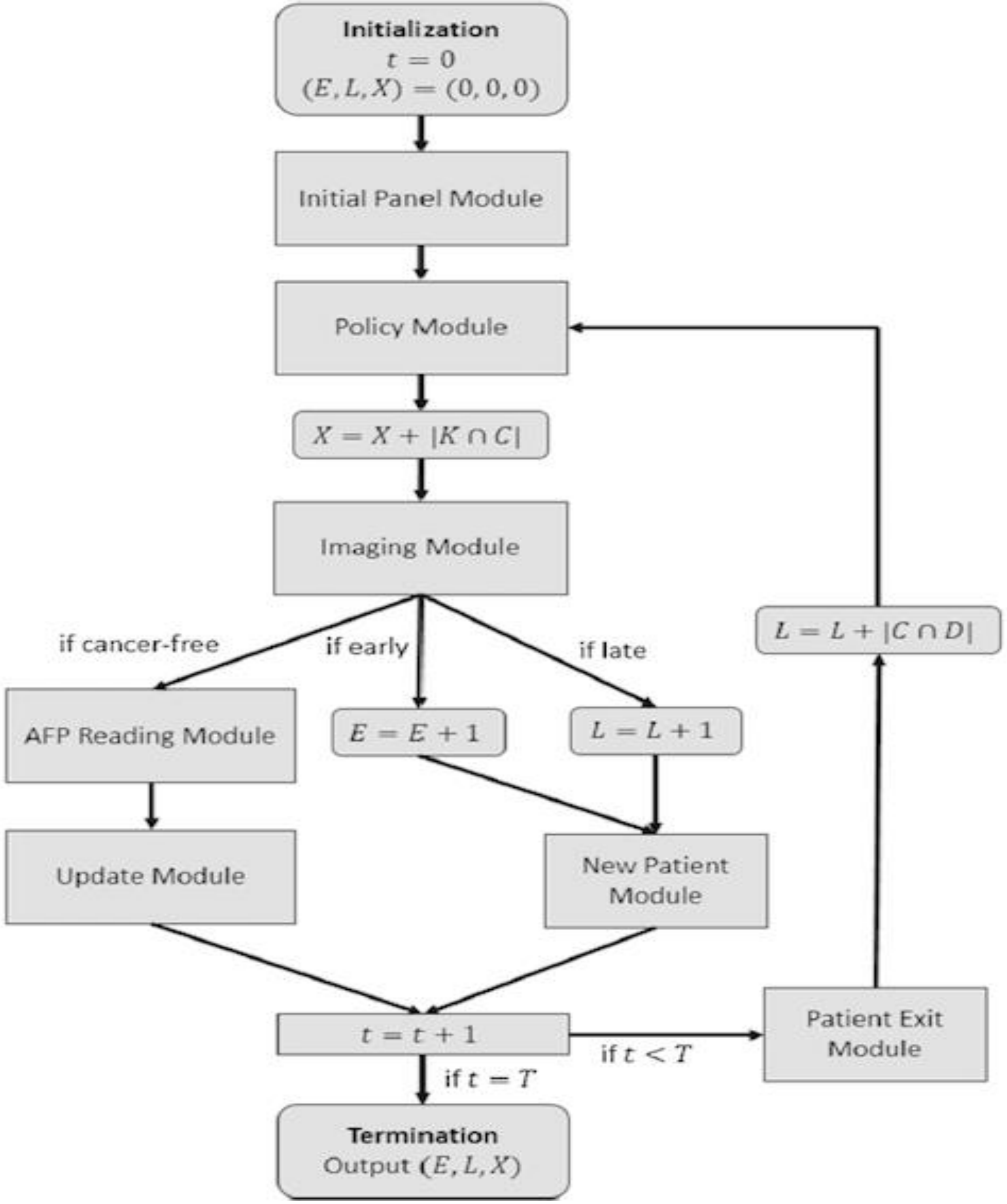
Pid	c1Bi	AFP	SS	RR	s	t
8	c1B8	89	0	0	0	0

Pid	c1Bi	AFP	SS	RR	s	t
9	c1B9	89	0	0	0	0



Run t=3

- Say we run Policy Module again, all of the selected are cancer-free
  - X will not change: X = 6
- We run the Imaging Module
  - They go to cancer-free subset, AFP and Update Module are run.
  - E will not change: E = 1
  - L will not change: L = 1
- Then we arrive at t = t + 1 = 4
- (t=4) = (T=4) → Termination



Time $t = 4$

$(t=4) = (T=4)$

Termination

Termination

At Termination, we output:

- **E = 1**
- **X = 6**
- **L = 1**

Performance measures:

1. The proportion of cancers detected in early stage $\frac{E}{E+L}$
2. The proportion of resources spent on patients who eventually develop cancer $\frac{X}{K \times T}$

1. 1/(1+1) = 0.5
2. 6/(3*4) = 0.5