

The Economic and Clinical Utility of Fecal Calprotectin Use by Family Physicians

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That's right, you voluntarily chose to attend this presentation involving the **mathematical analysis** of a **stool sample**...



$$\begin{aligned} & (388)[(1-P_n)(0.96) + (P_n)(1-0.93)] - 150 \\ & = 388[0.96 - 0.96P_n + 0.07P_n] - 150 \\ & = 222.48 - 388(0.89P_n) \end{aligned}$$

$$(165.52 + 345.32P_w)/(224.48 - 335.32P_n) < N/W < (13.3)(P_w/P_n).$$

Conflicts of interest

- **Financial:** none, but I'm open to ideas!
- **Personal:** you don't want to know...

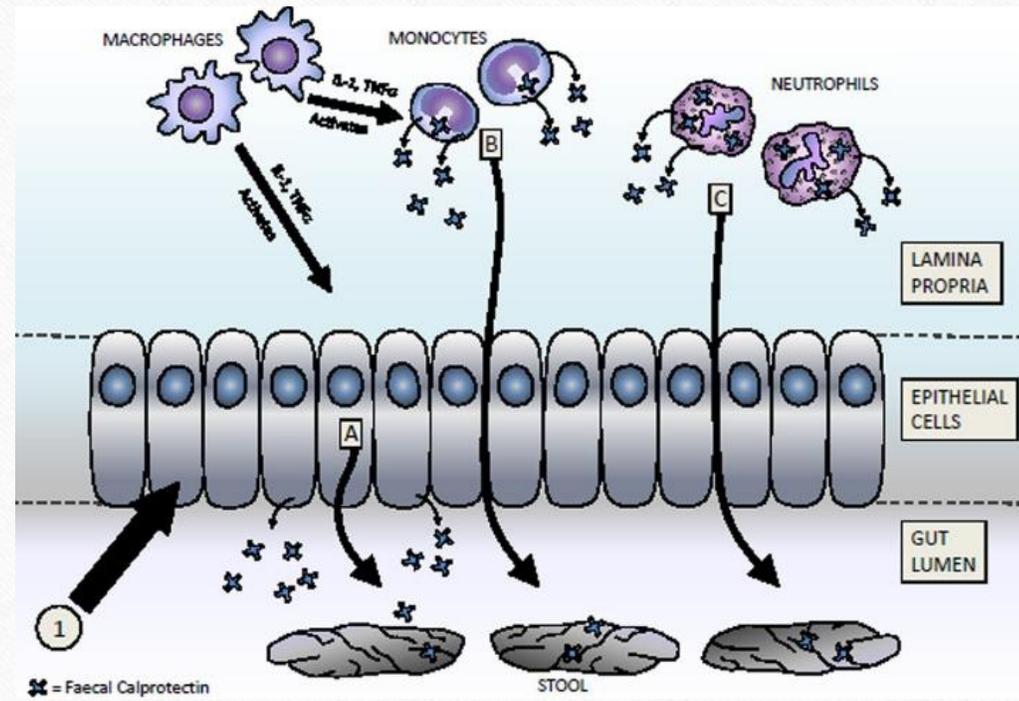
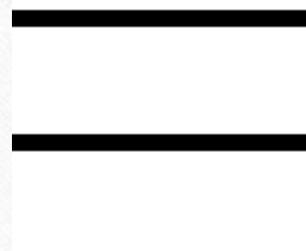
Mitigating any potential conflicts

- **Financial:** ???
- **Personal:** See Dr. Alexander Marchenko's paper (2017) RE: interpersonal conflicts with one's bowels.

Fecal Calprotectin (FC)...

What is it doin' in my stool?!

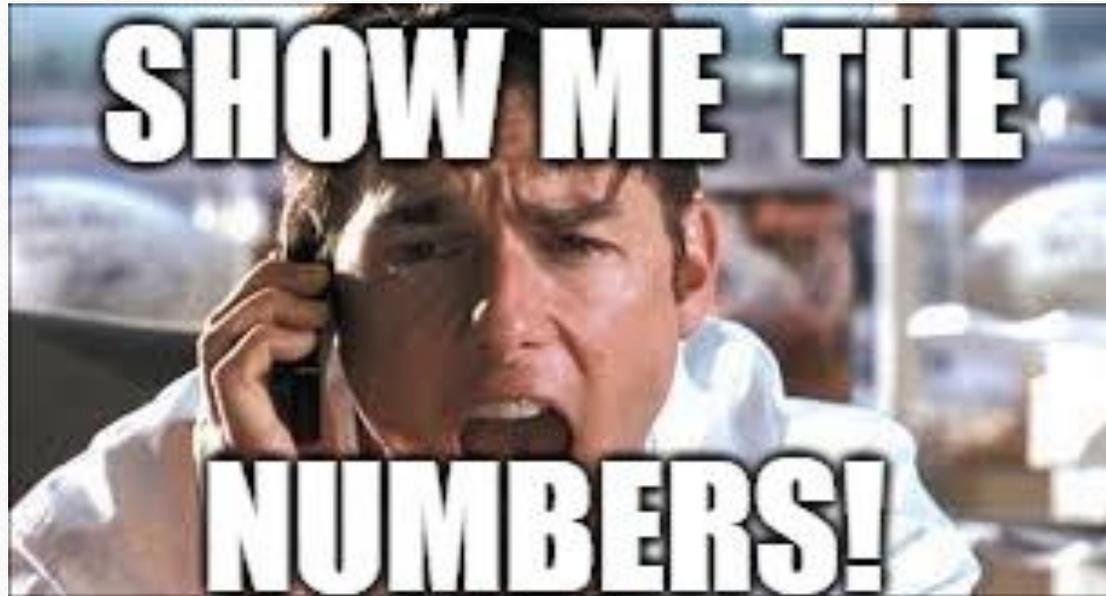
And what is it protectin'?!?



[inappropriate slide with wall of text already summarized; leave for awkward humor effect]

- Fecal calprotectin (FC) is a small protein that is especially abundant in neutrophils, in which it likely has an anti-microbial function. Accordingly, with the intestinal inflammation of IBD, as neutrophils move into the damaged intestinal mucosa, some of the neutrophils end up in the stool. Consequently, the abundant fecal calprotectin is also released into the stool.

Very nifty and all, but how useful is FC as a test?

