Pr(You Are a Bayesian) > 0.50

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A Problem of Inference

A Problem of Inference

10,000 Coins

9,999 Fair Coins (H/T)
1 Biased Coin (H/H)

Problem

1. I draw out one coin.
2. I will flip it repeatedly, and tell you the result.
3. You tell me when you decide whether I have the Biased Coin or not.

The Results

Number of Flips	Result	Biased Coin?

The Results

Number of Flips	Result	Biased Coin?
1	H	Y or N

The Results

Number of Flips	Result	Biased Coin?
1	H	Y or N
2	H	Y or N

The Results

Number of Flips	Result	Biased Coin?
1	H	Y or N
2	H	Y or N
3	H	Y or N

The Results

Number of Flips	Result	Biased Coin?
1	H	Y or N
2	H	Y or N
3	H	Y or N
4	H	Y or N

The Results

Number of Flips	Result	Biased Coin?
1	H	Y or N
2	H	Y or N
3	H	Y or N
4	H	Y or N
5	H	Y or N

The Results

Number of Flips	Result	Biased Coin?
1	H	Y or N
2	H	Y or N
3	H	Y or N
4	H	Y or N
5	H	Y or N
6	H	Y or N

The Results

Number of Flips	Result	Biased Coin?
1	H	Y or N
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5	H	Y or N
6	H	Y or N
7	H	Y or N

The Results

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The Results

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The Results

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The Results

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8	H	Y or N
9	H	Y or N
10	H	Y or N

Number of Flips	Result	Biased Coin?
11	H	Y or N

The Results

Number of Flips	Result	Biased Coin?
1	H	Y or N
2	H	Y or N
3	H	Y or N
4	H	Y or N
5	H	Y or N
6	H	Y or N
7	H	Y or N
8	H	Y or N
9	H	Y or N
10	H	Y or N

Number of Flips	Result	Biased Coin?
11	H	Y or N
12	H	Y or N

The Results

Number of Flips	Result	Biased Coin?
1	H	Y or N
2	H	Y or N
3	H	Y or N
4	H	Y or N
5	H	Y or N
6	H	Y or N
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Number of Flips	Result	Biased Coin?
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The Results

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Number of Flips	Result	Biased Coin?
11	H	Y or N
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14	H	Y or N

The Results

Number of Flips	Result	Biased Coin?
1	H	Y or N
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The Results

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16	H	Y or N

The Results

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The Results

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17	H	Y or N
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The Results

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18	H	Y or N
19	H	Y or N

The Results

Number of Flips	Result	Biased Coin?
1	H	Y or N
2	H	Y or N
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7	H	Y or N
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10	H	Y or N

Number of Flips	Result	Biased Coin?
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13	H	Y or N
14	H	Y or N
15	H	Y or N
16	H	Y or N
17	H	Y or N
18	H	Y or N
19	H	Y or N
20	H	Y or N

Two Perspectives

1. What is the probability of seeing N consecutive heads **IF** I have a fair coin?

2. What is the probability that I selected the biased coin **IF** I observe N consecutive heads from a coin randomly drawn from a bag of 9,999 fair coins and 1 biased coin?

Two Perspectives

1. **Pr (observed data | coin is fair)**

H_0: Coin is fair [i.e. pr(heads) = 0.50]

H_a: Coin is not fair [i.e. pr(heads) = 1.00]

Pr[N consecutive heads | fair coin] = $(0.50)^N$

Two Perspectives

1. **Pr (observed data | coin is fair)**

H_0: Coin is fair [i.e. pr(heads) = 0.50]
H_a: Coin is not fair [i.e. pr(heads) = 1.00]

Pr[N consecutive heads | fair coin] = $(0.50)^N$

Better known as the *p-value*

Frequentist perspective

Frequentist Results

Number of Flips	Result	p-value
1	H	0.500000000
2	H	0.250000000
3	H	0.125000000
4	H	0.062500000
5	H	0.031250000
6	H	0.015625000
7	H	0.007812500
8	H	0.003906250
9	H	0.001953125
10	H	0.000976563

Number of Flips	Result	p-value
11	H	0.000488281
12	H	0.000244141
13	H	0.000122070
14	H	0.000061035
15	H	0.000030518
16	H	0.000015259
17	H	0.000007629
18	H	0.000003815
19	H	0.000001907
20	H	0.000000954

