Ontario
Health Quality Ontario

Transient Elastography and Controlled Attenuation Parameter for Diagnosing Liver Fibrosis and Steatosis in Ontario: An Economic Analysis

K THAVORN, D COYLE

NOVEMBER 2015

Ontario Health Technology Assessment Series; Vol. 15: No. 19, pp. 1–58, November 2015

Suggested Citation

This report should be cited as follows:

Thavorn K, Coyle D. Transient elastography and controlled attenuation parameter for diagnosing liver fibrosis and steatosis in Ontario: an economic analysis. Ont Health Technol Assess Ser [Internet]. 2015 November;15(19):1–58. Available from: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series/transient-elastography-econ.

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ABSTRACT

Background

Liver fibrosis is characterized by a buildup of connective tissue due to chronic liver damage. Steatosis is the collection of excessive amounts of fat inside liver cells. Liver biopsy remains the gold standard for the diagnosis of liver fibrosis and steatosis, but its use as a diagnostic tool is limited by its invasive nature and high cost.

Objectives

To evaluate the cost-effectiveness and budget impact of transient elastography (TE) with and without controlled attenuation parameter (CAP) for the diagnosis of liver fibrosis or steatosis in patients with hepatitis B, hepatitis C, alcoholic liver disease, and nonalcoholic fatty liver disease.

Data Sources

An economic literature search was performed using computerized databases. For primary economic and budget impact analyses, we obtained data from various sources, such as the Health Quality Ontario evidence-based analysis, published literature, and the Institute for Clinical Evaluative Sciences.

Review Methods

A systematic review of existing TE cost-effectiveness studies was conducted, and a primary economic evaluation was undertaken from the perspective of the Ontario Ministry of Health and Long-Term Care. Decision analytic models were used to compare short-term costs and outcomes of TE compared to liver biopsy. Outcomes were expressed as incremental cost per correctly diagnosed cases gained. A budget impact analysis was also conducted.

Results

We included 10 relevant studies that evaluated the cost-effectiveness of TE compared to other noninvasive tests and to liver biopsy; no cost-effectiveness studies of TE with CAP were identified. All studies showed that TE was less expensive but associated with a decrease in the number of correctly diagnosed cases. TE also improved quality-adjusted life-years in patients with hepatitis B and hepatitis C. Our primary economic analysis suggested that TE led to cost savings but was less effective than liver biopsy in the diagnosis of liver fibrosis. TE became more economically attractive with a higher degree of liver fibrosis. TE with CAP was also less expensive and less accurate than liver biopsy.

Limitations

The model did not take into account long-term costs and consequences associated with TE and liver biopsy and did not include costs to patients and their families, or patient preferences related to diagnostic information.

Conclusions

TE showed potential cost savings compared to liver biopsy. Further investigation is needed to determine the long-term impacts of TE on morbidity and mortality in Canada and the optimal diagnostic modality for liver fibrosis and steatosis.

PLAIN LANGUAGE SUMMARY

The liver is the largest internal organ. It supports many body functions, including digestion, storing nutrients, and protecting the body from infection. Certain diseases can damage the liver, and if they are not caught and treated early, they can lead to liver cancer or liver failure. Most often, doctors test how healthy a patient's liver is by taking a tissue sample with a needle, but there are other ways to check liver health that don't require needles or tissue samples. One option is called *transient elastography*; it is a scan that measures how stiff the liver tissue is (the more stiff the tissue, the more damaged the liver). We reviewed the evidence and conducted a study to see whether using transient elastography would save money for the health care system. The results showed that transient elastography would be less expensive than taking a tissue sample.

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LIST OF ABBREVIATIONS

ALD	Alcoholic liver disease
APRI	Aspartate aminotransferase to platelet ratio index
ARFI	Acoustic radiation force impulse
CAP	Controlled attenuation parameter
HBV	Hepatitis B virus
HCV	Hepatitis C virus
ICER	Incremental cost-effectiveness ratio
ICES	Institute for Clinical Evaluative Sciences
NAFLD	Nonalcoholic fatty liver disease
QALY	Quality-adjusted life-year
TE	Transient elastography

BACKGROUND

The Ottawa Hospital Research Institute (OHRI) was commissioned by Health Quality Ontario to evaluate the cost-effectiveness of transient elastography for hepatitis B, hepatitis C, non-alcoholic fatty liver disease, and alcoholic liver disease. Published economic evaluations are reviewed, and the structure and inputs of the economic model used to estimate cost-effectiveness are summarized. The results of the economic analyses are presented for transient elastography versus liver biopsy, and the budget impact of implementing each intervention is estimated.

Health Quality Ontario conducts full evidence-based analyses, including economic analyses, of health technologies being considered for use in Ontario. These analyses are then presented to the Ontario Health Technology Advisory Committee, whose mandate is to examine proposed health technologies in the context of available evidence and existing clinical practice and to provide advice and recommendations to Ontario health care practitioners, the broader health care system, and the Ontario Ministry of Health and Long-Term Care.

DISCLAIMER: Health Quality Ontario uses a standardized costing method for its economic analyses. The main cost categories and associated methods of retrieval from the province's perspective are described below.

Hospital costs: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency department visit, and day procedure costs for the designated International Classification of Diseases diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in the estimated costs of the diagnoses and procedures under consideration. Due to difficulties in estimating indirect costs in hospitals associated with a particular diagnosis or procedure, Health Quality Ontario normally defaults to a consideration of direct treatment costs only.

Non-hospital costs: These include physician services costs obtained from the Ontario Benefits for Physician Services, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible, or from the device manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied (to both costs and effects/QALYs), as recommended by economic guidelines.

Downstream costs: All reported downstream costs are based on assumptions of population trends (i.e., incidence, prevalence, and mortality rates), time horizon, resource utilization, patient compliance, health care patterns, market trends (i.e., rates of intervention uptake or trends in current programs in place in the province), and estimates of funding and prices. These may or may not be realized by the Ontario health care system or individual institutions and are often based on evidence from the medical literature, standard listing references, and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach.

The economic analysis represents ***an estimate only***, based on the assumptions and costing methods explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

NOTE: Numbers may be rounded to the nearest decimal point, as they may be reported from an Excel spreadsheet.

Objective of Analysis

The objective of this study was to evaluate the cost-effectiveness and budget impact of the following diagnostic techniques for the diagnosis of liver fibrosis or steatosis in patients with hepatitis B, hepatitis C, alcoholic liver disease (ALD), or nonalcoholic fatty liver disease (NAFLD):

- Liver fibrosis
  - transient elastography (TE) versus liver biopsy

  - noninvasive diagnostic tests (TE, acoustic radiation force impulse [ARFI] and FibroTest) versus liver biopsy
- Liver steatosis
  - TE with controlled attenuation parameter (CAP) versus liver biopsy

Clinical Need and Target Population

Description of Disease/Condition

Liver fibrosis is characterized by the excessive accumulation of extracellular matrix protein, which occurs in response to chronic injury to the liver, such as infection and inflammation. (1) Fibrosis can reduce blood flow in the liver and lead to loss of liver function. If the scar tissue permanently changes blood circulation, fibrosis can lead to cirrhosis, which may result in severe complications, including portal hypertension, liver failure, and hepatocellular carcinoma. (2) The only curative treatment for end-stage cirrhosis is liver transplantation. As such, an accurate assessment of liver fibrosis is critical for predicting prognosis and starting appropriate therapy to prevent disease progression.

Hepatic steatosis, or fatty liver, is an accumulation of fat in the liver. It is a common histological finding in patients with metabolic syndrome, alcoholic hepatitis, or hepatitis C, or in patients exposed to certain medications (e.g., corticosteroids and amiodarone). (3, 4) Nonalcoholic fatty liver disease is the most common cause; its spectrum ranges from asymptomatic steatosis to nonalcoholic steatohepatitis, which has been recognized as an important cause of unexplained cirrhosis (5) and is associated with an increased risk of hepatocellular carcinoma. (6) More importantly, if steatosis coexists with other chronic liver diseases, it may accelerate fibrosis progression and cause poor treatment response. (4) An accurate diagnosis of hepatic steatosis is therefore essential for clinical decision-making and prognosis assessment.

Liver biopsy is currently the gold standard for the assessment of liver fibrosis and steatosis, (7, 8) but it is invasive, resource-intensive, and undesirable for patients (9, 10). It is associated with complications, including pain, bleeding, hypotension, viscous perforation, infection, pneumothorax, and, in rare cases, death. (11) It is difficult to perform liver biopsy for patients who need to be assessed repeatedly because of its invasiveness and high cost. As well, the accuracy of liver biopsy is questionable because biopsy samples are usually too small to accurately diagnose disease, (12, 13) and diagnostic opinions may differ between pathologists because of significant interobserver variability and interpretation error. (7, 14, 15) Furthermore, liver biopsy is subject to sampling variability depending on whether the individual underwent biopsy of the right or left hepatic lobe. (16)

In light of the limitations of liver biopsy, various noninvasive methods have been developed for the assessment of hepatic histology, (17, 18) including TE, (19, 20) ARFI, (21) and serological methods such as the aspartate aminotransferase to platelet ratio index (APRI) (22) and FibroTest. (23)

Prevalence and Incidence

Liver fibrosis is commonly caused by hepatitis B, hepatitis C, NAFLD, ALD, cholestatic liver disease, and liver transplant complications. Viral hepatitis (specifically chronic hepatitis B and C) affects more than 500 million people worldwide and approximately 600,000 Canadians. It has been estimated that about 10% of Canadians has some form of liver disease. Chronic viral

hepatitis, fatty liver disease, and liver cancer are responsible for nearly 95% of deaths from liver disease. (24)

Ontario Context

Data for the incidence and prevalence of chronic liver disease in Ontario are severely limited. According to the health administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES), ALD is the most prevalent liver disease in Ontario; its incidence has increased from 2003 to 2012. The incidence of hepatitis B, hepatitis C, and NAFLD has been stable over the past decade (Table 1).

Table 1: Incidence and Prevalence of Hepatitis B, Hepatitis C, ALD, and NAFLD in Ontario

Year	Incidence Per 100,000 Population				Prevalence Per 100,000 Population			
	Hepatitis B	Hepatitis C	ALD	NAFLD	Hepatitis B	Hepatitis C	ALD	NAFLD
2003	3.7	11.6	11.7	4.2	4.6	17.6	18.8	4.3
2004	3.5	10.9	12.2	4.2	4.5	16.6	19.4	4.3
2005	3.7	11.7	12.5	4.8	4.7	16.8	19.3	5.0
2006	4.5	12.6	12.9	4.0	5.8	18.8	20.3	4.1
2007	4.2	13.2	13.3	4.0	5.5	19.7	20.8	4.1
2008	3.9	12.5	13.6	4.0	5.2	18.7	21.2	4.2
2009	5.0	12.3	14.1	4.3	6.7	18.6	22.2	4.5
2010	4.5	12.1	14.6	4.1	6.7	18.8	23.0	4.3
2011	4.2	12.1	15.1	4.4	6.2	19.1	24.7	4.6
2012	4.3	11.5	15.5	4.4	6.1	18.9	25.5	4.5

Abbreviations: ALD, alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease.
Source: Institute for Clinical Evaluative Sciences.

Interventions Under Evaluation

Separate evaluations were conducted for liver fibrosis and steatosis. For both conditions, base case analyses were performed to compare the costs and effectiveness of TE (with and without CAP) with liver biopsy. Two other noninvasive tests— ARFI and FibroTest—were evaluated in a scenario analysis. Table 2 summarizes the interventions evaluated in the economic analysis, along with the comparator(s) for each intervention.