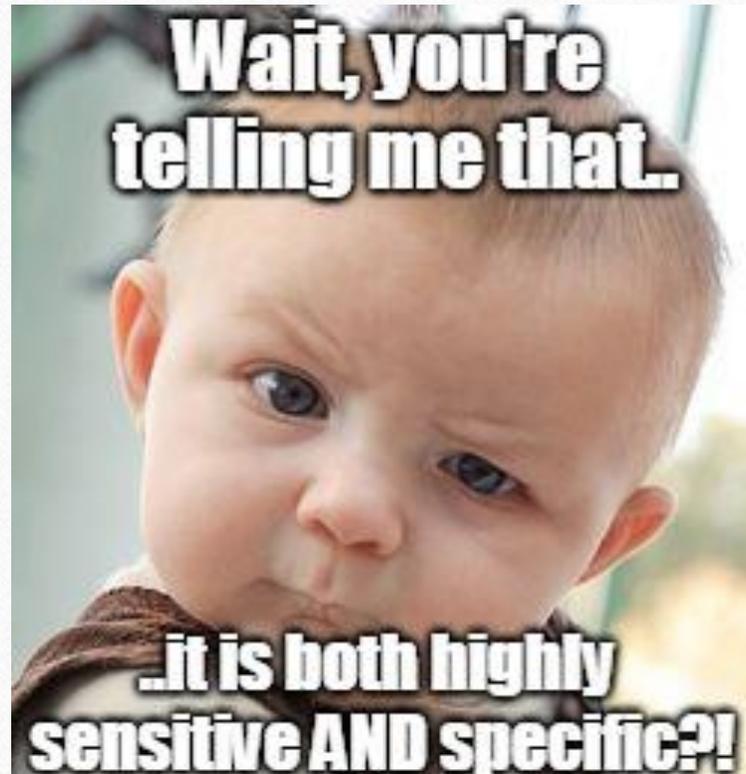


Sensitivity: 0.93 (95% confidence interval 0.85 to 0.97)

Specificity: 0.96* (0.79 to 0.99)

...for differentiating between IBS and IBD.

*More recent studies suggest an even higher specificity, as 57% of patients with +FC and normal colonoscopy actually had small bowel CD¹



¹Alzoubaidi D, Asser L, Price T, *et al* PWE-060 Is a false positive faecal calprotectin as false as you think? *Gut* 2015;**64**:A238.

Why these numbers should cause you to also have this skeptical yet excited grin

- **Family physicians** are often **challenged** to **differentiate** early or mild **IBD** from **IBS clinically**, thus resulting in reliance on observation over time or specialist referrals for colonoscopies.
- Given that such referrals for mild symptoms often involve waiting months, both strategies ultimately result in the **delayed diagnosis** and treatment of IBD, as well as **unnecessary colonoscopies** for some IBS patients.

Wait a minute, go back to the skeptical baby slide!



/PWE-060) Is a false positive faecal calprotectin as false as you think? Gut 2015;64:A238.

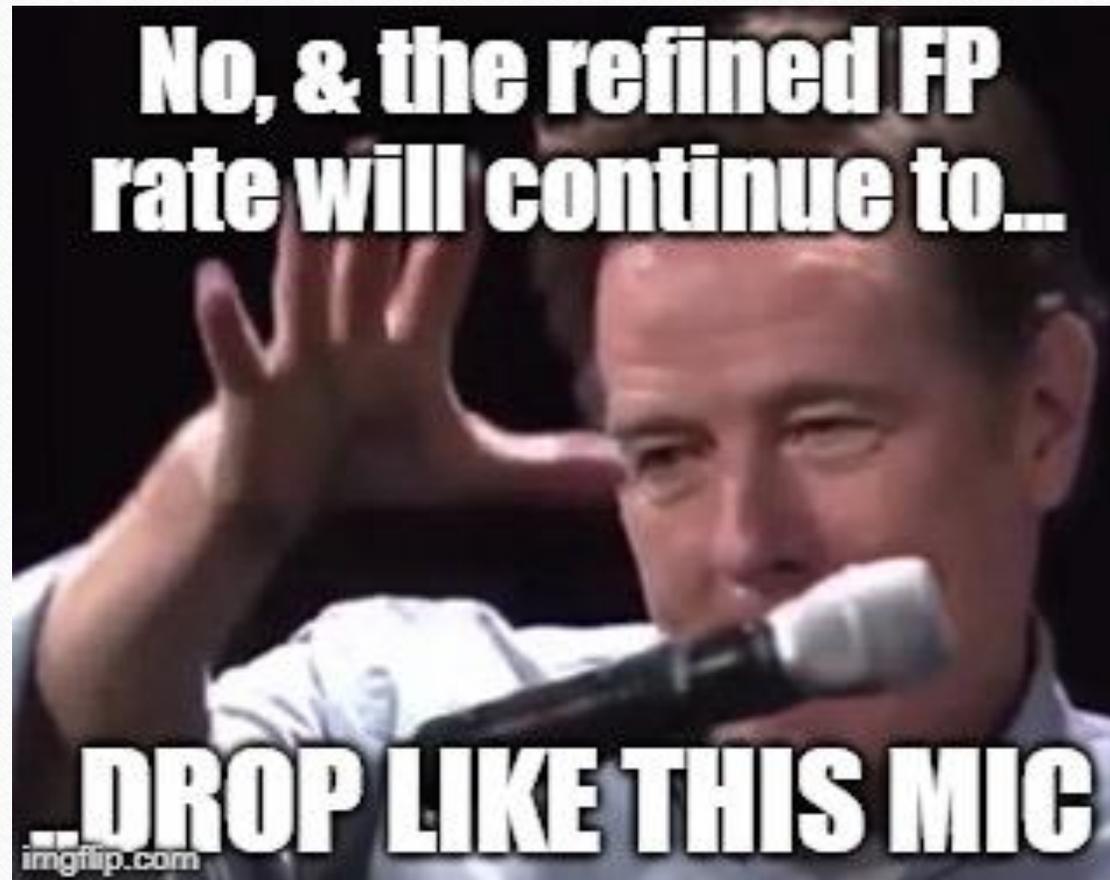
“Alzoubaidi D, Asser L, Price T, *et al*
PWE-060 Is a false positive
faecal calprotectin
as false as you think?
Gut 2015;64:A238”

→ 57% of patients with +FC and
normal colonoscopy actually had
small bowel Crohn's disease (!)