Frequentist Results

Number of Flips	Result	p-value
1	H	0.500000000
2	H	0.250000000
3	H	0.125000000
4	H	0.062500000
5	H	0.031250000
6	H	0.015625000
7	H	0.007812500
8	H	0.003906250
9	H	0.001953125
10	H	0.000976563

Number of Flips	Result	p-value
11	H	0.000488281
12	H	0.000244141
13	H	0.000122070
14	H	0.000061035
15	H	0.000030518
16	H	0.000015259
17	H	0.000007629
18	H	0.000003815
19	H	0.000001907
20	H	0.000000954

Two Perspectives

2. **Pr (coin is biased | observed data)**

If we have $\boldsymbol{Pr}(\boldsymbol{A}|\boldsymbol{B})$,
we want to obtain the conditional probability $\boldsymbol{Pr}(\boldsymbol{B}|\boldsymbol{A})$

Bayes Theorem (1763)*

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

$$P(A|B) = \frac{P(B|A)P(A)}{P(B|A)P(A) + P(B|A^c)P(A^c)}$$

*As formulated by Laplace (1812)

Bayesian Results

Number of Flips	Result	Pr(Biased Coin)
1	H	0.000200
2	H	
3	H	
4	H	
5	H	
6	H	
7	H	
8	H	
9	H	
10	H	

Number of Flips	Result	Pr(Biased Coin)
11	H	
12	H	
13	H	
14	H	
15	H	
16	H	
17	H	
18	H	
19	H	
20	H	

Bayesian Results

Number of Flips	Result	Pr(Biased Coin)
1	H	0.000200
2	H	0.000400
3	H	
4	H	
5	H	
6	H	
7	H	
8	H	
9	H	
10	H	

Number of Flips	Result	Pr(Biased Coin)
11	H	
12	H	
13	H	
14	H	
15	H	
16	H	
17	H	
18	H	
19	H	
20	H	

Bayesian Results

Number of Flips	Result	Pr(Biased Coin)
1	H	0.000200
2	H	0.000400
3	H	0.000799
4	H	0.001598
5	H	0.003190
6	H	0.006360
7	H	0.012639
8	H	0.024968
9	H	0.048711
10	H	0.092897

Number of Flips	Result	Pr(Biased Coin)
11	H	0.170001
12	H	0.290600
13	H	0.450333
14	H	0.621006
15	H	0.766198
16	H	0.867624
17	H	0.929121
18	H	0.963258
19	H	0.981285
20	H	0.990554

A Problem of Inference

100 Coins

99 Fair Coins (H/T)
1 Biased Coin (H/H)

Problem

1. I draw out one coin.
2. I will flip it repeatedly, and tell you the result.
3. You tell me when you decide whether I have the Biased Coin or not.

The Results

Number of Flips	Prior = 1/10,000 Pr(Biased Coin)	Prior = 1/100 Pr(Biased Coin)
1	0.000200	0.019802
2	0.000400	0.038835
3	0.000799	0.074766
4	0.001598	0.139130
5	0.003190	0.244275
6	0.006360	0.392638
7	0.012639	0.563877
8	0.024963	0.721127
9	0.048711	0.837971
10	0.092897	0.911843

Number of Flips	Prior = 1/10,000 Pr(Biased Coin)	Prior = 1/100 Pr(Biased Coin)
11	0.170001	0.953889
12	0.290600	0.976400
13	0.450333	0.988059
14	0.621006	0.993994
15	0.766198	0.996988
16	0.867624	0.998492
17	0.929121	0.999245
18	0.963258	0.999622
19	0.981285	0.999811
20	0.990554	0.999906

The Results

# of Flips	p-value	Prior = 1/10,000 Pr(Biased Coin)	Prior = 1/100 Pr(Biased Coin)
1	0.500000	0.000200	0.019802
2	0.250000	0.000400	0.038835
3	0.125000	0.000799	0.074766
4	0.062500	0.001598	0.139130
5	0.031250	0.003190	0.244275
6	0.015625	0.006360	0.392638
7	0.0078125	0.012639	0.563877
8	0.0039063	0.024963	0.721127
9	0.0019531	0.048711	0.837971
10	0.0009766	0.092897	0.911843