Table 2: Disease Interventions and Comparators Evaluated in the Economic Analysis

Interventions vs. Comparators	Patient Population	Outcomes
Liver fibrosis: TE vs. liver biopsy	Patients with hepatitis B, hepatitis C, ALD, or NAFLD	Incremental cost per correctly diagnosed fibrosis
Liver steatosis: TE with CAP vs. liver biopsy	All patients with chronic liver disease	Incremental cost per correctly diagnosed steatosis

Abbreviations: ALD, alcoholic liver disease; CAP, controlled attenuation parameter; NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

Transient Elastography

Transient elastography (brand name: FibroScan) has been approved for measuring liver stiffness. (25) It is performed using an ultrasound transducer probe mounted on the axis of a vibrator. The transducer transmits vibrations of mild amplitude and low frequency, inducing an elastic shear wave that propagates through the underlying tissues. Pulse-echo ultrasound acquisition is used to follow the propagation of the shear wave and measure its velocity, which is directly related to tissue stiffness: the stiffer the tissue, the faster the shear wave propagates. TE measures liver stiffness in a volume that approximates a cylinder 1 cm wide and 4 cm long, between 2.5 cm and 6.5 cm below the skin surface—at least 100 times more than a biopsy sample. (26)

Transient elastography is painless, rapid and simple. It can be performed at the bedside or in an outpatient clinic by medical or nonmedical personnel, under the supervision of a clinical practitioner. (27) Only limited training is required to use TE and obtain accurate results. (28) The operator performs at least 10 valid acquisitions, and the median value is then calculated. The results are immediately available and expressed in kilopascals (kPa), corresponding to the median value of 10 validated measurements and ranging from 2.5 to 75 kPa. (29) The success rate is calculated as the number of valid measurements divided by the total number of measurements. A success rate greater than 60% is considered reliable. (30) TE has been shown to be reliable for the assessment of liver fibrosis in patients with chronic hepatitis B, hepatitis C, ALD, NAFLD, and cholestatic liver disease. The major limitation of TE is its inability to obtain liver stiffness measurements in approximately 5% to 10% of cases, mainly in patients who are overweight, who have narrow intercostal space, or who have ascites. (31) Liver stiffness values may also be influenced by metabolic syndrome, even in the absence of biological features of NAFLD. (32)

Transient elastography has been licensed in Canada for liver assessment since August 2009. (33) Since its approval, it has been made available in 20 centres in Ontario. The device costs approximately $88,450, plus an additional $32,000 for each probe and a $2,500 annual maintenance fee. There is a standard probe (M probe), a probe for obese patients (XL probe), and a pediatric probe (S probe). The optimal frequency of patient testing has yet to be determined. TE is not currently covered by the Ontario Health Insurance Plan, so there are no billing codes associated with the procedure. Patients are required to pay approximately $90 (34) to $100 (35) out of their own pocket for a test if they do not have private insurance.

Controlled Attenuation Parameter

Controlled attenuation parameter is paired with TE to measure the degree of ultrasound attenuation by hepatic fat at the central frequency of TE. It has been shown to correlate well with hepatic steatosis and have excellent diagnostic performance. (36-38) Myer et al (39) found that CAP was moderately correlated with percentage of steatosis (ρ = 0.47) and steatosis grade (ρ = 0.51). For significant steatosis (10% of affected hepatocytes), the area under receiver operating characteristic curve for CAP was 0.81, while its sensitivity and specificity were 0.76 and 0.79, respectively. The device cost is $28,000 (personal communication, Shahid Khandker, KNS Canada Inc., January 19, 2015). A fee of $35 per CAP scan is currently charged in addition to the fee for the TE procedure. (34)

Liver Biopsy

Liver biopsy is the gold standard for assessing the degree of fibrosis and steatosis. The most common indication for liver biopsy is diagnosis or assessment of fibrosis in a patient with a known diagnosis, such as NAFLD or hepatitis C. Liver biopsy can be performed using one of three methods: percutaneous, transvenous (transjugular or transfemoral), and surgical/laparoscopic; (10) the choice of liver biopsy method is determined by the clinical situation. Percutaneous liver biopsy is the most commonly performed. Transvenous biopsy is available for patients with clinically demonstrable ascites; a known or suspected hemostatic defect; or a small, hard, cirrhotic liver. Surgical/laparoscopic biopsy may be performed if surgery or laparoscopy is being carried out for other purposes or if percutaneous liver biopsy is inconclusive. (40) According to the Canadian Association of Gastroenterology, (40) liver biopsy is generally indicated for the following:

- unexplained elevated liver enzyme levels
- elevated aminotransferase levels for 6 months or longer
- hepatomegaly of unclear etiology
- assessment of response to therapy for chronic liver disease
- unexplained jaundice without evidence of extrahepatic obstruction
- monitoring of hepatotoxicity related to drug therapy
- fever of unknown origin
- liver transplant evaluation

Outpatient biopsy with or without ultrasound guidance is advocated in select patients. (41) Most series have confirmed low rates of serious complications related to biopsy, including hemorrhage (0.3% to 0.6%) (42-44) and death (0.01% to 0.30%). (42, 43)

Based on utilization data from ICES, there was an overall decrease in the number of liver biopsies performed in Ontario between 2003 and 2012, especially in patients with hepatitis B and C. The number of liver biopsies decreased from 4,454 in 2003 to 2,053 in 2012 (Figure 1). The average number of biopsies per patient was one procedure per year.

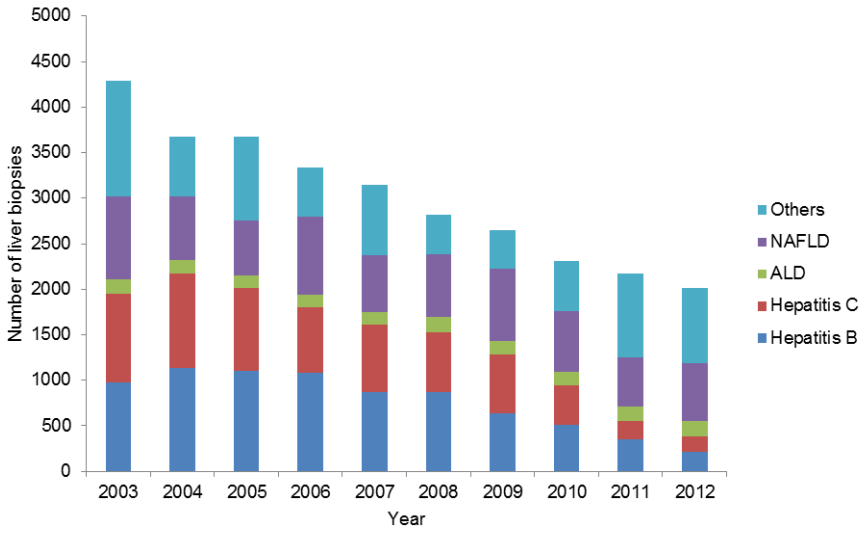

Figure 1: Liver Biopsies in Ontario by Type of Liver Disease, 2003 to 2012

Abbreviations: ALD, alcoholic liver disease; NAFLD, nonalcoholic fatty liver disease.

Other Technologies

Other noninvasive tests or markers can provide information about fibrosis stage in patients with chronic liver disease, including FibroTest, APRI, and ARFI. FibroTest is a composite of five serum biochemical markers associated with hepatic fibrosis (alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, gamma-glutamyltranspeptidase, and bilirubin). (45, 46) Several studies have assessed the diagnostic accuracy of FibroTest; Shaheen et al (47) showed that the area under the receiver operating characteristic curves for FibroTest ranged from 0.66 to 0.86.

APRI is a simple, inexpensive, and easily available assessment method, but its performance has varied in studies of patients with hepatitis C and hepatitis B. (48)

ARFI is performed using an ultrasound probe that automatically produces an acoustic push pulse, generating shear waves that propagate into the liver tissue; the higher the propagation speed, the more severe the fibrosis. (49) A recent meta-analysis suggested that ARFI had a predictive value similar to TE for significant fibrosis and cirrhosis. (49)

In a large Canadian survey of 237 physicians who manage patients with liver disease, 46.2% of respondents used liver biopsy as the primary diagnostic tool for assessment of liver fibrosis, followed by TE (39.4%) and FibroTest (7.7%). A large proportion of participating physicians (42.7%) believed that improved access to noninvasive methods would reduce the need for liver biopsy by at least 50%. (50)

ECONOMIC ANALYSIS

Research Questions

- What is the cost-effectiveness and 1-year budget impact of TE compared to liver biopsy for the diagnosis of liver fibrosis in patients living with hepatitis B, hepatitis C, ALD, or NAFLD?
- What is the cost-effectiveness and 1-year budget impact of TE with CAP compared to liver biopsy for the diagnosis of hepatic steatosis in patients living with chronic liver diseases?

Economic Literature Review

Research Methods

Literature Search

An experienced information specialist produced and tested preliminary electronic search strategies using an iterative process and in collaboration with the research team. An economic literature search was performed and updated on March 9, 2015, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Embase, Embase Classic, and the Cochrane Library (HTA database, NHSEED, DSR, DARE, and CENTRAL). There were no restrictions on any of the search strategies. (Appendix 1 provides details of the search strategies.)

We conducted grey literature searches for ongoing and unpublished studies. We also searched the websites of relevant organizations, including the Canadian Agency for Drugs and Technologies in Health, the Institute of Health Economics, the National Institute for Health and Care Excellence, EuroScan, and the Centre for Reviews and Dissemination database.

For practical reasons, we retrieved only full-text reports that were available electronically; we documented the exclusion of records without available full-text reports.

Screening and Selection

Citations de-duplicated in Reference Manager (Thomson Reuters, New York, NY) were uploaded into Distiller Systematic Review (Evidence Partners, Ottawa, ON) for level 1 and 2 screening. At level 1 screening, one reviewer assessed titles and abstracts for potential relevance; a second reviewer verified records that were deemed not relevant. At level 2 screening, two independent reviewers assessed full-text reports for eligibility. Disagreements between reviewers during full-text screening were resolved via consensus. Co-publications or multiple reports of the same study were identified as such. One reviewer extracted data from the full-text reports and a second reviewer verified the information.

Inclusion Criteria

- English/French-language full-text publications
- full economic evaluations: cost-utility analyses, cost-effectiveness analyses, cost-benefit analyses, cost-consequence analyses, cost-minimization analyses
- studies comparing TE to liver biopsy, FibroTest, or ARFI in patients with hepatitis B, hepatitis C, ALD, or NAFLD

Exclusion Criteria

- non-English/French-language publications
- abstracts, posters, letters/editorials, comments
- non-full-text publications
- animal studies

Results of Economic Literature Review

The database search yielded 241 citations published before March 9, 2015 (with duplicates removed). An additional 11 records were identified by bibliographic search. A flow diagram of the study selection process is shown in Figure 2.

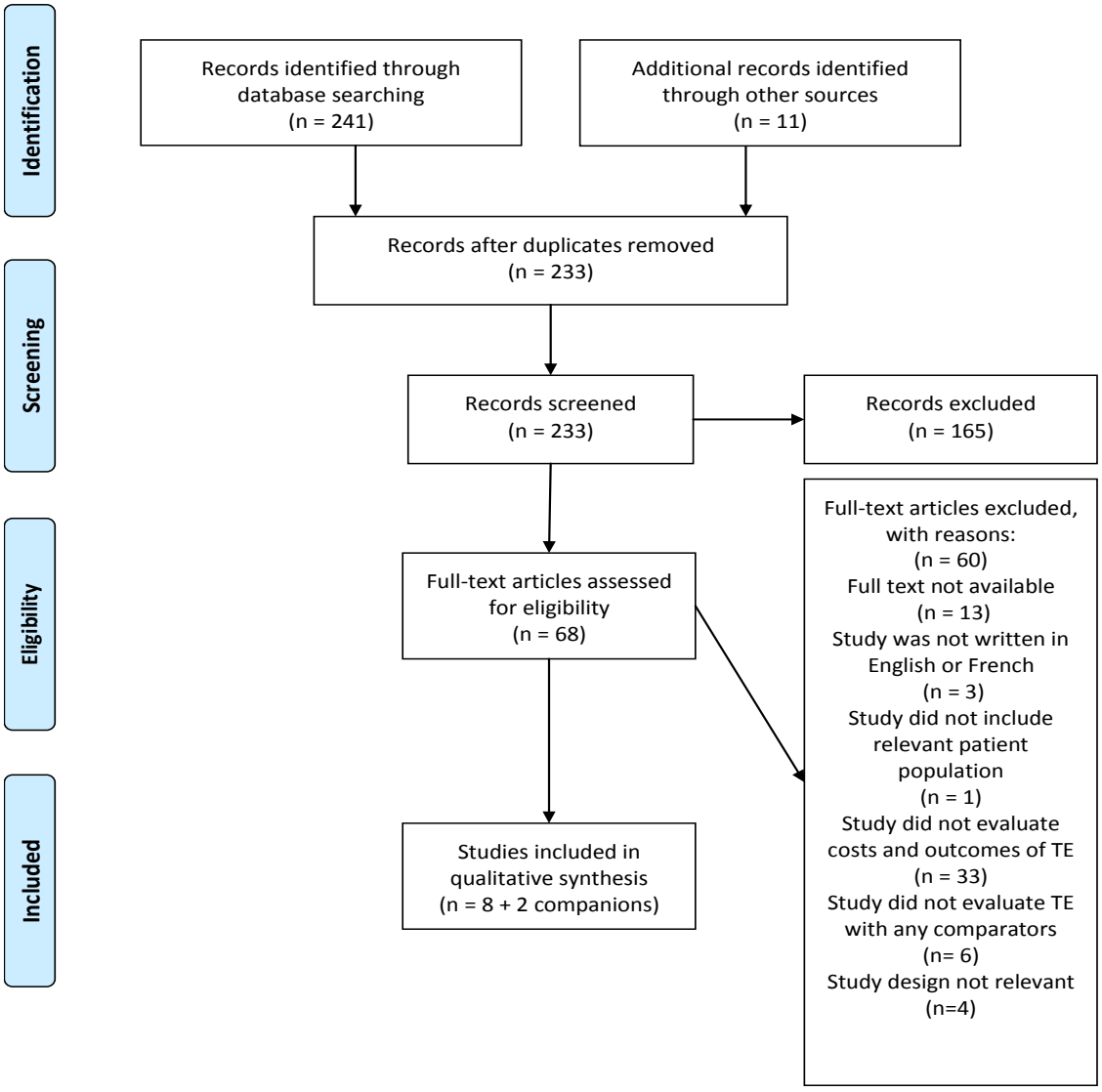

Figure 2: PRISMA 2009 Flow Diagram

Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TE, transient elastography.