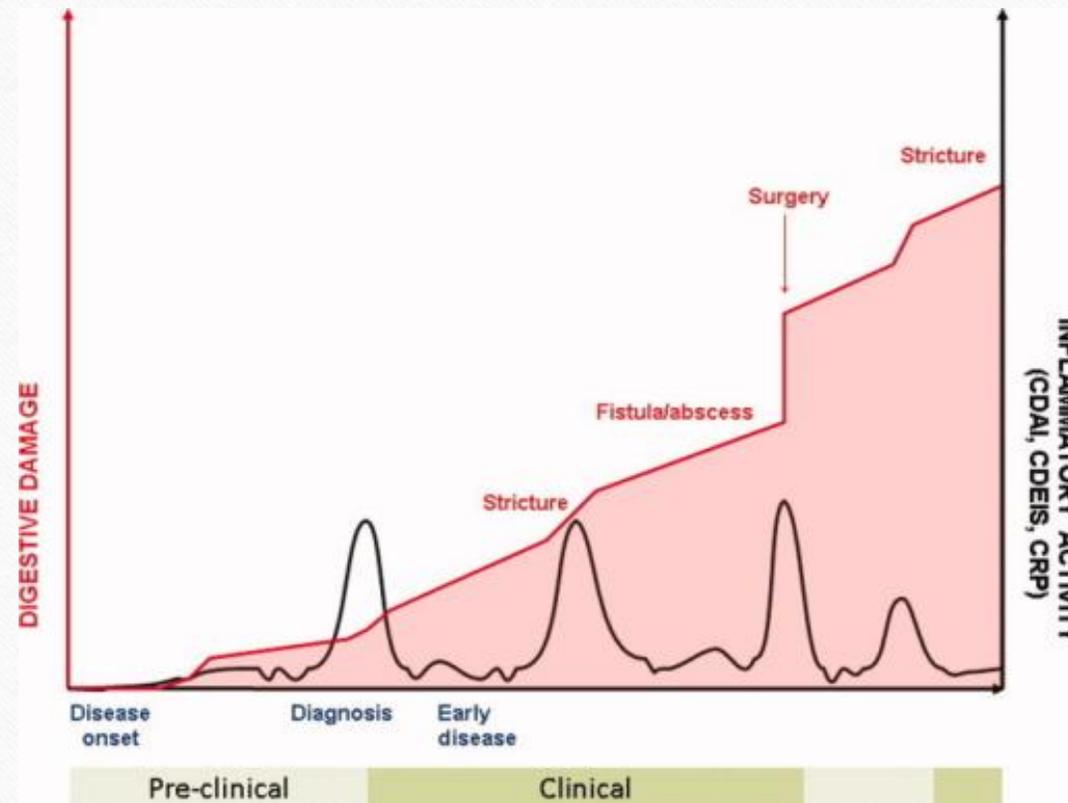
••• “Alzoubaidi D, Asser L, Price T, *et al*, PWE-060

Is a false positive [FP] faecal calprotectin as false as you think?

Gut 2015;64:A238”



Given the risk of IBD-related complications (including both short-term complications, such as severe exacerbations requiring surgery, as well as longer-term issues like cancer) and the general impairment to quality of life, **minimizing such delayed diagnoses can offer the potential for dramatic clinical improvements.**



Development of the Crohn's disease digestive damage score, the Lémann score.

Pariente B, Cosnes J, Danese S, Sandborn WJ, Lewin M, Fletcher JG, Chowers Y, D'Haens G, Feagan BG, Hibi T, Hommes DW, Irvine EJ, Kamm MA, Loftus EV, Louis E, Michetti P, Munkholm P, Oresland T, Panés J, Peyrin-Biroulet L, Reinisch W, Sands BE, Schoelmerich J, Schreiber S, Tilg H, Travis S, van Assche G, Vecchi M, Mary JY, Colombel JF, Lémann M - *Inflamm. Bowel Dis.* (2010)

And let's not forget the potential for reducing the number of unnecessary colonoscopies for our patients!*

*Results may vary, and this slide in no way guarantees a reduction in colonoscopies with FC testing, since they could actually increase depending on a number of factors. Consult your family doctor for further information, i.e., UpToDate.

BRACE YOURSELF



THE BOWEL PREP IS COMING

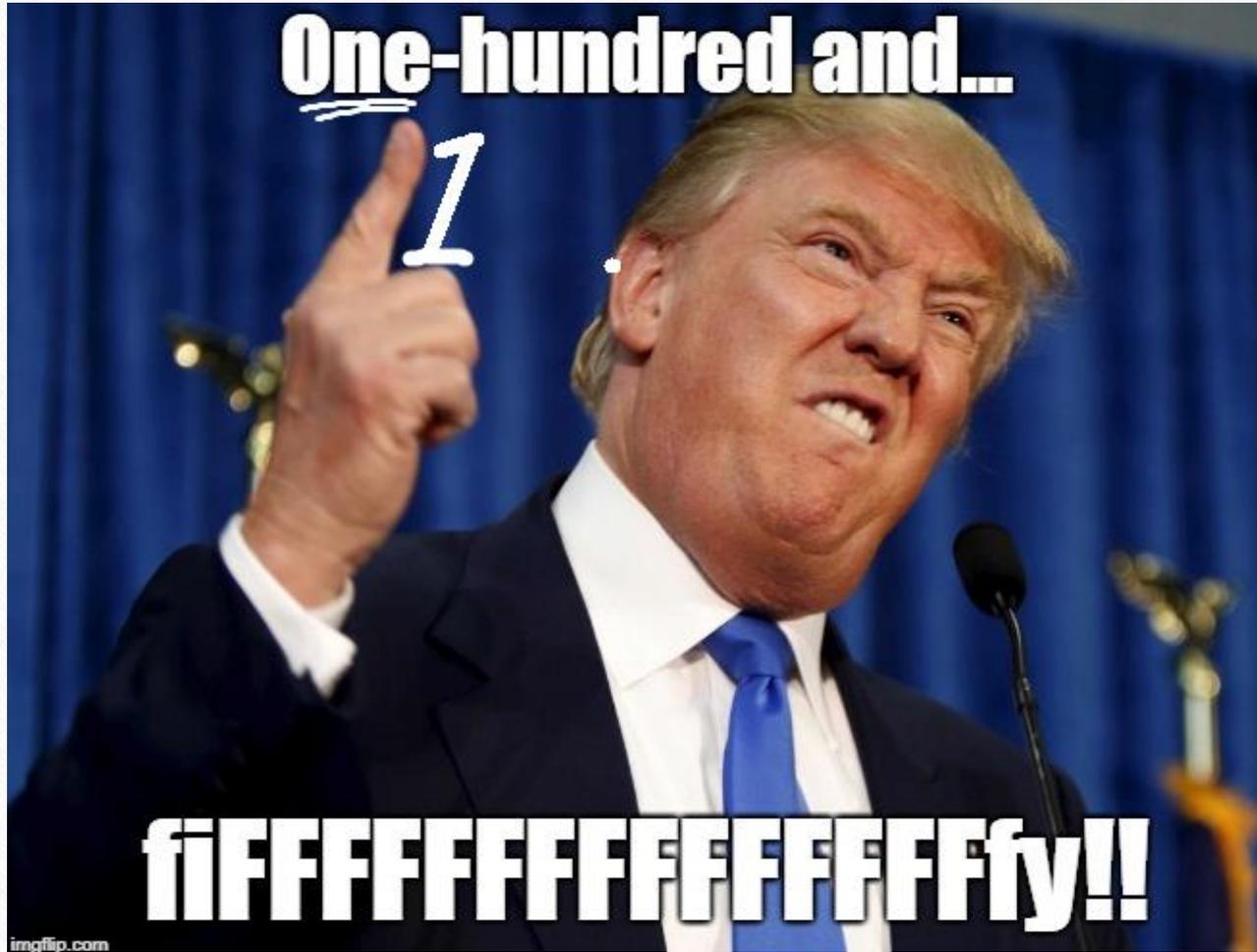
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OK...So, why isn't the **GP**
using the **FC**
in his or her **FP?**