# of Flips	p-value	Prior = 1/10,000 Pr(Biased Coin)	Prior = 1/100 Pr(Biased Coin)
11	0.0004882	0.170001	0.953889
12	0.0002441	0.290600	0.976400
13	0.0001220	0.450333	0.988059
14	0.0000610	0.621006	0.993994
15	0.0000305	0.766198	0.996988
16	0.0000153	0.867624	0.998492
17	0.0000076	0.929121	0.999245
18	0.0000038	0.963258	0.999622
19	0.0000019	0.981285	0.999811
20	0.0000010	0.990554	0.999906

The Results

# of Flips	p-value	Prior = 1/10,000 Pr(Biased Coin)	Prior = 1/100 Pr(Biased Coin)
1	0.500000	0.000200	0.019802
2	0.250000	[illegible]	[illegible]
3	0.125000	[illegible]	[illegible]
4	0.062500	[illegible]	[illegible]
5	0.031250	[illegible]	[illegible]
6	0.015625	[illegible]	[illegible]
7	0.0078125	[illegible]	[illegible]
8	0.0039063	[illegible]	[illegible]
9	0.0019531	0.048711	0.837971
10	0.0009766	0.092897	0.911843

# of Flips	p-value	Prior = 1/10,000 Pr(Biased Coin)	Prior = 1/100 Pr(Biased Coin)
11	0.0004882	0.170001	0.953889
[illegible]	[illegible]	[illegible]600	0.976400
[illegible]	[illegible]	[illegible]333	0.988059
[illegible]	[illegible]	[illegible]006	0.993994
[illegible]	[illegible]	[illegible]198	0.996988
[illegible]	[illegible]	[illegible]624	0.998492
[illegible]	[illegible]	[illegible]121	0.999245
[illegible]	[illegible]	[illegible]258	0.999622
19	0.0000019	0.981285	0.999811
20	0.0000010	0.990554	0.999906

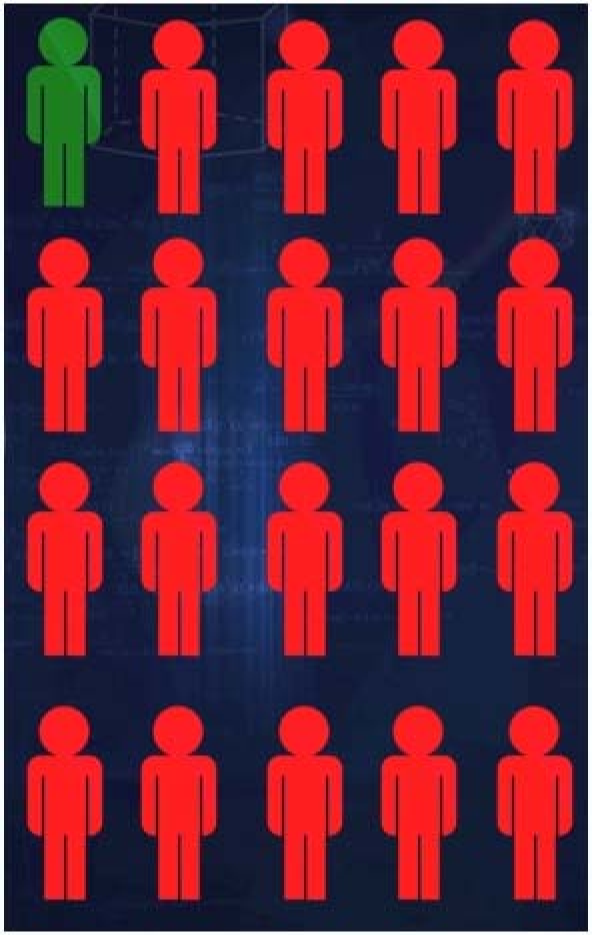
Note: The p-value never changes regardless of your prior knowledge!!!!

