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HPM 573: Project Report

Modeling Diagnostic Imaging for Appendicitis~ Balancing Cost, Cancer risk, and Sensitivity

Description and significance of policy-related question:

The appendix is a small tube with an unknown or vestigial function extending from the large intestine. Approximately 77,000 American children get appendicitis each year, and 1/3 of these cases result in the appendix rupturing before they reach the operating room (Johns Hopkins). Although adult appendicitis often presents with classic symptoms including nausea, vomiting, and pain localized in the lower right of the abdomen, symptom in children can differ making it harder to diagnose clinically. As a result, clinicians rely on diagnostic imaging to evaluate children suspected of having appendicitis (Johns Hopkins). If both options are available, clinicians must decide which to use. Computed Tomography (CAT Scan, CT) has higher diagnostic accuracy, however it is more expensive and exposes children to ionizing radiation. Exposing children to radiation can be more problematic and lead to higher cancer rates than exposing adults to radiation because children are more susceptible and have longer life-spans during which radiation-induced cancer can occur (Wan et al 2009, 379).

This analysis asks which strategy is more cost-effective in diagnosing children with appendicitis- ultrasound (US) or CAT scan (CT) when taking into account the cost of the test, complications of missed diagnosis, and radiation-induced cancer?

The natural history of the disease, diagnoses, and treatments:

The appendix is a finger-shaped pouch that projects from the colon on the lower right side of the abdomen. Appendicitis is inflammation of the appendix often caused by a blockage in the lining of the appendix causing the it to become inflamed, swollen, and filled with puss (Mayo Clinic 2018). Appendicitis occurs most frequently in those between the ages of 10 and 30. Symptoms include pain that begins at the navel and often shifts to the lower right side of the abdomen which can worsen with movement; nausea, vomiting, and loss of appetite, and a low-grade fever (May Clinic 2018).

Before a patient receives expensive and painful surgical intervention, cases of clinically suspected appendicitis are confirmed via ultrasound (US) or computed tomography (CT) (Wan et al. 2009, 380). While CT scans are more expensive, they are more accurate and have both higher specificity and sensitivity. CTs have a sensitivity of 0.94 and a specificity of 0.95 compared to USs which have a sensitivity of 0.88 and specificity of 0.94. The difference in sensitivity is particularly important; a higher sensitivity means a higher rate of appendicitis cases are accurately classified as positive for appendicitis as opposed to being missed. If the appendicitis is misdiagnosed resulting in a “false negative” then these cases are twice as likely to rupture (0.744 compared to 0.387. A rupture (also called a perforation) spreads infection throughout the abdomen, requires immediate attention, increases the risk of mortality, and increases the medical cost (Mayo Clinic 2018). However, increasing diagnostic sensitivity comes with tradeoffs: CTs are higher cost and increase the risk of cancer. If a child had a CT scan, he/she was exposed to radiation. This radiation increases the risk of various types of cancer throughout the child’s lifetime.

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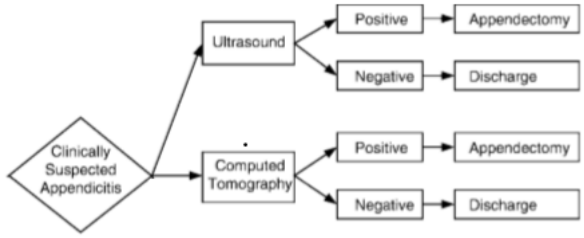
Those diagnosed with acute appendicitis receive surgery and either recover or, rarely, die. In some cases, a patient with a perforated appendix, pus needs to be drained from the abdomen and the patient receive antibiotics before surgery (Mayo Clinic 2018). This rarer complication is not included in our analysis. The death rates for those with appendicitis is lowest with a normal appendectomy, and almost twice as high (but still less than 0.25%) with a perforated appendicitis case. After surgery, children no longer have an appendix and can no longer suffer from appendicitis.