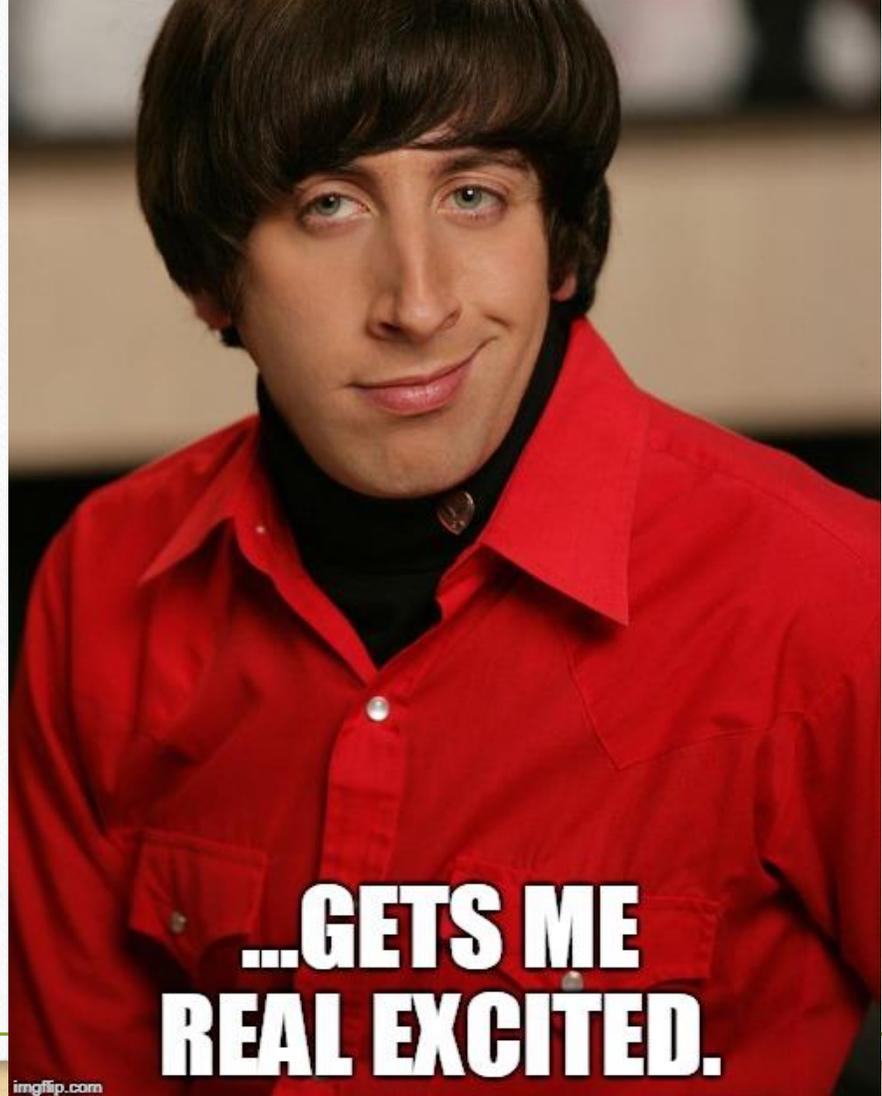
*Please, explain this sh...
..shameful waste of an
amazing diagnostic
option!*

- The test is **relatively new** (it only became more widely used around year 2000) so many family physicians in BC may still be unaware of the test.
- The test is **not covered** under the Medical Services Plan (MSP) of BC, so patients have to pay approximately **\$150** for the test.



\$150! In this economy?!

**BUT THAT SENSITIVITY
AND SPECIFICITY...**



**...GETS ME
REAL EXCITED.**

Should MSP cover FC?



More specifically:

- Under what conditions (if any) would it be economically advantageous (while maintaining superior diagnostic outcomes) if the MSP of BC paid for the use of FC by family physicians to differentiate between IBS and IBD in the patient population* with a low to moderate pre-test probability of having IBD?

**This patient population would also need the following exclusion criteria:*

- 1. No concerning features or risk factors for an alternative pathology such as colorectal cancer that would warrant a colonoscopy.*
- 2. No ongoing essential NSAID use that could not be temporarily stopped for around 3 weeks for FC testing.*

Ethical considerations

- Because all of the data used in this project is readily available to the public online (i.e., it is accessible in the public domain, in which there is no expectation for privacy), there are **no significant ethical considerations** with this project (besides the obvious psychological risks of presenting dangerously boring stool test math to a family medicine audience...)

Literature review

- A (very 😄) rapid review was conducted on literature pertaining to the sensitivity and specificity of fecal calprotectin; the pathophysiology of fecal calprotectin; and the pre-existing models for the estimated economic effectiveness of fecal calprotectin use.
- In addition, the official MSP billing documents were reviewed to gather information on the costs of colonoscopies and gastroenterologist referrals.

Existing literature

- There is extensive literature on the **sensitivity and specificity** of fecal calprotectin to differentiate between IBS and IBD.
- Moreover, there has been some work done with **models** in measuring and predicting the **effectiveness and cost-effectiveness** of using fecal calprotectin in this way.