Summary

- ✓ **Bayesian perspective makes inference directly about the question of interest**

A Problem of Prediction

A Problem of Prediction



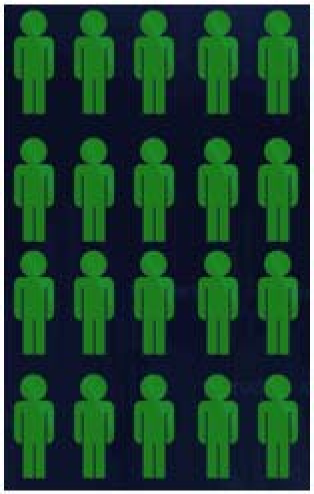
5% of Population have ALK gene

A Problem of Prediction

Diagnostic Kit

A Problem of Prediction

Patients

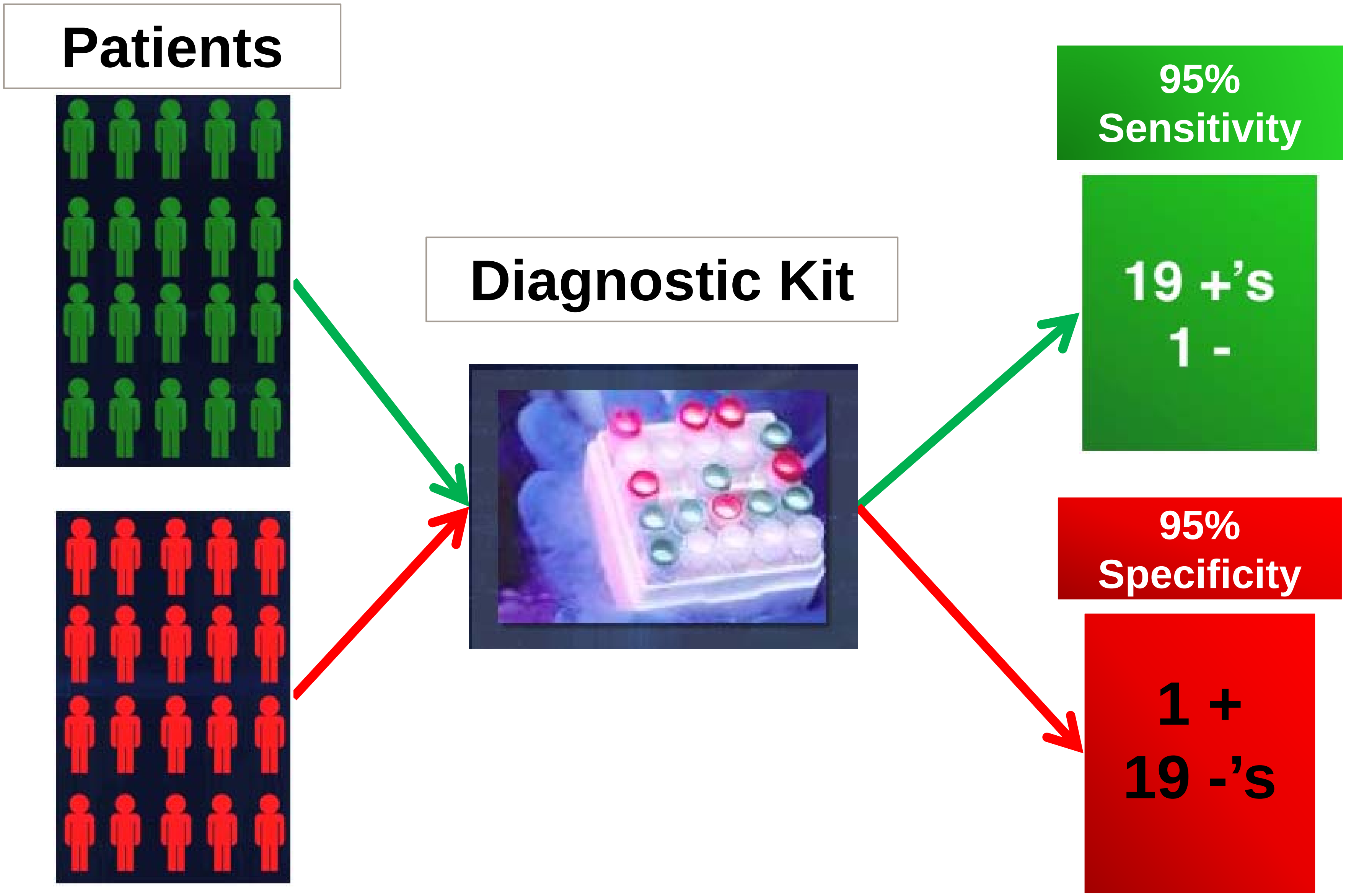


Diagnostic Kit

95% Sensitivity

19 +'s
1 -

A Problem of Prediction



A Problem of Prediction

Individual Patient

ALK(-)?