A summary of the characteristics and findings of the 10 included studies is presented in Table 2. The objective of all 10 studies was to assess the cost-effectiveness of TE compared to liver biopsy and other noninvasive tests (e.g., FibroTest and ARFI) in the diagnosis, staging, and monitoring of liver fibrosis associated with hepatitis C, hepatitis B, ALD, or NAFLD. The results of this systematic review suggested that compared to liver biopsy, TE incurred lower health care costs but yielded fewer correctly diagnosed cases than liver biopsy. TE was a cost-effective technology relative to liver biopsy for the diseases of interest when considering the long-term costs and outcomes associated with fibrosis.

The review found no economic studies that assessed the cost-effectiveness of TE with CAP in diagnosing liver steatosis; further investigation is needed to assess its value for money.

Table 3: Results of Economic Literature Review

Name, Year Location (Companion)	Study Design and Perspective	Population/ Comparator	Intervention(s)	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Steadman et al, 2012 (58) Canada (Steadman et al, 2013 (51))	*Type of analysis* SR/HTA *Perspective* Health care system *Included studies* 57 adult, 1 pediatric *Currency* Canadian dollars *Cost year* 2010 *Modelling methods* Decision tree	N = adult 14,943, pediatric 52 *Population* Adult: hepatitis B, hepatitis C, NAFLD, cholestatic liver disease, liver transplant Pediatric: nonalcoholic steatohepatitis *% Female* NR *Intervention* NR *Comparator* NR	*Intervention* TE *Comparator* Liver biopsy	NR	*Total cost* TE (per scan) $99.44 Liver biopsy $461.30 *Incremental costs* Potential cost savings were approximately $362 to replace each liver biopsy with TE	*ICER* Incremental cost per correct diagnosis ($/correct diagnosis gained); the additional cost per correct diagnosis using liver biopsy compared to TE varied from $1,427 to $7,030, depending on the disease group considered *Hepatitis B* F ≥ 2 $1,427; F ≥ 3 $1,985; F = 4 $2,010 *Hepatitis C* F ≥ 2 $1,861; F ≥ 3 $3,620; F = 4 $3,542 *NAFLD* F ≥ 2 $1,498; F ≥ 3 NR; F = 4 $6,798 *Cholestatic liver disease* F ≥ 2 $2,582; F ≥ 3 $4,569; F = 4 $7,030
Whitty et al, 2014 (57) Australia	*Type of analysis* Cost of illness/cost analysis *Perspective* Public hospital services in Queensland, Australia (Queensland Health) *Included studies (only SR/HTA)* NA *Currency* Australian dollars *Cost year* 2012 *Modelling methods* *NA*	N = 40 *Population* HCV-infected patients *% Female* 39 *Intervention* 40 *Comparator* 38	*Intervention* TE *Comparator* Liver biopsy	NR	*Total cost, mean ± SD; median (25th, 75th percentile)* TE AU$2,782 ± $565; AU$2,716 ($2,371, $3,116) Liver biopsy AU $5,822 ± $2,447; AU$5,005 ($3,790, $7,076) *Screening test cost mean ± SD; median (25th, 75th percentile)* TE AU $972 ± $407; AU$788 ($739, $887) Liver biopsy AU$2,210 ± $1,100; AU$2,050 ($1,632, $2,188)	NA

Name, Year Location (Companion)	Study Design and Perspective	Population/ Comparator	Intervention(s)	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Canavan et al, 2013 (55) United Kingdom	*Type of analysis* Cost-effectiveness analysis *Perspective* Hospital *Included studies (only SR/HTA)* NA *Currency* British pounds *Cost year* 2012 *Modelling methods* Markov model	N = hypothetical cohort of 10,000 patients *Population* Chronic hepatitis C *% Female* NR *Intervention* NR *Comparator* NR	*Intervention* • Intermittent biopsy, followed by ultrasound and blood test every 6 months • Annual biopsy, followed by liver cancer screening at 6-month intervals once cirrhosis was identified • Replacing intermittent liver biopsy by TE with confirmation liver biopsy, followed by liver cancer screening at 6-month intervals once cirrhosis is identified • Annual TE with confirmation liver biopsy, followed by liver cancer screening at 6-month intervals once cirrhosis is identified • Annual TE as a definitive test, followed by liver cancer screening at 6-month intervals once cirrhosis is identified *Comparator* No surveillance of fibrosis stage	*Incremental outcomes* Use of TE provided an additional 1.72 unadjusted life-years compared to the next best strategy	Lifetime extra cost of £98.78 per patient compared to the current strategy	*ICER* Annual definitive TE was cost-effective using a threshold of £30,000 per QALY

Name, Year Location (Companion)	Study Design and Perspective	Population/ Comparator	Intervention(s)	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Stevenson et al, 2012 (54) United Kingdom	*Type of analysis* SR/HTA *Perspective* hospital *Included studies (only SR/HTA)* 5 *Currency* NR *Cost year* NR *Modelling methods* *NR*	N = NR *Population* Known or suspected ALD and patients with mixed etiology *% Female* NR *Intervention* NR *Comparator* NR	*Intervention* TE *Comparator* Liver biopsy	*Incremental outcomes* NR	NR	*ICER* No estimate provided regarding incremental costs or incremental costs per QALY
Carlson et al, 2009 (56) United States	*Type of analysis* Cost-effectiveness analysis *Perspective* Hospital *Included studies (only SR/HTA)* NA *Currency* US dollars *Cost year* 2005 *Modelling methods* Decision analytic model	N = hypothetical cohort of 1,000 patients *Population* HCV *% Female* NR *Intervention* NR *Comparator* NR	*Intervention* • TE • Fibrosure • Fibrospect II *Comparator* Liver biopsy	*Incremental outcomes* Approximately 8% false positives and 10% false negatives	*Total evaluation cost per person* TE US$131 Liver biopsy US$1,255 Compared to liver biopsy, there was a cost savings of ~US$1,124 per person using TE	*ICER* Cost savings of US$1,124 per person, but a net decrease of 18% in the number of people accurately diagnosed The average cost per correct diagnosis with TE compared to liver biopsy was US$1,096
Murtagh et al, 2006 (27) Canada	*Type of analysis* SR/HTA *Perspective* NA *Included studies (only SR/HTA)* 7 *Currency* Canadian dollars and British pounds *Cost year* NR	N = NR *Population* Hepatitis C, other chronic liver disease, HIV and HCV coinfected *% Female* NR *Intervention* NR *Comparator* NR	*Intervention* TE *Comparator* Liver biopsy	NR	*TE* Estimates included equipment costs of $100,464, annual maintenance contract costs of $7,560, and negligible costs for consumables. At 20 and 150 examinations annually, the cost per examination would be $1,400 and $140, respectively *Liver biopsy*	NR

Name, Year Location (Companion)	Study Design and Perspective	Population/ Comparator	Intervention(s)	Results		
				Health Outcomes	Costs	Cost-Effectiveness
	Modelling methods *NR*				Costs ranged from $984 to $2,192 in European centres, and $1,146 to $3,047 in US centres, depending on the incidence of complications	
Centre for Evidence-based Purchasing, 2009 (53) United Kingdom	*Type of analysis* SR/HTA *Perspective* Health care system *Included studies (only SR/HTA)* NR *Currency* British pounds *Cost year* 2007 *Modelling methods* Decision tree	N = NR *Population* NR *% Female* NR *Intervention* NR *Comparator* NR	*Intervention* TE *Comparators* Liver biopsy, FibroTest	NR	*Total cost* TE £18.68 Liver biopsy £855.66 FibroTest £74.28 *Incremental costs* FibroTest vs. TE: total extra cost of TE for F2–F4 was £77,193.81; for F4 only was cost-saving TE vs. biopsy: total extra cost of biopsy for F2–F4 was £441,327.44; for F4 only was £659,863.01	*ICER, cost per CDF gained* FibroTest vs. TE: F2 to F4 £599.33; F4 only dominant TE vs. biopsy: F2 to F4 £2,626.95; F4 only £33,839.13
Crossan et al, 2015 (52) United Kingdom (Tsochatzis et al, 2014 (59))	*Type of analysis* SR/HTA *Perspective* Health care system *Included studies (only SR/HTA)* 302 *Currency* British pounds *Cost year* 2012 *Methods used to estimate costs* Decision tree and Markov model	N = NR *Population* HBV, HCV, ALD, NAFLD *% Female* NR *Intervention* NR *Comparator* NR	*Intervention* TE *Comparator* Liver biopsy, all noninvasive diagnostic tests (e.g., FibroTest, APRI, and ARFI)	*HBV e antigen-positive (QALYs)* TE 11.61 Liver biopsy 11.41 ARFI 11.71 FibroTest 11.62 *HBV e antigen-negative (QALYs)* TE 9.93 Liver biopsy 9.64 ARFI 10.10 FibroTest 9.93 *HCV (QALYs)* TE 14.28 Liver biopsy 14.03 ARFI 14.25 FibroTest 14.30 *ALD (QALYs)* TE 9.02 Liver biopsy 9.31 FibroTest (low cut-off): 9.13 FibroTest (high cut-	*HBV e antigen-positive* TE £79,004 Liver biopsy £75,957 ARFI £83,487 FibroTest £79,519 *HBV e antigen-negative* TE £73,007 Liver biopsy £70,274 ARFI £77,512 FibroTest £73,739 *HCV* TE £47,449 Liver biopsy £48,710 ARFI £47,126 FibroTest £48,327 *ALD* TE £20,009 Liver biopsy £17,801 FibroTest (low cut-off): £24,671 FibroTest (high cut-off): £19,054 *NAFLD* TE £51	At a willingness to pay of £30,000, TE was cost-effective for HBV, HCV, and ALD. TE was cost-saving compared to liver biopsy but also reduced the number of true positives and true negatives in patients with NAFLD

Name, Year Location (Companion)	Study Design and Perspective	Population/ Comparator	Intervention(s)	Results		
				Health Outcomes	Costs	Cost-Effectiveness
				off): 9.03 *NAFLD (test positive cases)* TE 155 Liver biopsy 189 FibroTest 158 ARFI 170 *NAFLD (test negative cases)* TE 681 Liver biopsy 811 FibroTest 783 ARFI 726	Liver biopsy £956.61 FibroTest £59.31 ARFI £51	

Abbreviations: ALD, alcoholic liver disease; ARFI, acoustic radiation force impulse; APRI, aspartate aminotransferase to platelet ratio index; CDF, correctly diagnosed fibrosis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; NA, not applicable; NAFLD, nonalcoholic fatty liver disease; NR, not reported; QALY, quality-adjusted life-year; SD, standard deviation; SR, systematic review; TE, transient elastography.
Costs in Canadian dollars unless otherwise specified.

Primary Economic Evaluation

The published economic evaluations identified in the literature review addressed the interventions of interest, but none of them took an Ontario perspective. Due to these limitations, a primary economic evaluation was conducted.

Research Methods

Type of Analysis

A cost-effectiveness analysis was conducted to compare the incremental costs and incremental outcomes of TE (with and without CAP) with liver biopsy for diagnosing liver fibrosis or steatosis in patients with hepatitis B, hepatitis C, ALD, and NAFLD. Because the diagnostic accuracy of TE was influenced by fibrosis prevalence and disease type, we conducted a separate cost-effectiveness analysis for each disease, each stage of liver fibrosis ($F \geq 2$, $F \geq 3$, and $F = 4$) and each stage of liver steatosis ($S \geq 1$, $S \geq 2$, and $S = 3$).

Interventions Evaluated

In the base case analyses, separate cost-effectiveness analyses were conducted for TE versus liver biopsy in liver fibrosis, and for TE with CAP in liver steatosis. We investigated the cost-effectiveness of two other noninvasive fibrosis tests—FibroTest and ARFI—in a scenario analysis.

Perspective

The analysis was conducted from the perspective of the Ontario Ministry of Health and Long-Term Care.

Discounting and Time Horizon

The time horizon was 1 year, so discounting was not required.

Target Population

The study population included all patients with chronic liver disease as a result of hepatitis B virus (HBV), hepatitis C virus (HCV), ALD, and NAFLD. We focused on these four causes of liver disease because staging of fibrosis is important for their prognosis and management. For all other causes of chronic liver disease, only the diagnosis of cirrhosis is important and liver biopsy is seldom performed for fibrosis staging.

Variability and Uncertainty

Variability and uncertainty in the model were assessed using one-way and probabilistic sensitivity analyses. Sensitivity analyses were undertaken to test the robustness of the model to changes in assumptions and data sources; one or more parameters were changed and the analysis was rerun to evaluate the impact of these changes on the results of the model.