Knowledge gap

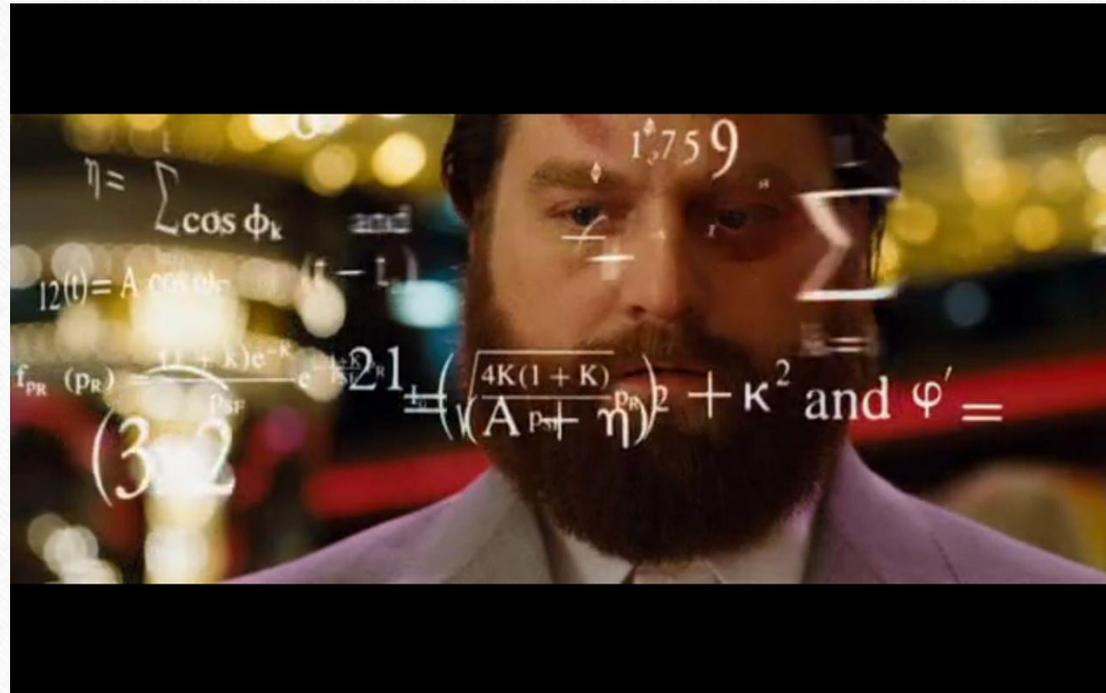


- However, there is no readily available analysis of this type applied to the **British Columbia medical system**.
- Also, the existing economic models are so complex as to **preclude simple modifications** to incorporate population-specific data in a different region.

Addressing the gap to answer my question (and breaking every PowerPoint rule on a single slide...)

- A basic **mathematical model** was created to approximate the immediate potential **cost-savings** if MSP paid for the use of FC by family physicians to differentiate between IBS and IBD in the patient population with a low to moderate pre-test probability of having IBD. This model also incorporated the **demand** (in the form of a mathematical constraint) of **reducing the number of missed diagnoses of IBD.**

A good mathematical journey begins with a clear set of axioms/assumptions, while maximizing the use of cool symbols ...



Perhaps the most painful slide ever created

VL = Population with a very low pre-test probability of having IBD,

W = Population with a low pre-test probability of having IBD,

N = Population with a moderate pre-test probability of having IBD (defined such that family doctors in BC refer patients for a colonoscopy when the pre-test probability is at or above this value),

VH = Population with a high pre-test probability of having IBD,

RF = **referral cost** = specialist consult fee + colonoscopy fee,

W_{+FC} = patients from population **W** with a positive FC test result,

N_{+FC} = patients from population **N** with a positive FC test result,

N_{-FC} = patients from population **N** with a negative FC test result,

No = patients from population **N** without IBD,

Np = patients from population **N** with IBD,

and (drum roll, please...)

Pn = **prevalence** of IBD in population **N**.

Never mind, this slide is even more painful...

Cost savings from implementing FC testing

$$= (\text{current costs}) - (\text{new costs})$$

$$= (\text{current number of referrals})(\text{RF}) - (\text{new number of referrals})(\text{RF}) - (\text{number of FC tests})(\$150)$$

$$= (\text{N} + \text{VH})(\text{RF}) - (\text{W}_{+\text{FC}} + \text{N}_{+\text{FC}} + \text{VH})(\text{RF}) - (\text{W} + \text{N})(\$150)$$

$$= (\text{N})(\text{RF}) - (\text{N}_{+\text{FC}})(\text{RF}) - (\text{N})(\$150) - (\text{W}_{+\text{FC}})(\text{RF}) - (\text{W})(\$150)$$

$$= (\text{N})(\text{RF}) - (\text{N} - \text{N}_{-\text{FC}})(\text{RF}) - (\text{N})(\$150) - (\text{W}_{+\text{FC}})(\text{RF}) - (\text{W})(\$150)$$

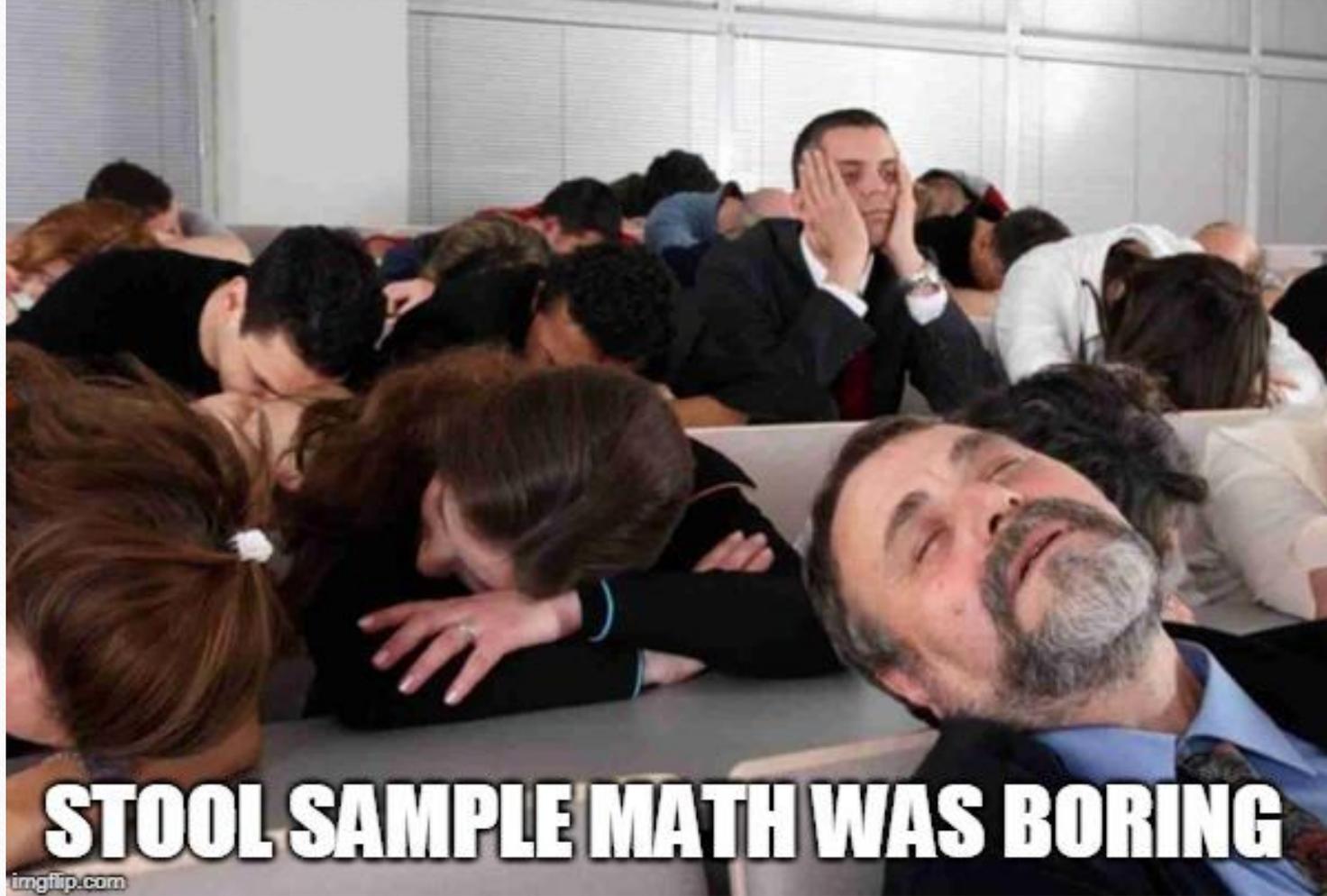
$$= (\text{N}_{-\text{FC}})(\text{RF}) - (\text{N})(\$150) - (\text{W}_{+\text{FC}})(\text{RF}) - (\text{W})(\$150)$$