(modified from Wan et al. 2009, 380)

Sources of Data and Calculations Performed to Obtain Needed Data:

- Background mortality:
  - According to the CDC, the average mortality in the US in 2015 was 844 deaths per 100,000 people.
- Prevalence of Appendicitis:
  - The prevalence of appendicitis used in the model is 57.2%. This comes from a study conducted by Pena et al. (2006) which studied 920 children clinically suspected of having appendicitis.
- Radiation Exposure:
  - According to Wan et al. (2009), the radiation needed for a successful CT scan would be 100mA.
- Baseline Cancer Incidence:

	Male Patients		Female Patients	
Malignancy	Radiation-induced Cancer Rate	Baseline Cancer Rate	Radiation-induced Cancer Rate	Baseline Cancer Rate
Bladder	3.2	3800	4.0	1200
Breast	NA	NA	2.2	12 800
Colon	6.7	5700	4.4	5200
Leukemia	2.9	700	2.2	600
Lung	2.4	8100	6.6	6400
Stomach	5.2	1100	6.7	700
Total	20.4	19 400	26.1	26 900

Note.—All rates are given as numbers per 100 000 patients. Data regarding baseline cancer rates are from reference 45. NA = not applicable.

(Wan et al. 2009)

  - Note: assume population is 50% female and 50% male.
  - Baseline Cancer Incidence:
    - Using the data from Wan et a. (2009), we calculated the average cancer incidence over a lifetime and divided by 95 years to get the average cancer per year for the patients in the model.
    - Normal cancer incidence, without exposure to radiation, was therefore equal to 0.002437 [((19400*0.5)+(26900*0.5))/100000].
  - Radiation Induced Cancer Incidence + Baseline Cancer Incidence:

Radiation Induced Cancer + Baseline			
	Men	Women	Average
Bladder	3.2	4	3.6
Breast	0	2.2	1.1
Colon	6.7	4.4	5.55
Leukemia	2.9	2.2	2.55
Lung	2.4	6.6	4.5
Stomach	5.2	6.7	5.95
		SUM	23.25
		Per 100,000	0.0002325
		Radiation Induced Cancer Per Year (95)	2.44737E-06
		Background Cancer	0.0024
		Total Cancer	0.002402447

- Cancer Mortality
    - Using data from the CDC, we estimated that 50% of people diagnosed with cancer each year would die (0.0012) and the rest would transition to the post-appendicitis state.
- Rate of Perforation
    - Newman et al. (2003) reported a median perforation rate at presentation of 38.7% and a rate of 77.4% for those misdiagnosed as not having appendicitis.
- Missed Appendicitis Cases:
    - Using the specificity of the test (UR or CT), we calculated the % of missed appendicitis cases that perforated.
        - For UR, 0.12*0.744 = 0.09288
        - For CT, 0.06*0.744 = 0.04644
- Appendicitis-Related Mortality Rates:
    - Table 1 in Wan et al.(2009) reports appendicitis mortality rates for various types of appendicitis, mortality and prevalence. Using this data, we calculated a weighted average for the overall appendicitis mortality rate:

Appendicitis	Percentage	Death Rate
Normal	0.52012	0.0014
Perforated At Presentation	0.387	0.0024
Missed then Perforated	0.09288	0.0166
	Average Death Rate	0.0032

- Utility:
    - In order to calculate utility, we used the average range of the utilities reported in Wan et al. (2009)

	Low	High	Average
Appendectomy			0.73
Well/Post-App	0.88	0.94	0.91
Cancer	0.74	0.92	0.83

- Cancer Cost:
    - For cost, we used the weighted average of the different

	Men	Women	Average	%	Cost	Weighted Cost
Bladder	3.2	4	3.6	0.15483871	$89,728.00	$ 13,893.37
Breast	0	2.2	1.1	0.04731183	$78,548.00	$ 3,716.25
Colon	6.7	4.4	5.55	0.23870968	$46,257.00	$ 11,041.99
Leukemia	2.9	2.2	2.55	0.10967742	$48,666.00	$ 5,337.56
Lung	2.4	6.6	4.5	0.19354839	$45,439.00	$ 8,794.65
Stomach	5.2	6.7	5.95	0.25591398	$28,088.00	$ 7,188.11
						$ 49,971.93

- Appendectomy Cost:
    - According to Wan et al. (2009), an appendicitis w/o rupture cost $10,361 and an appendicitis with rupture cost $20,072.