The model was also built probabilistically to take into account the uncertainty surrounding each parameter by assigning distributions around the point estimate. Beta distributions were used for parameters whose values were constrained between zero and one, including the prevalence of liver fibrosis or steatosis, and the sensitivity and specificity of diagnostic tests. Cost data, such as the cost of liver biopsy, were assumed to have a gamma distribution. No distributions were applied to certain variables based on assumptions (i.e., cost of TE). When the model was run, a value for each parameter was randomly selected from its respective distribution. The model was run repeatedly (1,000 times) to obtain mean cost and outcome values. Whenever possible,

results were presented as probability of cost-effectiveness by ceiling ratio or willingness-to-pay values and cost-effectiveness analysis planes.

Two further scenarios were performed. The first estimated the short-term cost-effectiveness of TE, FibroTest, ARFI, and liver biopsy. The second used long-term costs and quality-adjusted life-years (QALYs) reported in a study by Crossan et al (52) to simulate the long-term cost-effectiveness of TE compared to liver biopsy in HBV- and HCV-infected patients.

Validation

The model structure was developed in consultation with clinical experts as a reasonable simplification of the decision-making and disease processes. The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given the inputs. The model was peer-reviewed by a second experienced health economist from the Ottawa Hospital Research Institute. The results of the model were validated against cost-effectiveness findings reported in previous studies.

Interpretation

The results of cost-effectiveness analyses are presented as incremental cost-effectiveness ratios (ICERs), which were calculated by dividing the difference in costs associated with two alternative strategies by the difference in correctly diagnosed fibrosis or correctly diagnosed steatosis. The number of correct diagnoses was equal to the sum of true positive and true negative cases.

In a scenario analysis comparing four strategies, the ICER was calculated according to the following process:

- Interventions were ranked in terms of diagnostic accuracy from the most accurate to the least accurate.
- If an intervention was more expensive or the same price but less accurate than the preceding one, it was deemed to be “dominated” and was excluded from further analysis.
- ICERs were then calculated for each strategy compared with the next most accurate nondominated option. If the ICER for an intervention was lower than that of the next most effective strategy, then it was excluded by “extended dominance.”
- ICERs were recalculated, excluding any strategies subject to dominance or extended dominance.

An intervention was considered to be cost-effective if it was less expensive and more effective than alternative options, or if the increased cost of an intervention was deemed to be justified by its increased effectiveness.

Model Structure

Given the broad spectrum of liver conditions of interest and the paucity of data regarding the long-term impacts of TE on liver disease progression and mortality, we used a simple decision tree model. The model was created to address the clinical decisions faced by a physician requesting a diagnostic test for liver fibrosis or steatosis (Figure 3). In the model, a patient was screened using either TE or liver biopsy. The current prevalence of significant fibrosis was used to represent the likelihood that the model patient had liver fibrosis. Based on the diagnostic

accuracy of TE, the patient was classified as a true positive, a false positive, a true negative, or a false negative. True positives and true negatives were considered to be correct diagnoses.

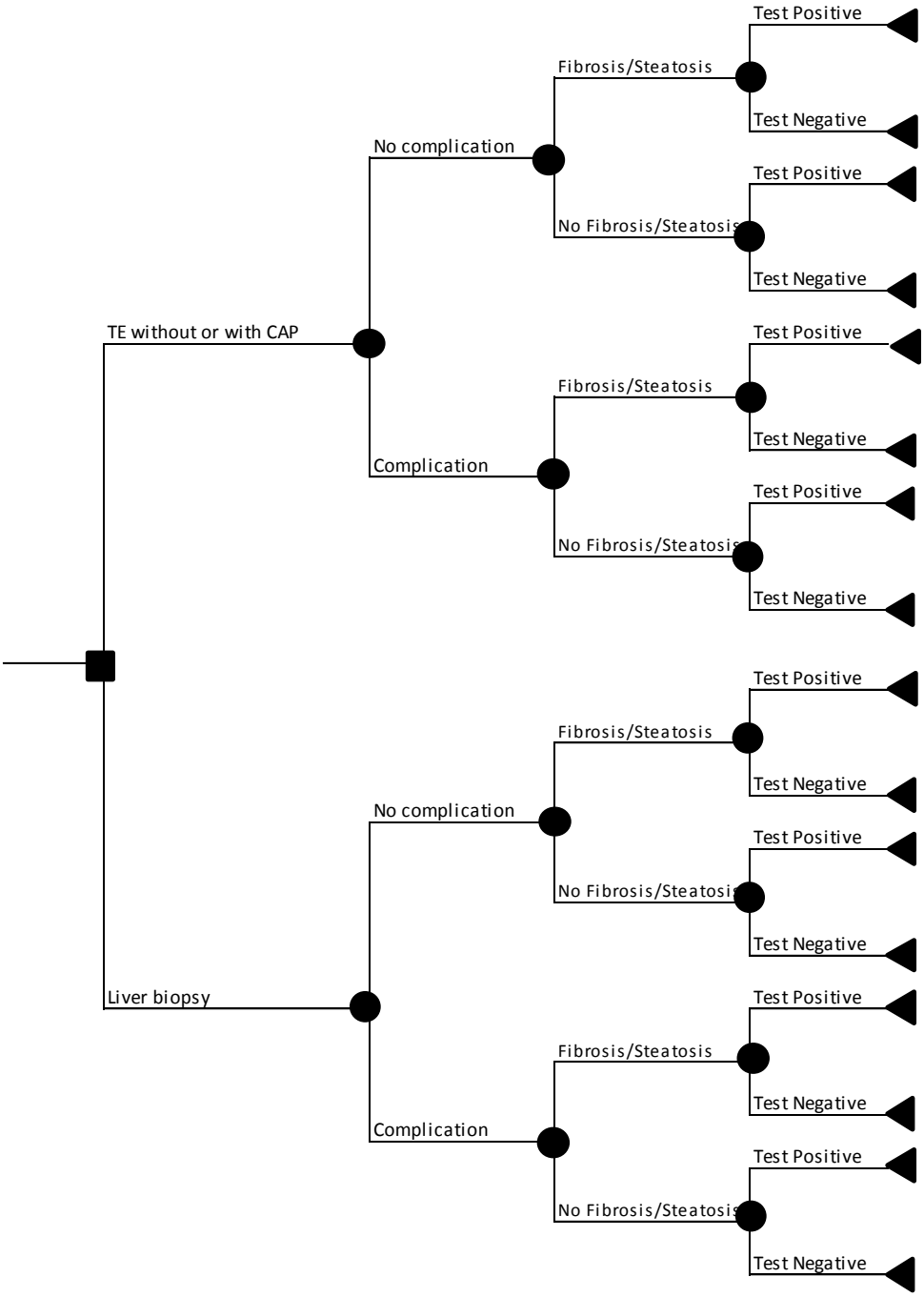

Figure 3: Model Structure

Abbreviations: CAP, controlled attenuation parameter; TE, transient elastography.

Model Input Parameters

Probabilities

A number of different input parameters were used to populate the model. These parameters were obtained from the Health Quality Ontario evidence-based analysis, (60) administrative databases housed at ICES, and the Ottawa Hospital Data Warehouse. Of the 13 systematic reviews evaluating TE for liver fibrosis included in the evidence-based analysis, we chose to obtain the accuracy of noninvasive tests and the prevalence of fibrosis from the systematic review conducted by Crossan et al, (52) because it was the most recent and most comprehensive. The review also reported diagnostic accuracy according to disease type and fibrosis stage. We obtained the accuracy of TE with CAP from a systematic review of nine studies that evaluated the accuracy of CAP compared to liver biopsy. (38) Since liver biopsy is considered the standard of care, we assumed that it correctly diagnosed 100% of patients (i.e., sensitivity and specificity were = 1).

Table 4: Input Parameters Used in the Economic Model

Model Parameters	Base Case Value	Range	Distribution	Reference
Prevalence of Liver Fibrosis				
Hepatitis B				
F ≥ 2	0.53	0.27–0.92	Beta	(52)
F ≥ 3	0.37	0.17–0.78	Beta	(52)
F = 4	0.21	0.00–0.60	Beta	(52)
Hepatitis C				
F ≥ 2	0.52	0.06–0.89	Beta	(52)
F ≥ 3	0.29	0.05–0.78	Beta	(52)
F = 4	0.17	0.03–0.68	Beta	(52)
ALD				
F ≥ 3	0.51	0.40–0.75	Beta	(52)
F = 4	0.45	0.15–0.97	Beta	(52)
NAFLD				
F ≥ 3	0.19	0.05–0.44	Beta	(52)
F = 4	0.13	0.04–0.91	Beta	(52)
Prevalence of Liver Steatosis				
S ≥ 1	0.47	NA	Fixed	(38)
S ≥ 2	0.29	NA	Fixed	(38)
S = 3	0.11	NA	Fixed	(38)
Sensitivity				
Hepatitis B				
TE				
F ≥ 2	0.71	0.62–0.78	Beta	(52)
F ≥ 3	0.69	0.58–0.78	Beta	(52)
F = 4	0.86	0.79–0.91	Beta	(52)
FibroTest				
F ≥ 2	0.66	0.57–0.75	Beta	(52)
F ≥ 3	0.49	0.01–0.99	Beta	(52)
F = 4	0.74	0.25–0.96	Beta	(52)
ARFI				
F ≥ 2	0.71	0.59–0.80	Beta	(52)

Model Parameters	Base Case Value	Range	Distribution	Reference
F ≥ 3	NA	NA	NA	(52)
F = 4	NA	NA	NA	(52)
Hepatitis C				
TE				
F ≥ 2	0.79	0.74–0.84	Beta	(52)
F ≥ 3	0.88	0.82–0.92	Beta	(52)
F = 4	0.89	0.84–0.92	Beta	(52)
FibroTest				
F ≥ 2	0.68	0.58–0.77	Beta	(52)
F ≥ 3	0.73	0.56–0.85	Beta	(52)
F = 4	0.60	0.43–0.76	Beta	(52)
ARFI				
F ≥ 2	0.79	0.75–0.83	Beta	(52)
F ≥ 3	0.85	0.69–0.94	Beta	(52)
F = 4	0.84	0.72–0.91	Beta	(52)
ALD				
TE				
F ≥ 3	0.81	0.70–0.88	Beta	(52)
F = 4	0.86	0.76–0.92	Beta	(52)
FibroTest				
F ≥ 3	0.84	0.77–0.88	Beta	(52)
F = 4	1.00	0.95–1.00	Beta	(52)
ARFI				
F ≥ 3	NA	NA	NA	(52)
F = 4	NA	NA	NA	(52)
NAFLD				
TE				
F ≥ 3	0.82	0.74–0.88	Beta	(52)
F = 4	0.86	0.79–0.91	Beta	(52)
FibroTest				
F ≥ 3	0.88	0.68–0.99	Beta	(52)
F = 4	0.74	0.54–0.87	Beta	(52)
ARFI				
F ≥ 3	0.90	0.77–0.96	Beta	(52)
F = 4	NA	NA	NA	(52)
TE with CAP				
S ≥ 1	0.78	0.69–0.84	Beta	(38)
S ≥ 2	0.85	0.74–0.92	Beta	(38)
S = 3	0.76	0.76–0.89	Beta	(38)
Liver biopsy	1	NA	Fixed	Assumed
Specificity				
Hepatitis B				
TE				
F ≥ 2	0.84	0.74–0.91	Beta	(52)
F ≥ 3	0.84	0.79–0.89	Beta	(52)
F = 4	0.85	0.78–0.89	Beta	(52)

Model Parameters	Base Case Value	Range	Distribution	Reference
FibroTest				
F ≥ 2	0.80	0.72–0.86	Beta	(52)
F ≥ 3	0.71	0.53–0.84	Beta	(52)
F = 4	0.90	0.83–0.94	Beta	(52)
ARFI				
F ≥ 2	0.67	0.30–0.90	Beta	(52)
F ≥ 3	NA	NA	NA	(52)
F = 4	NA	NA	NA	(52)
Hepatitis C				
TE				
F ≥ 2	0.83	0.77–0.88	Beta	(52)
F ≥ 3	0.90	0.85–0.93	Beta	(52)
F = 4	0.91	0.89–0.93	Beta	(52)
FibroTest				
F ≥ 2	0.72	0.70–0.77	Beta	(52)
F ≥ 3	0.73	0.56–0.85	Beta	(52)
F = 4	0.86	0.81–0.91	Beta	(52)
ARFI				
F ≥ 2	0.89	0.84–0.93	Beta	(52)
F ≥ 3	0.89	0.72–0.97	Beta	(52)
F = 4	0.77	0.50–0.92	Beta	(52)
ALD				
TE				
F ≥ 3	0.82	0.67–0.91	Beta	(52)
F = 4	0.83	0.74–0.89	Beta	(52)
FibroTest				
F ≥ 3	0.65	0.55–0.75	Beta	(52)
F = 4	0.50	0.42–0.58	Beta	(52)
ARFI				
F ≥ 3	NA	NA	NA	(52)
F = 4	NA	NA	NA	(52)
NAFLD				
TE				
F ≥ 3	0.84	0.78–0.89	Beta	(52)
F = 4	0.89	0.85–0.92	Beta	(52)
FibroTest				
F ≥ 3	0.73	0.56–0.85	Beta	(52)
F = 4	0.92	0.88–0.95	Beta	(52)
ARFI				
F ≥ 3	0.90	0.82–0.94	Beta	(52)
F = 4	NA	NA	NA	(52)
TE with CAP				
S ≥ 1	0.79	0.68–0.86	Beta	(38)
S ≥ 2	0.79	0.71–0.85	Beta	(38)
S = 3	0.79	0.68–0.87	Beta	(38)
Liver biopsy	1	NA	Fixed	Assumed

Model Parameters	Base Case Value	Range	Distribution	Reference
Probability of Experiencing Complications Associated With the Test				
Liver biopsy	0.0008	NA	Beta	(44)
Annual Utilization of TE				
Number of scans	793[a]	496[b]–1,553[c]	Gamma	(58)

Abbreviations: ALD, alcoholic liver disease; ARFI, acoustic radiation force impulse; CAP, controlled attenuation parameter; NA, not applicable; NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.
[a]Ottawa Warehouse Database.
[b]Foothills Hospital, Calgary.
[c]Personal communication, Liver Centre, Toronto Western Hospital, March 6, 2015.