$$= (\text{TN}_{\text{N}} + \text{FN}_{\text{N}})(\text{RF}) - (\text{N})(\$150) - (\text{TP}_{\text{W}} + \text{FP}_{\text{W}})(\text{RF}) - (\text{W})(\$150)$$

$$= [\text{N}(1 - \text{Pn})(0.96) + \text{N}(\text{Pn})(1 - 0.93)](\$388) - (\text{N})(\$150) - [(0.93)(\text{Pw})(\text{W}) + (1 - 0.96)(1 - \text{Pw})(\text{W})](\$388) - (\text{W})(\$150)$$

*Using the data from the British Columbia Ministry of Health Medical Services Commission Payment Schedule, we see that a colonoscopy fee is \$230, while a gastroenterologist consultation fee is \$158. Therefore, RF can be approximated by \$388.

STOOL SAMPLE MATH SOUNDED BORING



STOOL SAMPLE MATH WAS BORING

Just hold on, we are almost done the
(especially) dry part...



Besides being boring, the model derived so far is also weak in the following way:

- **It fails to take into account the costs associated with missed or delayed diagnoses of IBD.** Admittedly, it is very difficult to quantify such costs. However, we can work around this difficulty by **introducing a constraint** into the model such that we **demand** that the implementation of FC testing result in a **decrease of missed/delayed diagnoses.**

Thus, we now have **two demands**:

1. Cost savings > 0

and

2. (Missed diagnoses of IBD *with* FC) $<$ (Missed diagnoses of IBD *without* FC).

We now need to explore a model for the second constraint, which means....

[Leave blank to avoid overwhelming the senses]

..more neat symbols & parameters!



Let X = number of **missed*** diagnoses of IBD in population VL ,
and

W_p = number of patients from population W *with* IBD.

*We define “missed” such that significantly delayed diagnoses fall under this category.

Then, sparing you some of the intermediate mathematical gymnastics, we get the following

- (Missed diagnoses of IBD *with* FC) < (Missed diagnoses of IBD *without* FC) equates to

$$(W)(P_w)(0.07) + (N)(P_n)(0.07) + X < (W)(P_w) + X$$

$$\rightarrow 0.07(WP_w + NP_n) < (W)(P_w)$$

$$\rightarrow 0.07NP_n < 0.93WP_w$$

$$\rightarrow N/W < (0.93/0.07)(P_w/P_n)$$

$$\rightarrow N/W < (13.3)(P_w/P_n).$$

Therefore, our two constraints, namely

1. Cost savings > 0

and

2. (Missed diagnoses of IBD *with* FC) $<$ (Missed diagnoses of IBD *without* FC),

are equivalent to

$$[N(1-P_n)(0.96) + N(P_n)(1-0.93)](\$388) - (N)(\$150) - [(0.93)(P_w)(W) + (1-0.96)(1-P_w)(W)](\$388) - (W)(\$150) > 0$$

and

$$N/W < (13.3)(P_w/P_n).$$

This ultimately leads to the following

- $(165.52 + 345.32P_w)/(224.48 - 335.32P_n) < N/W < (13.3)(P_w/P_n)$

In other words, the above inequality needs to be satisfied in order for the implementation of FC testing in the primary care setting to result in a net cost savings while simultaneously reducing the number of missed (or significantly delayed) diagnoses of IBD.

For your reference (if you're actually reading this during the presentation, reference "Code bravo" afterwards to claim your prize):

N = Population with a *moderate* pre-test probability of having IBD

W = Population with a *low* pre-test probability of having IBD

P_n = prevalence of IBD in population N

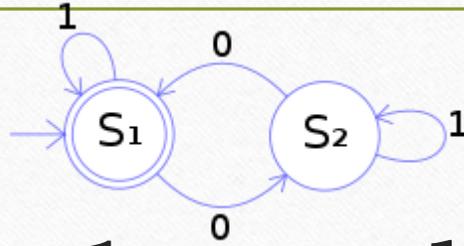
P_w = prevalence of IBD in population W

THE PRESENTATION ISN'T OVER YET?



THE PRESENTATION ISN'T OVER YET.

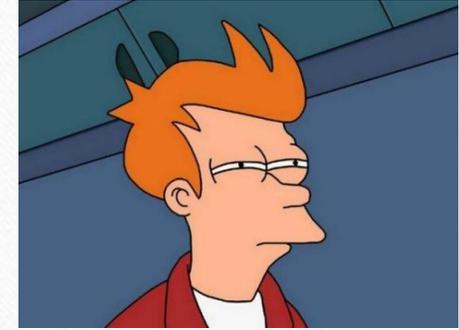
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Applying the model... now what?

- Naturally, we would like to input actual **province-specific data** for N , W , P_n , and P_w to determine whether FC implementation would achieve the stated goals.
- Unfortunately, such data is **not readily available**.
- Moreover, P_n and P_w actually **depend** on how we exactly **define** (in terms of precise numbers) “very low, low, moderate, and high” **pre-test probabilities**.

Oh, I see where this is going...



- Ultimately, such **definitions reflect** the suggested **guidelines** for when family physicians should order FC testing in a patient with IBD or IBS symptoms.
- Of course, **N** and **W** also **depend** on such definitions, since they are clearly a function of **P_n** and **P_w**, respectively.



Transforming weaknesses into strengths

- Accordingly, while we are **limited** by the **lack of data**, we are also **empowered** by the **flexibility** in considering the different choices for the pre-test probabilities we feel are appropriate for FC testing.
- With this in mind, we will now **explore** the range of outcomes when considering a spectrum of **possible parameter values**.