ALK(+)?

A Problem of Prediction

Individual Patient

ALK(-)?

ALK(+)?

Sample

Diagnostic Kit

A Problem of Prediction

Individual Patient

ALK(-)?

ALK(+)?

Sample

Diagnostic Kit

Result

+

A Problem of Prediction

Individual Patient

ALK(-)?

ALK(+)?

Sample →

Diagnostic Kit

Result → **+**

Pr(Patient is ALK+) = ?

Diagnostic Decision-Making

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Patient Characteristic</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Diagnostic Test</td><td>Positive</td><td></td><td></td></tr>
<tr><td>Negative</td><td></td><td></td></tr>
</table>

Diagnostic Decision-Making

		Patient Characteristic	
		Positive	**Negative**
Diagnostic Test	**Positive**	True Positive 95% (Sensitivity)	False Positive 5%
	Negative	False Negative 5%	True Negative 95% (Specificity)

Diagnostic Decision-Making

Developing/Designing the "Assay"

Conditional Probability

		Patient Characteristic	
		Positive	**Negative**
Diagnostic Test	**Positive**	True Positive 95% (Sensitivity)	False Positive 5%
	Negative	False Negative 5%	True Negative 95% (Specificity)

Prob (diagnostic test is positive IF the patient has the characteristic)

Diagnostic Decision-Making

Interpreting an Observed Result

		Patient Characteristic (Unknown Truth) Positive	*Patient Characteristic (Unknown Truth)* Negative	Conditional Probability
Diagnostic Test	Positive	True Positive 95%	False Positive 5%	Positive Predictive Value
Diagnostic Test	Negative	False Negative 5%	True Negative 95%	Negative Predictive Value

Prob (patient has the characteristic IF the diagnostic test is positive)

Diagnostic Decision-Making

Underlying Prevalence for ALK gene is 5%

		Have the ALK Gene		
		Positive (5%)	Negative (95%)	
Diagnostic Test	Positive	True Positive 95%	False Positive 5%	Positive Predictive Value
	Negative	False Negative 5%	True Negative 95%	Negative Predictive Value

Diagnostic Decision-Making

Underlying Prevalence for ALK gene is 5%

		Have the ALK Gene		
		Positive (5%)	Negative (95%)	
Diagnostic Test	Positive	True Positive 95%	False Positive 5%	Positive Predictive Value
	Negative	False Negative 5%	True Negative 95%	Negative Predictive Value
		100	**1900**	**2000**

Diagnostic Decision-Making

Underlying Prevalence for ALK gene is 5%

		Have the ALK Gene		
		Positive (5%)	Negative (95%)	
Diagnostic Test	Positive	95 True Positive 95%	95 False Positive 5%	Positive Predictive Value
	Negative	5 False Negative 5%	1805 True Negative 95%	Negative Predictive Value
		100	1900	2000

Diagnostic Decision-Making

Underlying Prevalence for ALK gene is 5%

		Have the ALK Gene		
		Positive (5%)	**Negative (95%)**	
Diagnostic Test	**Positive**	**95** True Positive 95%	**95** False Positive 5%	**50%** Positive Predictive Value
	Negative	**5** False Negative 5%	**1805** True Negative 95%	**99.7%** Negative Predictive Value
		100	**1900**	**2000**

Diagnostic Decision-Making

Underlying Prevalence for gene XYZ is 50%

		Have the XYZ Gene		
		Positive (50%)	Negative (50%)	
Diagnostic Test	Positive	True Positive 95%	False Positive 5%	Positive Predictive Value
	Negative	False Negative 5%	True Negative 95%	Negative Predictive Value

Diagnostic Decision-Making

Underlying Prevalence for gene XYZ is 50%

		Have the XYZ Gene		
		Positive (50%)	**Negative (50%)**	
Diagnostic Test	**Positive**	**950**	**50**	**95%**
	Negative	**50**	**950**	**95%**
		1000	**1000**	**2000**

Diagnostic Decision-Making

KEY MESSAGES

- Sensitivity and Specificity are the focus of ***assay design and development***
- The **Positive (Negative) Predictive Values** are the focus of ***interpreting results*** (assay outputs)
- **THE PPV (NPV) ARE DEPENDENT ON THE UNDERLYING PREVALENCE OF THE CHARACTERISTIC (e.g. disease/marker status)**