Costs

Because this study took the perspective of the health care system, only direct costs were included. Cost data were obtained from various sources, and all cost parameters are shown in Table 5.

Table 5: Cost Parameters Used in the Economic Model

Cost Parameters	Base Case Value	Range	Distribution	Reference
TE	$174.90	$162.70–$189.70	Fixed	Estimated
TE with CAP	$199.90	$165.30–$197.80	Fixed	Estimated
FibroTest	$72.00	NA	Fixed	Estimated
ARFI	$174.90	$162.70–$189.70	Gamma	Assumed
Liver biopsy	$400.00	$349.11–$451.86	Gamma	(64)
Complications due to liver biopsy	$1,840.00	$1,084.79–$7,390.26	Gamma	(44, 61)

Abbreviations: ARFI, acoustic radiation force impulse; CAP, controlled attenuation parameter; TE, transient elastography.
All costs in Canadian dollars.

For TE and CAP, we included the cost of the device, annual maintenance costs, and the physician cost. The device and annual maintenance costs were obtained from the local distributor. In the base case, the cost of the device was amortized over an anticipated lifetime of 7 years, with an annual utilization rate of 793 scans (based on the 2013 average at the Ottawa Hospital).

Physician fees for TE with and without CAP were assumed to be $150 and $170, respectively, as proposed in the Ontario Health Technology Advisory Committee application.

We assumed that TE was performed within existing infrastructure, so no capital costs were included in the model (e.g., cost of room for TE device).

The cost of FibroTest was obtained from the Ottawa Hospital and Regional Hepatitis Program and estimated to be $72 per procedure. Because ARFI is not widely available in Canada, we assumed that its cost was equal to that of TE.

Costs of liver biopsy were gathered from the Ontario Case Costing Initiative database and the Ottawa Hospital Data Warehouse. The cost of complications associated with liver biopsy was estimated from a population-based study of 3,627 patients in the Calgary Health Region (44) and an economic analysis of ultrasound-guided liver biopsy. (61) These costs were varied in the sensitivity analysis.

All costs were converted and inflated to 2014 Canadian dollars using the Bank of Canada exchange rates (62) and the Statistics Canada health care consumer price index. (63)

Results of Primary Economic Evaluation

Base Case Analysis

Liver biopsy was more expensive and more effective than TE in all disease type and fibrosis stage subgroups. On average, liver biopsy cost $225.64 more per procedure than TE.

The ICERs fell in the southwest quadrant of the cost-effectiveness plane, suggesting that TE lowered costs but reduced the number of correctly diagnosed fibrosis cases. Specifically, in HBV-infected patients with stage F2 fibrosis, TE was associated with a cost savings of $22,711.01 but a net decrease of 23% in the number of patients accurately diagnosed (8% false positives and 15% false negatives). In HCV-infected patients with stage F2 fibrosis, TE led to a net decrease of 19% in the number of patients accurately diagnosed (8% false positives and 11% false negatives). For ALD and NAFLD, TE was associated with a decrease of 19% (9% false positives and 10% false negatives) and 16% (3% false positives and 13% false negatives) in the number of patients accurately diagnosed, respectively. (The number of correctly diagnosed fibrosis and steatosis cases is shown in Appendix 2.)

It is worth noting that the decision rule for the southwest quadrant is opposite to the northeast quadrant; that is, the higher the ICER, the more economically attractive the intervention is.

As shown in Table 6, the incremental cost per correct diagnosis gained for TE compared to liver biopsy varied from $993.31 to $2,431.59, depending on the subgroup considered. ICERs increased with severity of liver fibrosis, indicating that compared to liver biopsy, TE lowered health care costs substantially, with a minimal reduction in the number of correctly diagnosed cases.

Table 7 shows the cost-effectiveness of TE with CAP compared to liver biopsy for diagnosing liver steatosis. TE with CAP led to a cost savings of $20,212.94 regardless of steatosis stage, but it decreased the number of correctly diagnosed steatosis cases by 19% to 21%.

Table 6: Base Case Analysis—TE Versus Liver Biopsy for the Diagnosis of Liver Fibrosis, by METAVIR Stage

Strategy	Total Costs	Incremental Cost	F ≥ 2			F ≥ 3			F = 4		
			Total CDF, n	Incremental CDF, n	ICER	Total CDF, n	Incremental CDF, n	ICER	Total CDF, n	Incremental CDF, n	ICER
Hepatitis B											
Liver biopsy	$40,196.15	—	100	Reference		100	Reference		100	Reference	
TE	$17,485.14	–$22,711.01	77	–23	993.31	78	–22	1,053.88	85	–15	1,535.46
Hepatitis C											
Liver biopsy	$40,196.15	—	100	Reference		100	Reference		100	Reference	
TE	$17,485.14	–$22,711.01	81	–19	1,189.81	89	–11	2,146.19	91	–9	2,431.59
ALD											
Liver biopsy	$40,196.15	—	NA	NA	NA	100	Reference		100	Reference	
TE	$17,485.14	–$22,711.01	NA	NA	NA	81	–19	1,227.03	84	–16	1,450.63
NAFLD											
Liver biopsy	$40,196.15	—	NA	NA	NA	100	Reference		100	Reference	
TE	$17,485.14	–$22,711.01	NA	NA	NA	84	–16	1,387.19	89	–11	1,994.99

Abbreviation: ALD, alcoholic liver disease; CDF, correctly diagnosed fibrosis; ICER, incremental cost-effectiveness ratio; NA, not applicable; NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.
Note: Results are presented per 100 individuals requiring the diagnostic test.

Table 7: Base Case Analysis—TE With CAP Versus Liver Biopsy for the Diagnosis of Liver Steatosis, by Steatosis Stage

Strategy	Total Costs	Incremental Cost	S ≥ 1			S ≥ 2			S = 3		
			Total CDS, n	Incremental CDS, n	ICER	Total CDS, n	Incremental CDS, n	ICER	Total CDS, n	Incremental CDS	ICER
Liver biopsy	$40,202.49	—	100	Reference		100	Reference		100	Reference	
TE with CAP	$19,989.55	–$20,212.94	79	–21	941.54	81	–19	1,048.82	79	–21	983.69

Abbreviations: CAP, controlled attenuation parameter; CDS, correctly diagnosed steatosis; ICER, incremental cost-effectiveness ratio; TE, transient elastography.
Note: Results are presented per 100 individuals requiring the diagnostic test.

Scenario Analyses

Scenario 1: Cost-effectiveness of noninvasive tests (TE, FibroTest, ARFI) versus liver biopsy for diagnosing liver fibrosis in patients with hepatitis B, hepatitis C, ALD, and NAFLD

Table 8 demonstrates that when using liver biopsy as a reference, TE was the most cost-effective option for F ≥ 3 fibrosis in HBV-infected patients, F ≥ 3 and F = 4 fibrosis in HCV-infected patients, and F = 4 fibrosis in patients with ALD.

FibroTest was the most cost-effective for F ≥ 2 fibrosis in hepatitis B patients, F ≥ 3 fibrosis in ALD patients, and F = 4 fibrosis in NAFLD patients.

ARFI was the most-cost effective for F ≥ 2 fibrosis in hepatitis C patients and F ≥ 3 fibrosis in NAFLD patients.

The cost-effectiveness results of the noninvasive tests compared to liver biopsy are shown in Figures 4 to 7.

Table 8: Scenario Analysis—TE, FibroTest, and ARFI Versus Liver Biopsy for the Diagnosis of Liver Fibrosis by METAVIR Stage

Strategy	Total Costs	F ≥ 2				F ≥ 3				F = 4			
		Total CDF, n	ΔCost	ΔCDF, n	ICER	Total CDF, n	ΔCost	ΔCDF, n	ICER	Total CDF, n	ΔCost	ΔCDF, n	ICER
Hepatitis B													
Liver biopsy	$40,196.15	100	Reference			100	Reference			100	Reference		
TE	$17,485.14	77	–$22,711.01	–23	$993.31	78	–$22,711.01	–22	$1,053.88	85	–$22,711.01	–15	Dominated
ARFI	$17,485.14	69	$0	–8	Dominated	NA	NA	NA	NA	NA	NA	NA	NA
FibroTest	$7,200.00	73	–$10,285.14	–4	$2,271.45	63	–$ 10,285.14	–16	$659.73	87	–$32,996.15	–13	$2,472.73
Hepatitis C													
Liver biopsy	$40,196.15	100	Reference			100	Reference			100	Reference		
TE	$17,485.14	81	–$22,711.01	–19	Dominated	89	–$22,711.01	–11	$2,146.19	91	–$22,711.01	–9	$2,431.59
ARFI	$17,485.14	84	$0	–16	$1,400.19	88	$0	–1	Dominated	78	$0	–12	Dominated
FibroTest	$7,200.00	70	–$10,285.14	–14	$741.65	70	–$10,285.14	–18	$534.18	82	–$10,285.14	–9	$1,132.72
ALD													
Liver biopsy	$40,196.15	NA	NA	NA	NA	100	Reference			100	Reference		
TE	$17,485.14	NA	NA	NA	NA	81	–$22,711.01	–19	$1,227.03	84	–$22,711.01	–16	$1,450.63
ARFI	$17,485.14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FibroTest	$7,200.00	NA	NA	NA	NA	75	–$10,285.14	–7	$1,508.08	72	–$10,285.14	–12	$861.11
NAFLD													
Liver biopsy	$40,196.15	NA	NA	NA	NA	100	Reference			100	Reference		
TE	$17,485.14	NA	NA	NA	NA	84	–$22,711.01	–16	Dominated	89	–$22,711.01	–11	Dominated
ARFI	$17,485.14	NA	NA	NA	NA	90	$0	6	$2,271.10	NA	NA	NA	NA
FibroTest	$7,200.00	NA	NA	NA	NA	76	–$10,285.14	–14	$723.80	90	–$10,285.14	1	$998.17

Abbreviations: ALD, alcoholic liver disease; ARFI, acoustic radiation force impulse; CDF, correctly diagnosed fibrosis; ICER, incremental cost-effectiveness ratio; NA, not applicable; NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

Note: Results are presented per 100 individuals requiring the diagnostic test.