Time to explore!



- For example, suppose we **define** “very low, low, moderate, and high” pre-test probabilities such that $P_n = 20\%$ and $P_w = 5\%$.
- This is a **reasonable** consideration, since a **meta-analysis** (involving patients from many regions outside of BC) showed a **prevalence** of **IBD** in the total population of patients **suspected of having IBD** (as demonstrated via referrals for colonoscopies for this reason) of **32%**.
- Therefore, since this population corresponds to the combined populations of N and VH in our model, this meta-analysis would suggest that $P_n < 32\%$ while $P_{vh} > 32\%$ (where P_{vh} is the prevalence of IBD in our VH population).

Furthermore, the total **prevalence** of **IBD** in **BC** is 323 per 100,000 i.e. 0.323/100 or **0.323%**.

Combining all of this, we get

$$0.764 < N/W < 3.325.$$

In other words, for $P_n = 20\%$ and $P_w = 5\%$, in order for FC testing implementation to reduce costs while simultaneously decreasing missed or significantly delayed IBD diagnoses, N would need to be between 0.764 and 3.325 times the size of W .

Suppose we choose a value approximately midway in this range, such that $N = 2W$. Then

$$\text{Cost savings} = N(\$94.81)$$

and

$$\text{Expected number of reduced missed (or severely delayed) IBD diagnoses} = W(0.0185).$$

Blah blah blah... I bet no one is reading this.....

In other words ...

- Approximately **\$100** would be saved for each patient in population **N** being tested with FC (which is equivalent to saying \$50 per patient from population **W**).
- Since we know that FC testing would reduce the number of such missed diagnoses for our parameters in this situation, the true cost savings (when taking into account the **costs** associated with **missed or severely delayed diagnoses**) should exceed these values.



But it is not all about the money...

- Recall that our constraints demanded that the number of missed/delayed diagnoses be reduced with FC implementation; we can quantify this benefit.
- Since $1/0.0185 = 54$, this means that you would need to order **FC** for 54 patients from population **W** in order to **prevent 1 missed or significantly delayed** diagnosis of IBD (as compared to present practice); i.e., “NNT” = 54 for **population W**.

Let's get back to reality



- In order to most effectively advocate for our patients while also respecting our duties as managers of scarce resources, we need **practical tools** to guide our **clinical decision making** and inform our collective stance (and hopeful influence) on **MSP-related spending** decisions.
- With that in mind, we can make the **model simpler to use** by more rigorously **isolating** the **variable** we **choose** (namely, the **pre-test probability** range over which family doctors should order FC).

Some more symbols (the last of them, I promise)

- w_L = pre-test probability above which **FC** testing should be ordered
- w_H = pre-test probability above which patients are currently being sent for colonoscopy in the absence of **FC** use.
- Then w_H is not something we choose; rather, it is a fixed value in our model that reflects the current pattern of practice. In contrast, w_L is something **we can choose**. In fact, our population W is defined as those patients with a pre-test probability between w_L and w_H .

Simpler = Stronger

- Then, **incorporating prevalence data** from a meta-analysis, we get the following **simplified** approach:
- **Choose wL within the range 5.7% to 31% such that**
 $2.35 < N/W < 41.23P_w$.

Recall that N is a constant reflecting current practice; in contrast, W and P_w depend on wL and so can be computed from a chosen wL value. I.e., **$P_w = P_w(wL)$, $N = \text{constant}$.**

Conclusions: the 3 main uses of the model

1. To elicit the conditions under which FC testing would achieve our goals of simultaneously reducing total costs AND missed/delayed diagnoses of IBD.
2. To choose such pre-test probabilities and hence develop a guideline for FC use in primary care.
3. To quantify the financial and diagnostic benefits expected from any given pre-test probability (i.e., guideline) being considered.

So, in short, the model shows the following
RE: achieving our stated goals:

1. When it is possible.

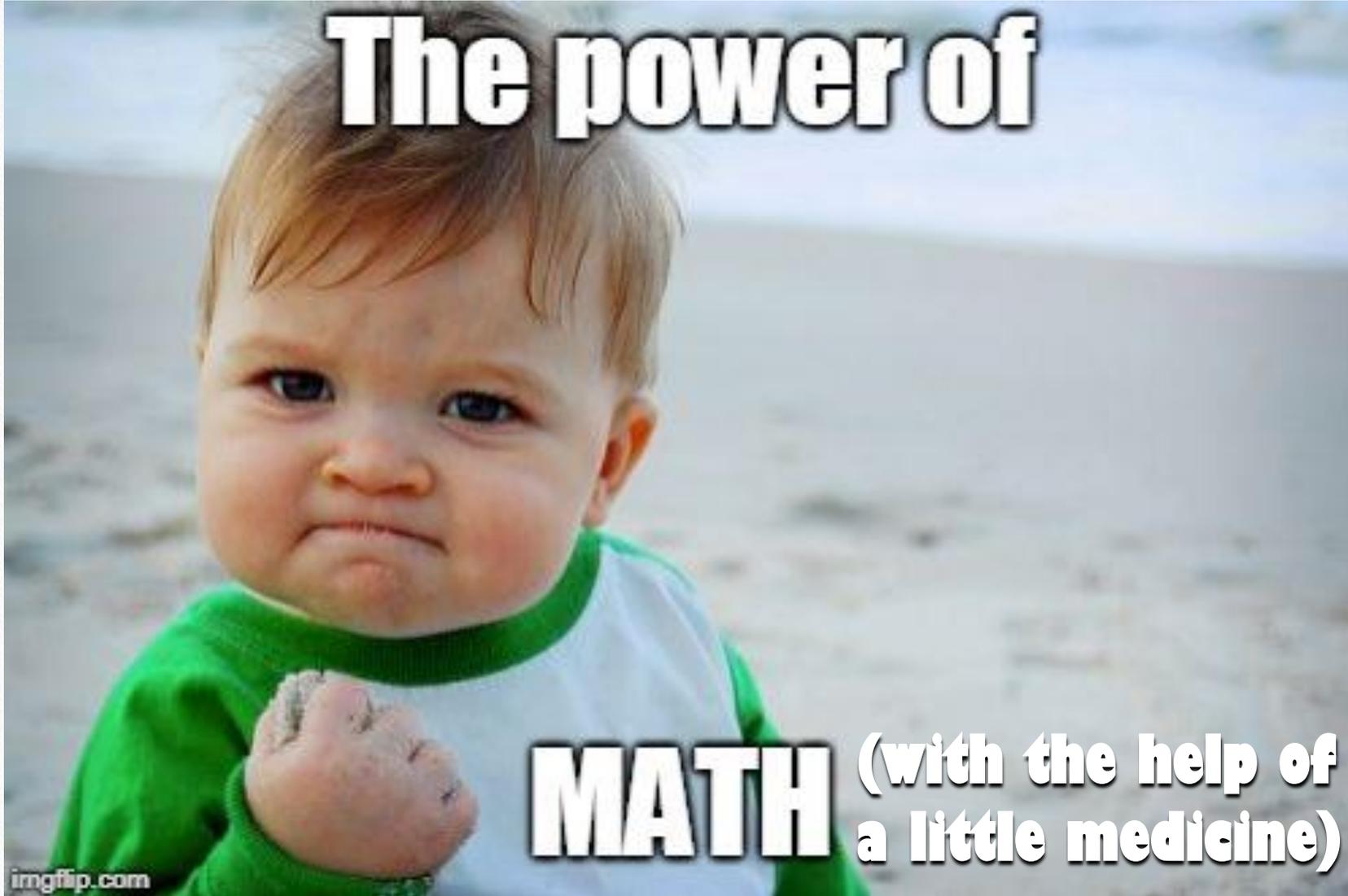
2. How to do it.