Modeling Approach:

We used a Markov Model to conduct a cost-effectiveness analysis of US vs. CT. The model followed two cohorts of 5-year-olds who presented with appendicitis-like symptoms. In one cohort, the child would receive a CT, in the other an ultrasound. The cohorts of children were then followed until they turned 100 or died, tracking the cancer mortality and costs associated with the cohorts. The CT cohort had an enhanced rate of cancer diagnosis.

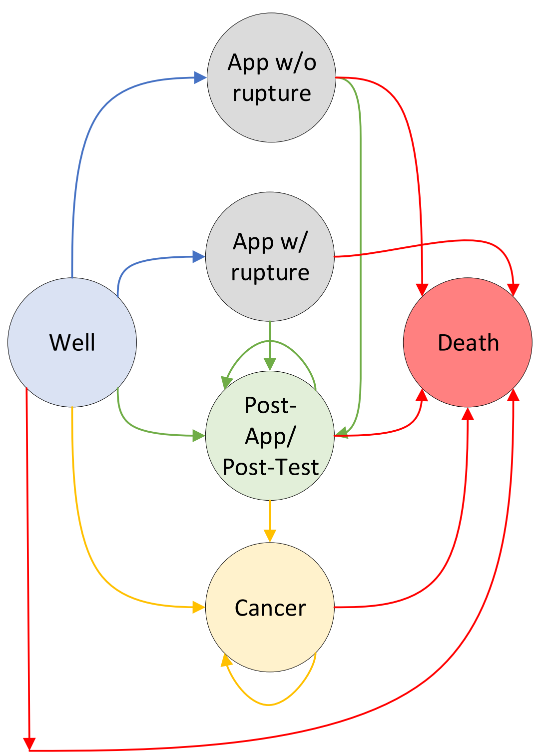
The model used the following parameters:

- Alpha = 0.05
- Discount rate = 0.03
- Delta = 1/52 → modeling changes per week
- Cohort Size = 1000
- Transition matrices calculated using the data above:

	Ultrasound Transition Matrix						
	Well	**Appendicitis (no rupture)**	**Appendicitis (rupture)**	**Post-Appendicitis**	**Cancer**	**Dead**	**Sum**
Well	0	0.3241	0.2479	0.41716	0.0024	0.00844	1.000
Appendicitis (no rupture)	0	0	0	1	0	0	1.000
Appendicitis (rupture)	0	0	0	1	0	0	1.000
Post-Appendicitis and Post-Testing	0	0	0	0.9944	0.0024	0.0032	1.000
Cancer	0	0	0	0.5	0.4988	0.0012	1.000
Dead	0	0	0	0	0	1	1.000

	Cat Scan Transition Matrix						
	Well	Appendicitis (no rupture)	Appendicitis (rupture)	Post-Appendicitis and Post-Testing	Cancer	Dead	Sum
Well	0	0.337354	0.234646	0.41716	0.0024	0.00844	1.000
Appendicitis (no rupture)	0	0	0	1	0	0	1.000
Appendicitis (rupture)	0	0	0	1	0	0	1.000
Post-Appendicitis and Post-Testing	0	0	0	0.994397553	0.002402447	0.0032	1.000
Cancer	0	0	0	0.5	0.4988	0.0012	1.000
Dead	0	0	0	0	0	1	1.000

Patients would start in “well” which is when they are presenting at the clinic with symptoms before they are determined to have appendicitis. Then they would be tested. Those testing negative would transition to post-testing, and those with appendicitis would go to an appendicitis state. From the appendicitis temporary states, the patients would receive surgery and go to the post-appendicitis state where they live out the rest of their lives unless they get cancer or die due to other causes (background mortality). Those that get cancer can either die, still have cancer, or move back to the post-appendicitis/post-testing state.



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Simplifying assumptions that will be held by the model:

Below are some of the assumptions used in the model (in addition to those stated in the data sources and calculations section).