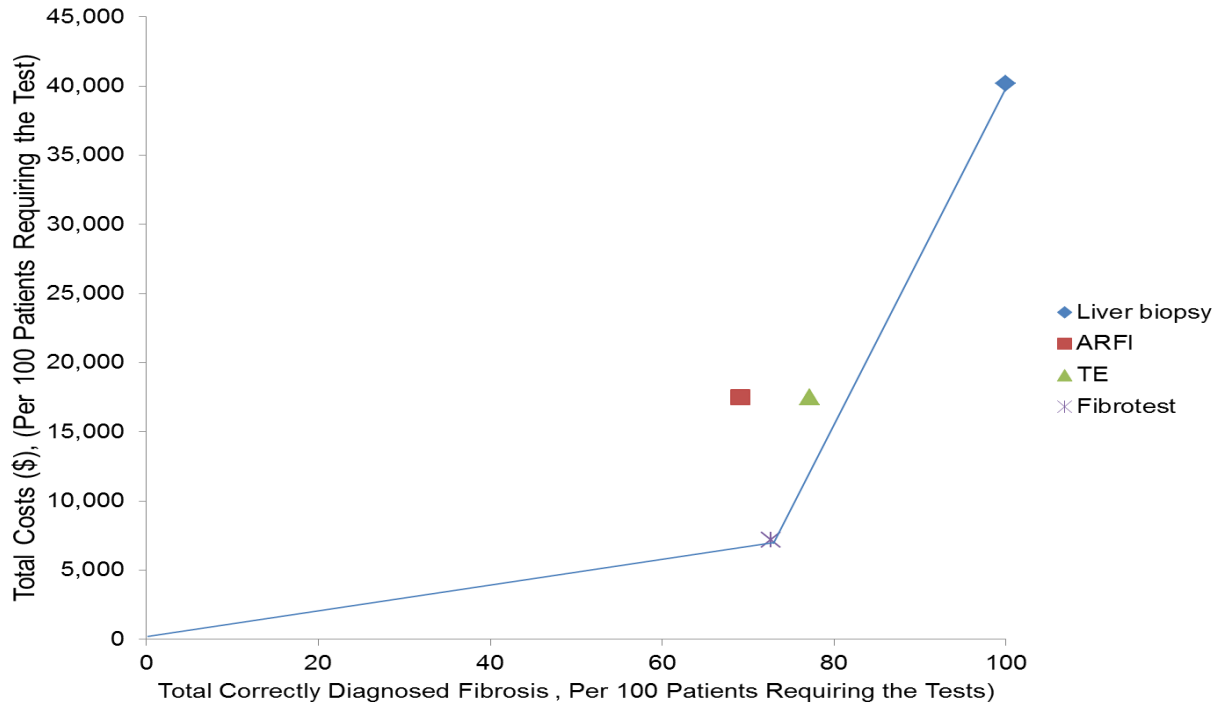

Figure 4: Cost-Effectiveness Efficiency Frontier for HBV (F ≥ 2)

Abbreviations: ARFI, acoustic radiation force impulse; HBV, hepatitis B virus; TE, transient elastography.

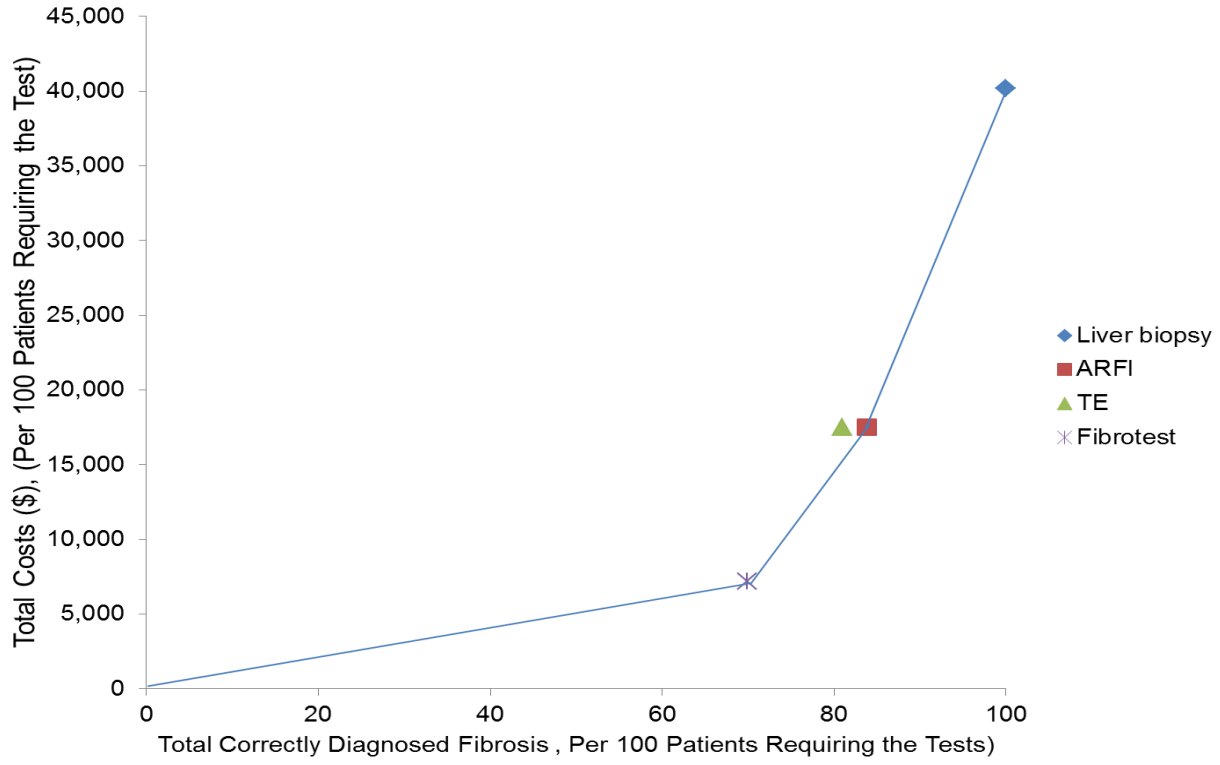

Figure 5: Cost-Effectiveness Efficiency Frontier for HCV (F ≥ 2)

Abbreviations: HCV, hepatitis C virus; TE, transient elastography.

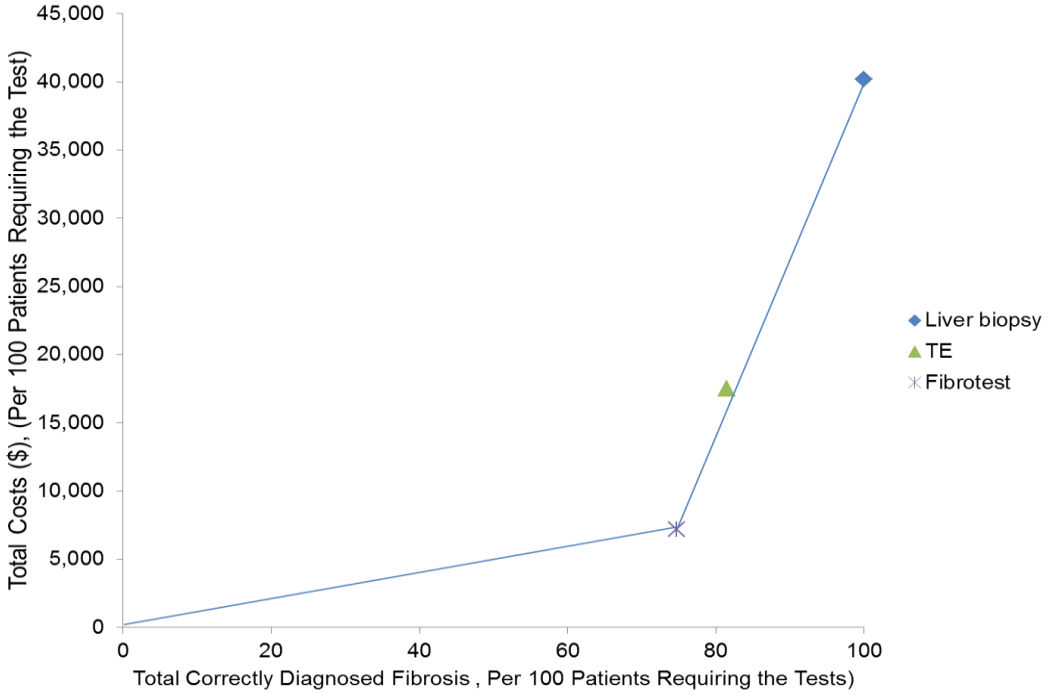

Figure 6: Cost-Effectiveness Efficiency Frontier for ALD (F ≥ 3)

Abbreviations: ARFI, acoustic radiation force impulse; ALD, alcoholic fatty liver disease; TE, transient elastography.

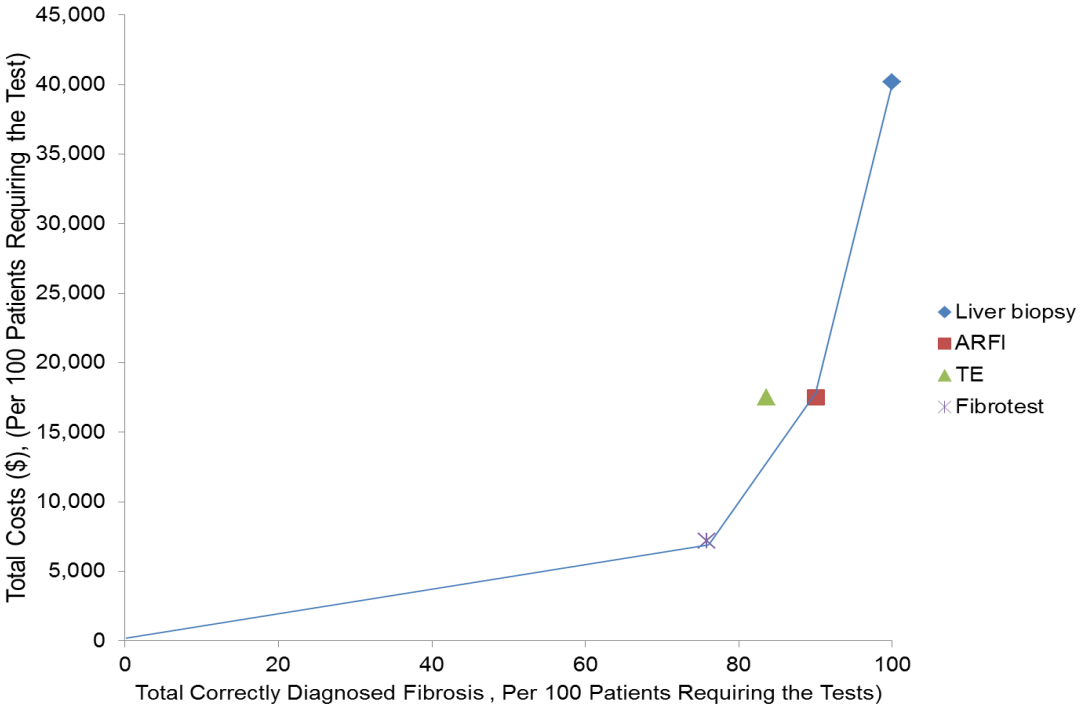

Figure 7: Cost-Effectiveness Efficiency Frontier for NAFLD (F ≥ 3)

Abbreviations: NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

Scenario 2: Long-term cost-effectiveness of TE versus liver biopsy for diagnosing liver fibrosis in patients with hepatitis B and hepatitis C

In patients with hepatitis B or C, test results may lead to a different course of treatment and different health outcomes. Therefore, we conducted a scenario analysis to estimate the long-term cost-effectiveness of TE compared to liver biopsy in HBV- or HCV-infected patients. Long-term costs and QALYs were obtained from a recent health technology assessment report from the United Kingdom. (52) Using the same approach, we constructed separate cost-effectiveness models of TE for hepatitis B e antigen–positive and hepatitis B e antigen–negative patient cohorts due to differences in natural history between groups (e.g., starting age, treatment effectiveness).

Results of the long-term cost-effectiveness are shown in Table 9. TE improved both quantity and quality of life (i.e., QALYs) at lower costs than liver biopsy in HCV-infected patients. TE was also a cost-effective diagnostic option for both hepatitis B e antigen–positive and hepatitis B e antigen–negative patients at a common willingness to pay of $50,000 per QALY. These findings were based on assumptions that treatments for HBV and HCV in the United Kingdom and Canada were similar, and the same annual discount rate (3.5%) was applied for both costs and outcomes.

Table 9: Scenario Analysis—TE Versus Liver Biopsy for the Diagnosis of Liver Fibrosis, by METAVIR Stage[a]

Strategy	Average Total Cost	Incremental Cost	Total QALYs	Incremental QALYs	ICER
HCV					
Liver biopsy	$75,760.83	—	14.30	Reference	
Transient elastography	$75,664.20	–$96.63	14.46	0.16	Dominated
Hepatitis B e Antigen–Positive					
Liver biopsy	$120,939.70	—	11.59	Reference	
Transient elastography	$126,380.16	$5,440.46	11.71	0.77	7,035
Hepatitis B e Antigen–Negative					
Liver biopsy	$109,994.04	—	11.59	Reference	
Transient elastography	$115,311.62	$5,317.58	11.71	0.80	6,645

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TE, transient elastography.
Note: Results are presented per 100 individuals requiring the diagnostic test.
[a]Used long-term outcomes from Crossan et al. (52)

Sensitivity Analysis

A one-way sensitivity analysis was performed to assess the influence of key parameters on cost-effectiveness findings.

Results suggested that the cost of TE had the greatest impact on the cost-effectiveness of TE for the diagnosis of liver fibrosis in all disease subgroups, followed by the cost of liver biopsy for hepatitis B and hepatitis C (Figure 8) and the specificity of TE for ALD and NAFLD (Figure 9). As the cost of TE increased, there was a decrease in incremental cost per correct diagnosis gained, indicating that TE was a less favourable option.

A similar pattern was observed for the cost-effectiveness of TE with CAP for detecting liver steatosis. Cost-effectiveness ratios were negatively associated with physician fees and cost of TE, but they were positively associated with the cost of liver biopsy and the sensitivity and specificity of TE.