The Clinical Trial Analogy

- The diagnostic test is the clinical trial
- The patient characteristic is whether the treatment meets its Critical Success Factors (unknown truth)
- Sensitivity and (1-Specificity) are analogous to “power” and “significance level” of the hypothesis test
- The PPV (NPV) is analogous to the “Bayesian posterior probability” that the treatment meets (fails) the CSF
- **THE PPV (NPV) ARE DEPENDENT ON THE PRIOR PROBABILITY OF THE TREATMENT MEETING THE CSF**

The Clinical Trial Analogy

Entering Ph 2 ⇒ Pr(drug meets CSFs) = 20%

	Unknown →	***Meets CSFs***		
		Yes (20%)	**No (80%)**	
CT Result	**Positive**			Positive Predictive Value
	Negative			Negative Predictive Value

The Clinical Trial Analogy

Entering Ph 2 ⇒ Pr(drug meets CSFs) = 20%

Unknown →

Moderately Rigorous Ph 2 Trial Design

		Meets CSFs: Yes (20%)	*Meets CSFs*: No (80%)	
CT Result	Positive	True Positive 80% ("Power" for a Ph 2 Trial)	False Positive 10% ("Significance Level" for Ph 2)	Positive Predictive Value
CT Result	Negative	False Negative 20%	True Negative 90%	Negative Predictive Value

The Clinical Trial Analogy

Entering Ph 2 ⇒ Pr(drug meets CSFs) = 20%

Moderately Rigorous Ph 2 Trial Design

		Unknown → *Meets CSFs* Yes (20%)	No (80%)	
CT Result (Observed ↑)	Positive	320	160	66.7%
	Negative	80	1440	94.7%
		400	1600	2000

The Clinical Trial Analogy

Entering Ph 2 ⇒ Pr(drug meets CSFs) = 20%

"Prior"

Moderately Rigorous Ph 2 Trial Design

Unknown →

		Meets CSFs: Yes (20%)	*Meets CSFs*: No (80%)	
CT Result	Positive	True Positive 80% 320	False Positive 10% 160	66.7%
CT Result	Negative	80	1440	94.7%
		400	1600	2000

"Posterior"

↑ Observed

Summary

✓Bayesian posterior probabilities should be used to interpret trial outcomes (i.e. used predict the likelihood of events)

A Problem of Evidence

Bayes Factor*

Let p_0 = prior probability that H_0 is false

(i.e. the drug works)

Bayes Factor*

Let p_0 = prior probability that H_0 is false
(i.e. the drug works)

Let p = observed p-value for test statistics for H_0

Bayes Factor*

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(i.e. the drug works)

Let p = observed p-value for test statistics for H_0

Bayes factor* **[$-e \times p \times \ln(p)$]** used to compute upper bound on posterior probability that H_0 is false

*Sellke et al (2001) Calibration of p Values for Testing Precise Null Hypotheses. The American Statistician, February 2001, Vol. 55, No. 1, pp 62-71.

Bayes Factor*

Let p_0 = prior probability that H_0 is false

(i.e. the drug works)

Let p = observed p-value for test statistics for H_0

Bayes factor* **[-e × p × ln(p)]** used to compute upper bound on posterior probability that H_0 is false

Posterior probability** for H_0 being false is

$$\mathbf{p_1 \leq \{1 + [(1-p_0)/p_0] \times [-e \times p \times \ln(p)]\}^{-1}}$$

***Sellke et al (2001) Calibration of p Values for Testing Precise Null Hypotheses. The American Statistician, February 2001, Vol. 55, No. 1, pp 62-71.**

**If $p < 1/e = .368$

Bayes Factor*

Let p_0 = prior probability that H_0 is false

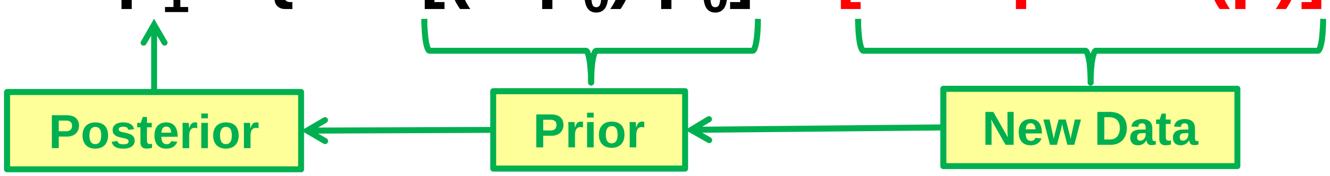
(i.e. the drug works)