3. What the magnitude of the expected benefits would be (quantified).

Thus, we have answered our main question:

“Under what conditions (if any) would it be economically advantageous (while maintaining superior diagnostic outcomes) if the MSP of BC paid for the use of FC by family physicians to differentiate between IBS and IBD in the patient population with a low to moderate pre-test probability of having IBD?”

And we did this through...



The power of

MATH (with the help of
a little medicine)

imgflip.com

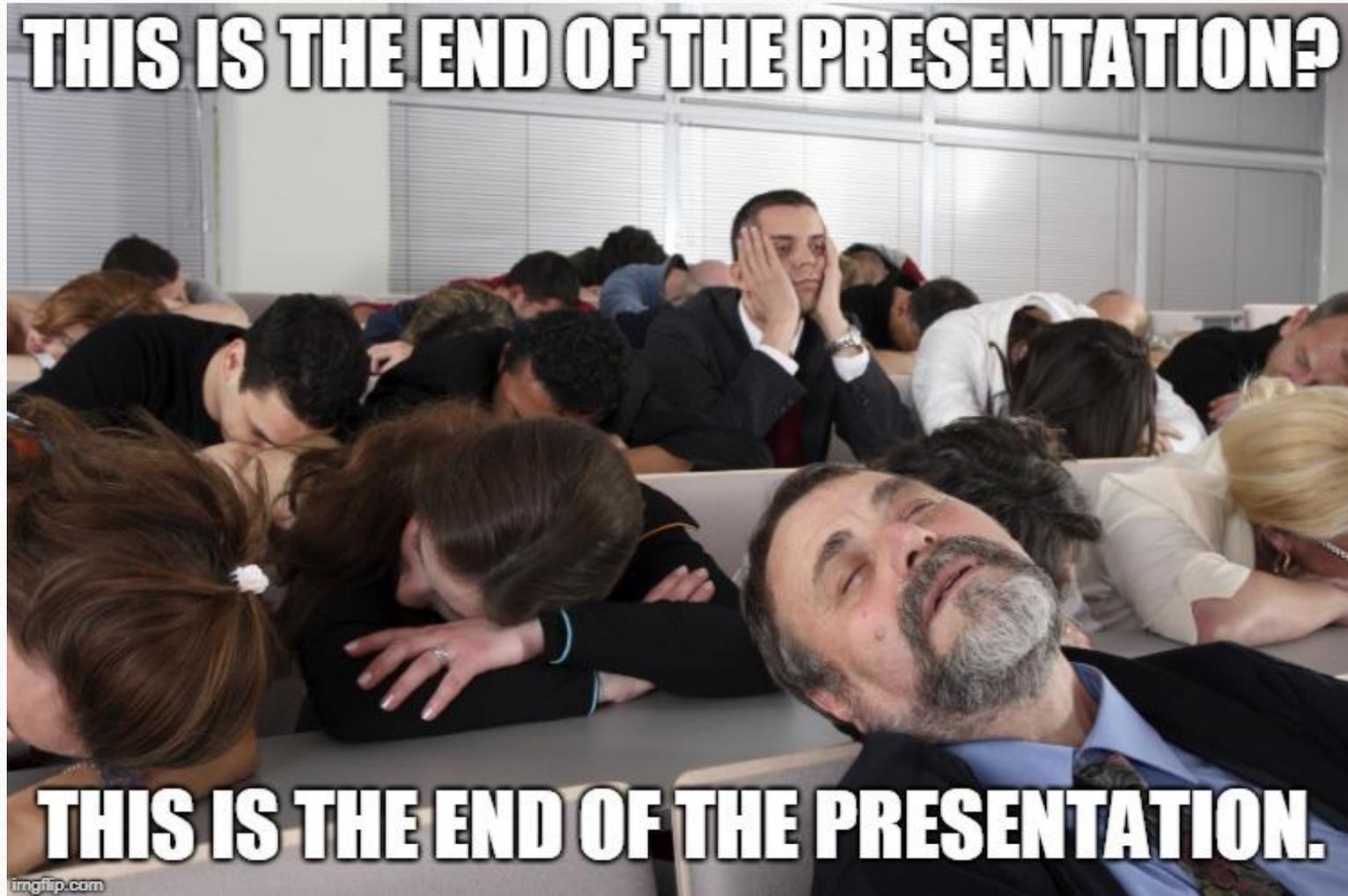
Main conclusion:

- In conclusion, analysis with this model suggests that the **use of FC by family physicians in BC to differentiate between IBS and IBD** (in the patient population with a low to moderate pre-test probability of having IBD) would result in significant cost-savings to the BC health care system while reducing the number of missed and significantly delayed diagnoses of IBD (i.e., we would expect improved diagnostic outcomes).
- Therefore, coverage of this test by the provincial health insurance plan should be considered.

Potential barriers to implementation

- **Logistical:** it could be challenging to educate enough family doctors about estimating the pre-test probability of IBD in relation to the corresponding threshold for ordering FC.
- **Financial:** presumably, some organizations are more interested in balancing their specific budgets rather than making decisions based on a more global, long-term fiscal picture.
- **Patient preference:** very few people enjoy colonoscopies, yet most people also aren't keen about providing stool samples.
- **Perceptions:** although the proposed FC protocol is for a very specific population without concerning features of something like colon cancer, many patients and physicians may still nevertheless feel a colonoscopy is a safer approach as it can identify many pathologies beyond IBD, especially colorectal cancers.

THIS IS THE END OF THE PRESENTATION?



THIS IS THE END OF THE PRESENTATION.

imgflip.com



Questions?