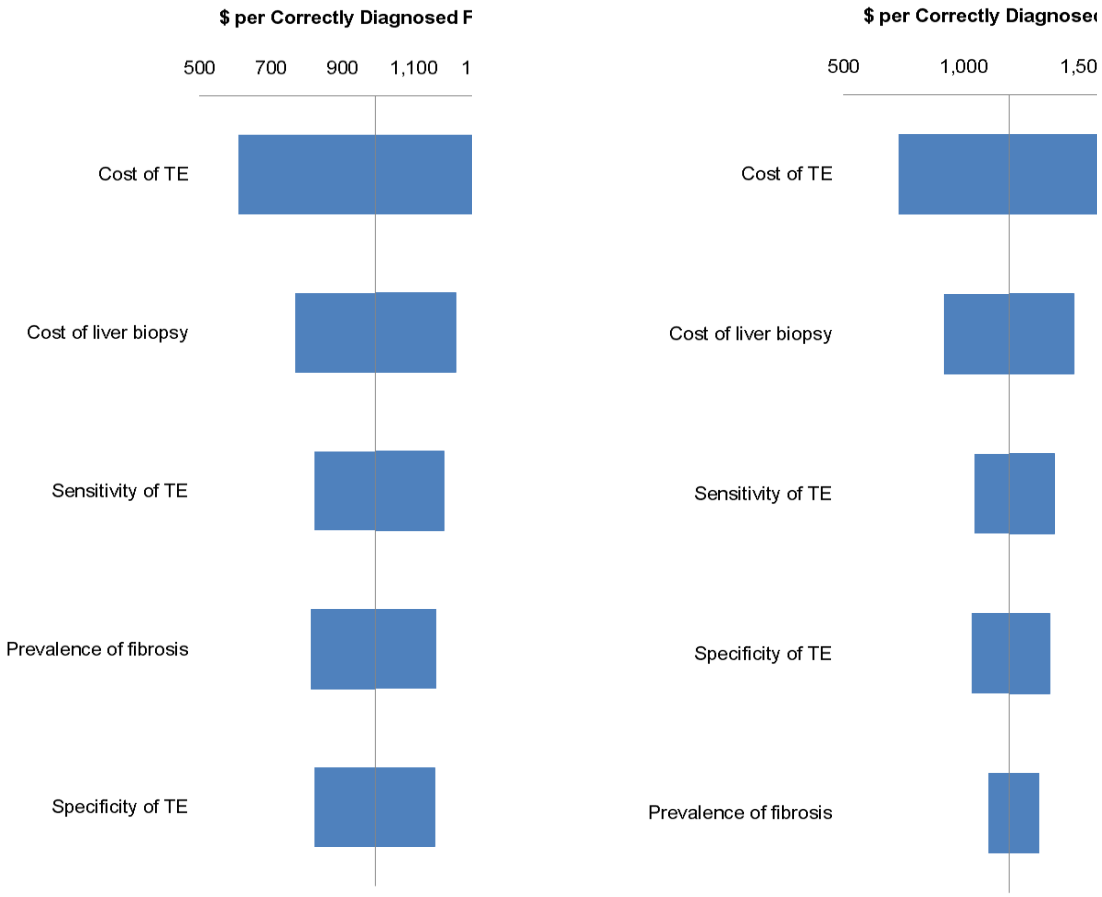

Figure 8: Tornado Diagram for Hepatitis B (F ≥ 2) (Left) and Hepatitis C (F ≥ 2) (Right)

Abbreviation: TE, transient elastography.

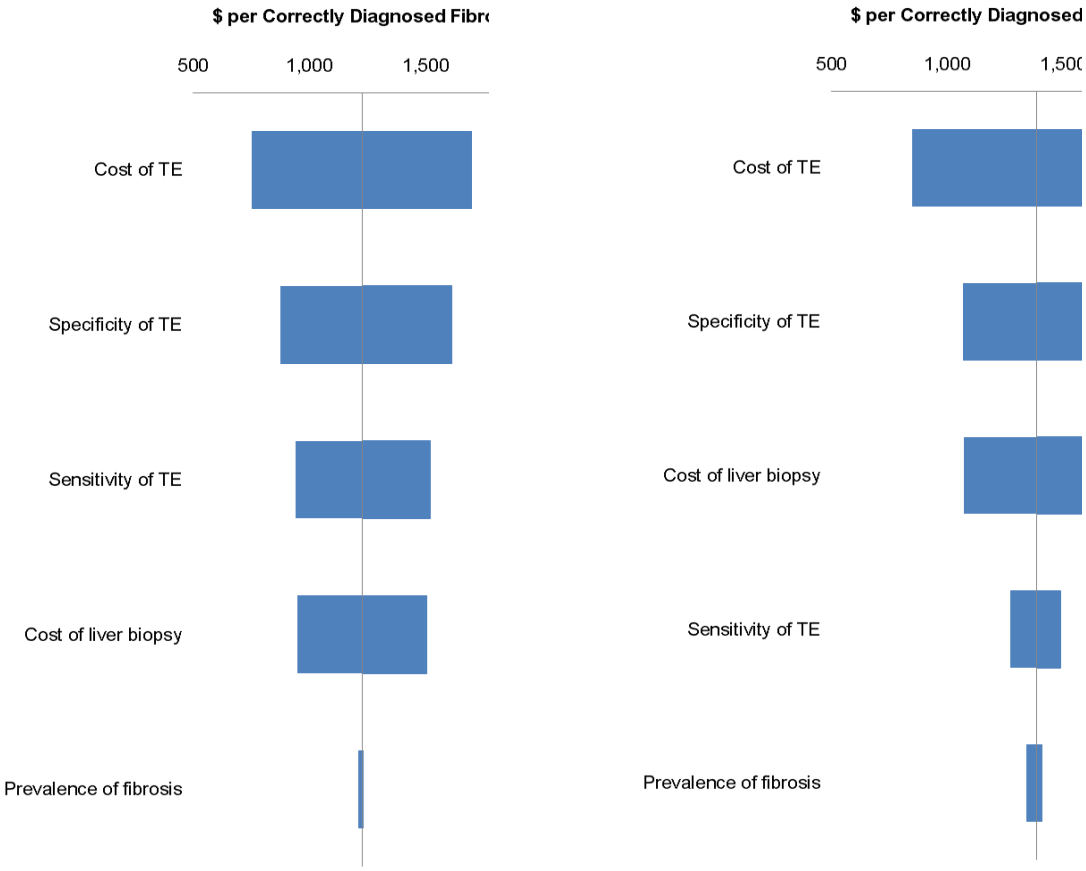

Figure 9: Tornado Diagram for ALD (F ≥ 3) (Left) and NAFLD (F ≥ 3) (Right)

Abbreviations: ALD, alcoholic liver disease; NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

Tables 10 and 11 show the results of the sensitivity analysis for liver fibrosis and steatosis, respectively. Results of the probabilistic sensitivity analysis are shown as scatter plots; figures 10 and 11 show that TE with and without CAP remained cost-saving in 100% of 1,000 probabilistic sensitivity analysis simulations, but the cost-effectiveness of TE with CAP had greater uncertainty.

Table 10: One-Way Sensitivity Analysis—ICERs for TE Versus Liver Biopsy

Parameters	Hepatitis B (ΔCost/ΔCDF)			Hepatitis C (ΔCost/ΔCDF)			ALD (ΔCost/ΔCDF)		NAFLD (ΔCost/ΔCDF)	
	F ≥ 2	F ≥ 3	F = 4	F ≥ 2	F ≥ 3	F = 4	F ≥ 3	F = 4	F ≥ 3	F = 4
Base case	993.31	1,053.88	1,535.46	1,189.81	2,146.19	2,431.59	1,227.03	1,450.63	1,387.19	1,994.99
Cost of TE										
Low	1,375.68	1,459.56	2,126.53	1,647.82	2,972.37	3,367.62	1,699.37	2,009.04	1,921.18	2,762.96
High	610.94	648.19	944.39	731.79	1,320.02	1,495.55	754.68	892.21	853.19	1,227.02
Cost of Biopsy										
Low	768.61	815.48	1,188.12	920.66	1,660.70	1,881.54	949.46	1,122.48	1,073.39	1,543.71
High	1,218.00	1,292.27	1,882.80	1,458.95	2,631.68	2,981.63	1,504.59	1,778.77	1,700.98	2,446.28
Sensitivity of TE										
Low	822.39	886.46	1,397.26	1,046.69	1,842.23	2,228.75	942.05	1,127.88	1,271.61	1,543.71
High	1,184.84	1,246.49	1,652.19	1,378.26	2,411.45	2,572.03	1,519.54	1,751.31	1,488.66	2,446.28
Specificity of TE										
Low	823.34	919.47	1,117.23	1,034.39	1,607.63	2,064.64	877.75	1,101.19	1,068.45	1,527.10
High	1,161.09	1,234.29	1,953.30	1,360.10	2,686.10	2,957.16	1,611.85	1,839.84	1,846.12	2,590.22
Prevalence of Fibrosis										
Low	1,164.85	1,223.32	1,514.07	1,316.43	2,248.17	2,508.95	1,234.03	1,371.02	1,410.62	2,042.91
High	814.16	819.89	1,577.59	1,103.98	1,965.30	2,191.76	1,211.38	1,612.20	1,345.44	1,655.20

Abbreviations: ALD, alcoholic liver disease; CDF, correctly diagnosed fibrosis; ICER, incremental cost-effectiveness ratio; NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.
Note: Results are presented per 100 individuals requiring the diagnostic test.

Table 11: One-Way Sensitivity Analysis—ICERs for TE With CAP Versus Liver Biopsy

Parameters	(ΔCost/ΔCDS)		
	S ≥ 1	S ≥ 2	S = 3
Base case	941.54	1,048.82	983.69
Cost of TE			
Low	1,407.10	1,567.44	1,470.10
High	475.97	530.21	497.28
Cost of Biopsy			
Low	709.09	789.89	740.84
High	1,173.99	1,307.76	1,226.55
Sensitivity of TE			
Low	787.11	900.75	947.23
High	1,083.22	1,171.36	1,017.26
Specificity of TE			
Low	739.86	809.55	666.98
High	1,139.14	1,347.53	1,502.60

Abbreviations: CAP, controlled attenuation parameter; CDS, correctly diagnosed steatosis; ICER, incremental cost-effectiveness ratio; TE, transient elastography.
Note: Results are presented per 100 individuals requiring the diagnostic test.

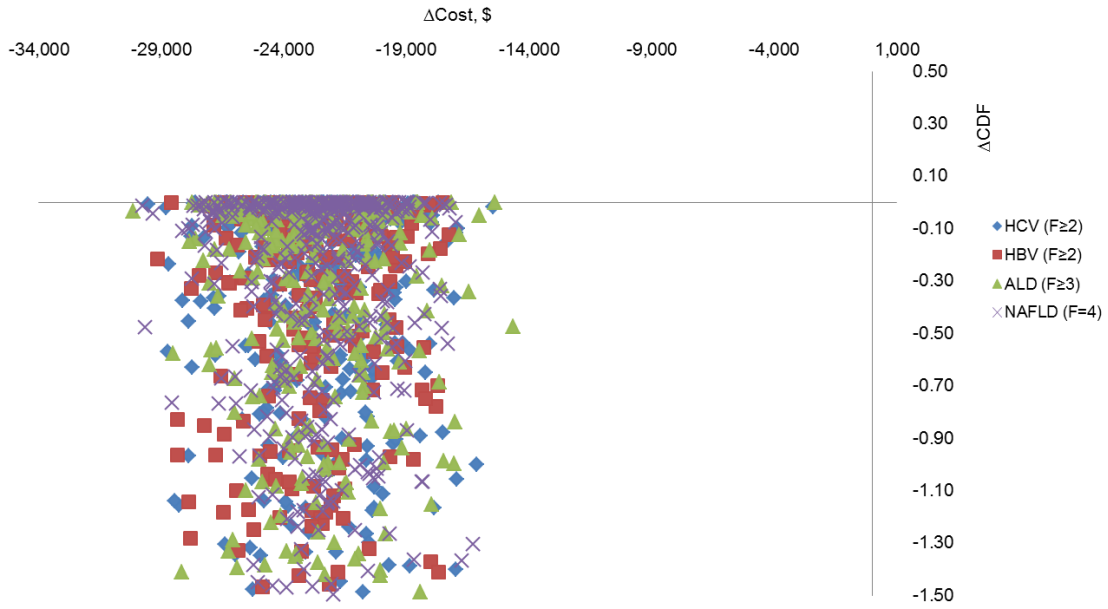

Figure 10: Probabilistic Sensitivity Analysis—TE in the Diagnosis of Liver Fibrosis

Abbreviation: ALD, alcoholic liver disease; CDF, correctly diagnosed fibrosis; HCV, hepatitis C virus; HBV, hepatitis B virus; NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