Cohort:

- The model is based on a cohort of 5-year-old children clinically suspected of having appendicitis. Children rarely get appendicitis before the age of 5, and young children who get appendicitis are most at risk for long-term damage due to radiation exposure.
- Children can have appendicitis only once, and they do so at the age of 5.
- The model assumes that the diagnostic ultrasound and cat scans are the only ones the children receives.
- The model follows patients from the age of 5 until death or age 100.

Diagnostic Testing:

- The model assumes that the lowest possible radiation settings on the CT machine will be used when estimating radiation-induced cancer.

Incidence:

- Although the paper this model is based on uses year-by-year data for background mortality, cancer incidence, and cancer mortality, we used lifetime averages divided by the 95-years of the study for the yearly rates.
- The model does not include a risk-free latent period after radiation exposure as these are small in comparison to the 95-years of the study.

Costs:

- The model includes only direct-costs (scan costs, surgery costs) and does not include indirect costs such as parent's lost wages due to time-off from work.
- Although in real life, people can get multiple cancers or have the same cancer recur, the model assumes that individuals get one cancer and eventually die or get well.
- The model also assumes that no one with cancer (not-radiation induced) gets appendicitis. This rate would be incredibly small.

Economic Evaluation Results:

With the baseline parameter stipulations discussed above, the simulated Markov model indicated a cost-effective advantage in using CT screening over US for appendicitis in children. The results report an incremental cost-effectiveness ratio (ICER) of $16,274.19 per quality-adjusted life year (QALY), which is within the $50,000 per QALY typically quoted as acceptable level of cost-effectiveness tradeoff.

Cost-Effectiveness Analysis:

Name	E[Cost]	E[Effect]	E[dCost]	E[dEffect]	ICER
Ultrasound	1,750 (1,609, 1,892)	4.62 (4.37, 4.88)	-	-	-
Computed Tomography	2,229 (2,097, 2,363)	4.65 (4.40, 4.90)	480 (135, 824)	0.03 (-0.60, 0.66)	16,274.19 (-34,891.26, 48,287.40)

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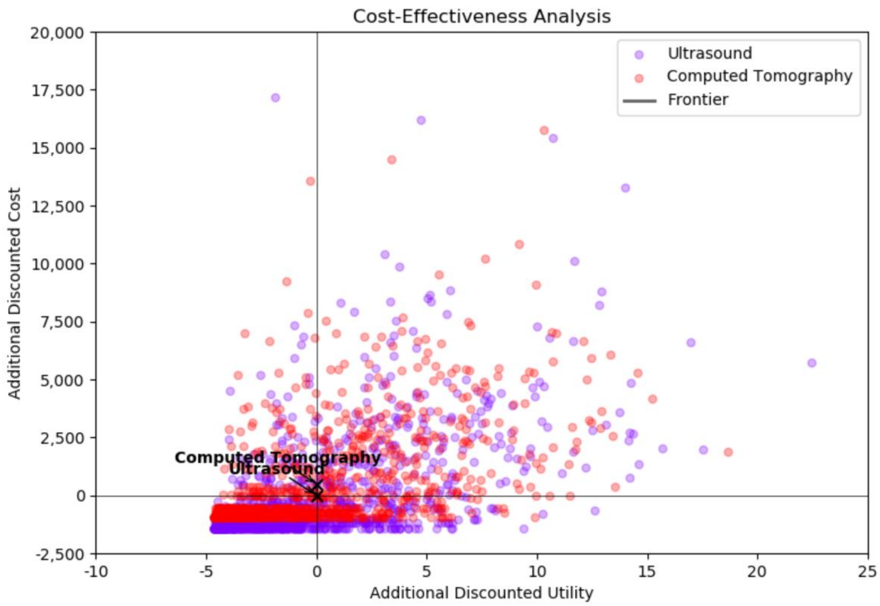

Sensitivity Analysis:

To understand how variation in several key parameters will impact the results of our evaluation, a one-way deterministic sensitivity analysis was performed on the following parameters:

- *Cancer incidence*:
  Increasing the probability that cancer will result at some point in life from a single event of radiation will impact both costs and utilities. A high enough economic cost and personal disutility could render CT an inferior alternative to US. Cancer incidence contributes by far the largest amount of uncertainty in the model—not only is the value capturing the additional risk a very small number, but also limited evidence to directly observe the accuracy of such number.