Let p = observed p-value for test statistics for H_0

Bayes factor* $[-e \times p \times \ln(p)]$ used to compute upper bound on posterior probability that H_0 is false

Posterior probability** for H_0 being false is

$$p_1 \leq \{1 + [(1-p_0)/p_0] \times [-e \times p \times \ln(p)]\}^{-1}$$



*Sellke et al (2001) Calibration of p Values for Testing Precise Null Hypotheses. The American Statistician, February 2001, Vol. 55, No. 1, pp 62-71.

**If $p < 1/e = .368$

Bayes Factor

- If your prior is 30% probability of success (i.e. H_0 being false) entering Phase 2 …

Observed Phase 2 p-Value	Upper Bound on Posterior Probability for H_0 Being False*
0.20	.329
0.10	.406
0.05	.513
0.01	.774

***Using Bayes factor for converting p-values into posterior probabilities**

Bayes Factor

- ♦ If your prior is 30% probability of success (H_0 being false) entering Phase 2 …
- ♦ And you want to exit Phase 2 with an 70% probability of success …
- ♦ Then you need* …
  - 1 study with a p-value of 0.016
  - 2 studies each with p-values of 0.05**

***Using Bayes factor for converting p-values into posterior probabilities**
****Successive application of Bayes factor**

FDA Approval

- Suppose FDA wants to be 95% sure that H_0 is false
- Substantial evidence
  - **Consider one-tailed p-values < 0.025 for two Ph 3 CT**

Prior Probability Against H_0 Entering Phase 3	Posterior Probability for H_0 Being False with Two p-values of 0.025 (≤)
0.50	.941
0.60	.960
0.70	.974

FDA Approval

- Suppose FDA wants to be 95% sure that H_0 is false
- Substantial evidence
  - **What p-value is needed for a single Ph 3 CT?**

Prior Probability Against H_0 Entering Phase 3	Posterior Probability for H_0 Being False with Two p-values of 0.025 (≤)
0.50	.941
0.60	.960
0.70	.974

FDA Approval

- Suppose FDA wants to be 95% sure that H_0 is false
- Substantial evidence
  - **What p-value is needed for a single Ph 3 CT?**

Prior Probability Against H_0 Entering Phase 3	Posterior Probability for H_0 Being False with Two p-values of 0.025 (≤)	Single p-value for 95% Posterior Probability of H_0 Being False (≤)
0.50	.941	0.003
0.60	.960	0.006
0.70	.974	0.010

FDA Approval

- So, what’s the big deal?

FDA Approval

- ♦ So, what's the big deal?
- ♦ Suppose two Ph 3 CT's result in (two-tailed)
  - $p = 0.02$
  - $p = 0.08$
- ♦ Not Approved!
- ♦ Suppose you have a 0.60 prior that H_0 is false.
  - $p = 0.02$
  - $p = 0.08$
- ♦ Bayes factor ➔ pr (H_0 is false) $\leq .972$

A Problem of Evidence

"Is a p-value < 0.05 strong **evidence** against the null hypothesis?"

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- ✓It depends!
  - ✓… on your prior belief
  - ✓… on how small the p-value is

A Problem of Evidence

"Is a p-value < 0.05 strong **evidence** against the null hypothesis?"

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✓Very Bayesian notions of substantial evidence !!!

Summary

✓Bayesian probabilities quantify evidence related to a hypothesis of interest

Conclusion

- A p-value is not interpretable without understanding prior belief about the hypothesis of interest
  - It is more amenable to a black and white rule for decision-making

Conclusion

– A p-value is not interpretable without understanding prior belief about the hypothesis of interest
  + It is more amenable to a black and white rule for decision-making

+ A Bayesian posterior probability provides the likelihood of a hypothesis being true/false
  – It requires more sophisticated, flexible use of data for decision-making

Pr(I Thank You) = 1.00