- *Appendicitis incidence*:
  A lower likelihood of appendicitis in children reduces the potential occurrence of both appendicitis with rupture and appendicitis without rupture. Given a low enough incidence, using a more sensitive CT could provide no effective benefit, given the balance of higher cost than US and the increased risk for radiation-induced cancer.

- *Perforation incidence after missed diagnosis:*
  The implication of an initial missed diagnosis is the increased likelihood of a costly ruptured appendicitis episode. However, if the probability of perforation incidence after a missed diagnosis is lower than baseline expectation, then there is an overestimation of the cost-effectiveness of a CT scan.

- *Cost of ruptured appendicitis:*

> Because ruptured appendicitis is such a costly event (even compared to a non-ruptured event), the advantage of a CT is to lower the likelihood of encountering perforation. However, if the economic impact of ruptured appendicitis is less than baseline expectation, it results in overestimation of the cost-effectiveness of a CT scan.

The table below summarizes the results of the sensitivity analysis. While not every parameter was systematically analyzed, the ones that were examined here would suggest that our baseline evaluation results are quite resistant to parameter uncertainty. In each of the test scenarios, the use of CT screening was cost-effective, with the ICER below the widely accepted threshold of $50,000 per QALY. In other words, only a radical departure from the values we assumed for each model parameter could result in an evaluation where CT is no longer cost-effective over US. For instance, if the appendicitis incidence was reduced to a mere 4% (from the baseline 57.2%), the sensitivity analysis would then indicate that CT is no longer cost-effective, and US should be the proper recourse for screening.

One-way Sensitivity (Deterministic Sensitivity Analysis)

	ICER			
	P(cancer incidence)	P(appendicitis incidence)	P(perforation after MD)	Cost of ruptured appendicitis
100%	41989.01			
50%	39253.13			
25%	26840.80			
10%	20540.62			
Baseline	16274.19	16274.19	16274.19	16274.19
-10%		28975.31	16280.52	16258.48
-25%		28906.63	16280.52	16234.92
-50%		28813.82	16293.19	16195.65

Parameter Range (as % of Baseline)

	Cancer incidence	Appendicitis incidence	Perforation incidence after MD	Cost of ruptured appendicitis
100%	0.004804894			
50%	0.003603671			
25%	0.003003059			
10%	0.002642692			
Baseline	0.002402447	0.5720	0.7740	20072.00
-10%		0.5148	0.6966	18064.80
-25%		0.4290	0.5805	15054.00
-50%		0.2860	0.3870	10036.00

Works Cited

American Cancer Society Medical and Editorial Content Team. 2018. "Lifetime Risk of Developing or Dying From Cancer." *American Cancer Society*. https://www.cancer.org/cancer/cancer-basics/lifetime-probability-of-developing-or-dying-from-cancer.html

"Appendicitis" 2018. *Mayo Clinic*. https://www.mayoclinic.org/diseases-conditions/appendicitis/symptoms-causes/syc-20369543

CDC. 2018. "National Vital Statistics Program: Mortality Data." *Centers for Disease Control*. https://www.cdc.gov/nchs/nvss/deaths.htm

Johns Hopkins Medicine. 2007. "Does This Child Have Appendicitis? Watch Out for Key Signs." https://www.hopkinsmedicine.org/news/media/releases/does_this_child_have_appendicitis_watch_out_for_key_signs

Newman K, Ponsky T, Kittle K, et.al. 2003. "Appendicitis 2000: variability in practice, outcomes, and resource utilization at thirty pediatric hospitals." *J Pediatr Surg* 38(3): 372–379.

Pena BM, Taylor GA, Fishman SJ, Mandl KD. 2002. "Effect of an imaging protocol on clinical outcomes among pediatric patients with appendicitis." *Pediatrics* 110(6):1088– 1093.

Wan, Michael, Murray Krahn, Wendy Ungar, Edona Caku, Lillian Sung, L. Santiago Medina, and Andrea Doria. 2009. "Evidence Based Practice: Acute Appendicitis in Young Children: US versus CT." *Radiology* 250(2): 378-386.