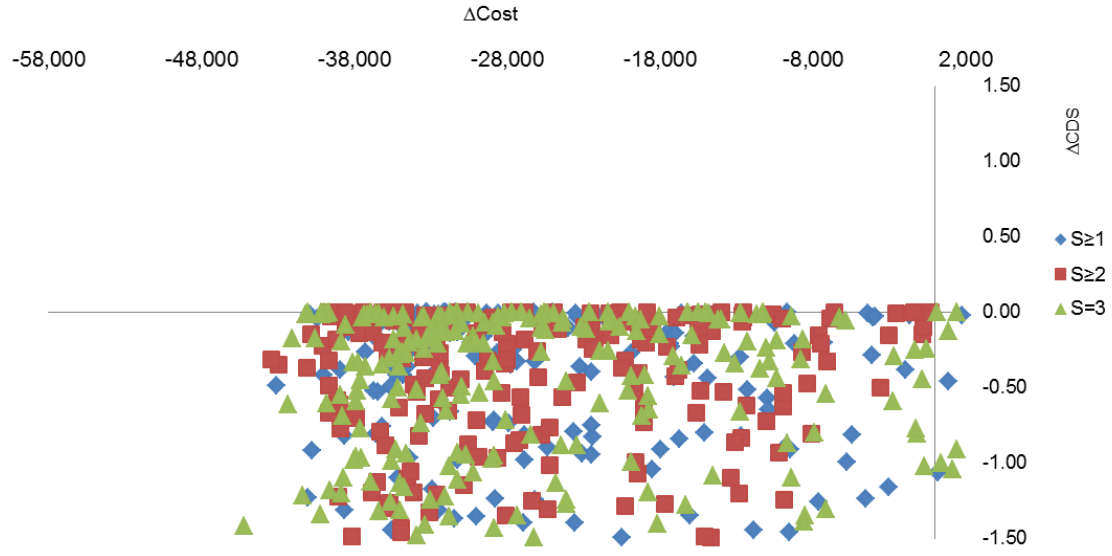

Figure 11: Probabilistic Sensitivity Analysis—TE With CAP in the Diagnosis of Liver Steatosis

Abbreviation: CAP, controlled attenuation parameter; CDS, correctly diagnosed steatosis; TE, transient elastography.

Budget Impact Analysis

We estimated the budget impact of TE without and with CAP to replace liver biopsy for diagnosing liver fibrosis or liver steatosis in patients living with hepatitis B, hepatitis C, ALD, and NAFLD.

Research Methods

Patients and Database

The total population in Ontario was obtained from Statistics Canada. (65) The overall prevalence of hepatitis B, hepatitis C, ALD, or NAFLD from 2003 to 2012 were based on data from ICES. These rates were used to project the number of patients with chronic liver disease and those who received liver biopsies in 2013 and 2014 (Table 12). In the base case analysis, we assumed that 53% of patients with the four chronic liver conditions listed above received a liver biopsy in 2014 (estimated from ICES data). For TE with CAP, we assumed that the prevalence of steatosis was equal to that of NAFLD, because the true prevalence of steatosis in Ontario is unknown.

Table 12: Patients Living With Hepatitis B, Hepatitis C, ALD, and NAFLD in Ontario, 2003 to 2014

Year	Hepatitis B, n	Hepatitis C, n	ALD, n	NAFLD, n	Total, n
2003	563	2,155	2,302	526	5,546
2004	558	2,057	2,404	533	5,551
2005	589	2,105	2,418	626	5,738
2006	734	2,380	2,570	519	6,204
2007	702	2,515	2,655	523	6,395
2008	670	2,409	2,731	541	6,351
2009	871	2,418	2,885	585	6,759
2010	880	2,469	3,021	565	6,935
2011	822	2,533	3,276	610	7,242
2012	818	2,535	3,420	603	7,376
2013[a]	782	2,499	3,437	588	7,306
2014[a]	766	2,511	3,494	600	7,372

Abbreviations: ALD, alcoholic liver disease; NAFLD, nonalcoholic fatty liver disease.
[a]Predicted from 2003 to 2012 data.
Source: Institute for Clinical Evaluative Sciences.

Cost Data and Resource Use

In the base case analysis, the cost of TE included cost of the machine, annual maintenance costs, and a physician fee. We assumed that TE was performed within the existing infrastructure, so no capital costs were included (e.g., cost of a room for the TE device). Assuming an annual utilization rate of 793 scans, the total cost of TE per scan was $174.90.

The cost of liver biopsy was obtained from the OCCI database and was $400 per procedure.

The annual cost of TE and liver biopsy were estimated by multiplying the total number of Ontario patients living with the four included chronic liver diseases by each procedure's unit cost. Because the current utilization of TE across Ontario is unknown, we varied the uptake of

TE utilization from 0% to 100% and assumed that TE was used to replace liver biopsy in the diagnosis of liver fibrosis. In other words, an increase in TE use would lead to a proportional decrease in the use of liver biopsy.

The cost of TE with CAP was assumed to be $199.90 per scan. Its unit cost included the cost of the TE equipment, annual maintenance, the probe, and the physician fee.

We conducted two scenario analyses to assess the influence of the device costs on the budget impact of TE without and with CAP. First, we assumed that the Ministry of Health and Long-Term Care did not reimburse the costs for the TE devices, probes, and maintenance fees; only the physician fees of $150 and $170 (for TE without and with CAP, respectively) were reimbursed. We assumed that the costs of TE equipment were supported from hospitals' foundations or charities, and it was not necessary to purchase any new TE devices and probes. Second, we used a hospital liver biopsy cost of $1,311.50 rather than the $400 per procedure used above, because the lower figure did not take into account surgical pathology fees and hospital surgical supply. This hospital cost was determined using 2013/2014 case costing data from the Ottawa Hospital Data Warehouse.

All costs were reported in 2014 Canadian dollars.

Results of Budget Impact Analysis

The total estimated annual cost of TE and liver biopsy for the diagnosis of liver fibrosis and steatosis in 2014 is shown in Tables 13 and 14. In the base case analysis, we assumed that 53% of patients with one of the four included chronic liver diseases received a liver biopsy; switching from liver biopsy to TE would lead to cost savings of $219,875 to $879,502, depending on the proportion of TE use compared to liver biopsy (Table 13).

Table 13: Budget Impact of Replacing Liver Biopsy With TE in 2014

% Replacement of Liver Biopsy By TE	Budget Impact by % of Patients Who Require Liver Biopsy, $				
	25	50	53	75	100
0	Reference	Reference	**Reference**	Reference	Reference
25	–103,715	–207,430	**–219,875**	–311,144	–414,859
50	–207,430	–414,859	**–439,751**	–622,289	–829,719
75	–311,144	–622,289	**–659,626**	–933,433	–1,244,578
100	–414,859	–829,719	**–879,502**	–1,244,578	–1,659,437

Abbreviation: TE, transient elastography.

Similarly, using TE with CAP instead of liver biopsy would save the province $17,498 to $69,992 (Table 14). These savings were even greater when we assumed that 100% of patients with chronic liver disease required liver biopsy.

Table 14: Budget Impact of Replacing Liver Biopsy With TE With CAP in 2014

% Replacement of Liver Biopsy By TE	Budget Impact by % of Patients Who Require Liver Biopsy, $				
	25	50	53	75	100
0	Reference	Reference	**Reference**	Reference	Reference
25	–8,254	–16,508	**–17,498**	–24,761	–33,015
50	–16,508	–33,015	**–34,996**	–49,523	–66,030
75	–24,761	–49,523	**–52,494**	–74,284	–99,045
100	–33,015	–66,030	**–69,992**	–99,045	–132,060

Abbreviations: CAP, controlled attenuation parameter; TE, transient elastography.

Results of the scenario analyses showed that the cost savings from replacing liver biopsy depended on the costs of both TE (Table 15) and liver biopsy (Table 16). The use of TE would result in more cost savings to the province if its unit cost were $150 per scan or if the cost of liver biopsy were $1,311.50 per procedure.

Table 15: Scenario Analysis 1—Cost of TE Was $150 Per Scan

% Replacement of Liver Biopsy By TE	Budget Impact by % of Patients Who Require Liver Biopsy, $				
	25	50	53	75	100
0	Reference	Reference	**Reference**	Reference	Reference
25	–115,188	–230,375	**–244,198**	–345,563	–460,750
50	–230,375	–460,750	**–488,395**	–691,125	–921,500
75	–345,563	–691,125	**–732,593**	–1,036,688	–1,382,250
100	–460,750	–921,500	**–976,790**	–1,382,250	–1,843,000

Abbreviation: TE, transient elastography.

Table 16: Scenario Analysis 2—Cost of Liver Biopsy Was $1,311.50 Per Procedure

% Replacement of Liver Biopsy By TE	Budget Impact by % of Patients Who Require Liver Biopsy, $				
	25	50	53	75	100
0	Reference	Reference	**Reference**	Reference	Reference
25	–523,705	–1,047,410	**–1,110,254**	–1,571,114	–2,094,819
50	–1,047,410	–2,094,819	**–2,220,508**	–3,142,229	–4,189,638
75	–1,571,114	–3,142,229	**–3,330,762**	–4,713,343	–6,284,457
100	–2,094,819	–4,189,638	**–4,441,017**	–6,284,457	–8,379,276

Abbreviation: TE, transient elastography.

Limitations

Our study has a number of limitations that merit discussion.

First, most input parameters used in our analysis were based on studies conducted in other countries. In particular, diagnostic accuracy was based on one recent systematic review from the United Kingdom. Although the generalizability of these parameters to the Ontario health care system may be questionable, we estimated and presented our cost-effectiveness analysis as incremental costs per correctly diagnosed cases gained. Our approach should have minimized the impact of differences in health systems and treatment pathways on the cost-effectiveness findings. In addition, our sensitivity analyses revealed that the cost-effectiveness results remained robust to changes in diagnostic accuracy; any additional studies may not have a substantial impact on our analysis. Future studies should consider evaluating the long-term cost and effectiveness of TE in the Canadian context.

Second, the prevalence of liver fibrosis and steatosis used in this study may be overestimated, because it was taken from studies conducted in tertiary care settings.

Third, although liver biopsy is considered the gold standard for fibrosis and steatosis assessment, it has inherent limitations due to sample and intra- and interobserver variability. As a result, our cost-effectiveness results may undervalue TE for the diagnosis of liver fibrosis and steatosis.

Fourth, our analysis assumed that TE was used to replace liver biopsy as a definitive investigation. In clinical practice, TE may be used as an adjunct to radiological, histological, and serological tests. (66, 67) The cost-effectiveness of the optimal screening modality for liver fibrosis or steatosis still requires further investigation.

Finally, TE without and with CAP is already in use in the Ontario health care system, but current uptake is unclear. Knowing the adoption rate and market share of TE would allow for a more accurate estimate of budget impact. In addition, the budget impact presented here may be underestimated because the prevalence used in this study included only patients with chronic liver conditions who interacted with the health care system. Our analysis may exclude patients who were unaware of their condition and did not use health services.

CONCLUSIONS

Ten studies showed the cost-effectiveness of using TE compared to liver biopsy for the diagnosis of liver fibrosis in patients with chronic liver disease. The majority of these studies estimated the short-term impacts of TE and expressed its benefit as the number of correctly diagnosed cases. These studies consistently suggested that compared to liver biopsy, the use of TE led to cost savings, but also to a decrease in correctly diagnosed cases. Two studies assessed the long-term cost-effectiveness of TE and suggested that TE was a cost-effective option compared to liver biopsy and other noninvasive tests. No published studies assessed the cost-effectiveness of TE with CAP for the diagnosis of liver steatosis.

Based on the probabilistic decision analytic model, TE without or with CAP was a cost-saving option compared to liver biopsy, but it was associated with a net decrease in the number of patients accurately diagnosed. There was variation in the incremental cost per correctly diagnosed cases gained, depending on fibrosis or steatosis stage, the diagnostic accuracy of TE, the cost of TE, the cost of liver biopsy, the prevalence of fibrosis, and the prevalence of steatosis.

The budget impact analysis revealed that replacing liver biopsy with TE for the diagnosis of liver fibrosis in patients with hepatitis B, hepatitis C, ALD, or NAFLD could save the province $219,875 to $879,502 annually. In addition, if TE with CAP was used to detect liver steatosis instead of liver biopsy, the province could save $17,498 to $69,992 per year.

ACKNOWLEDGEMENTS

Editorial Staff
Jeanne McKane, CPE, ELS(D)

Medical Information Services
Becky Skidmore, MLS
Raymond Daniel, BA

Research Support
Kusala Pussegoda, MSc
Mona Ghannad, MSc

Data Support
Shudong Li, MSc
Kristy Zhou, MM

Expert Advisory on: An Economic Analysis of Transient Elastography and Controlled Attenuation Parameter in Diagnosing Liver Fibrosis and Steatosis in Ontario

Name	Appointment(s)	Affiliation(s)
Jordan Feld	Scientist	Toronto General Research Institute
	Assistant Professor	Department of Medicine, University of Toronto
Curtis Cooper	Scientist	Ottawa Hospital Research Institute
	Associate Professor	Department of Medicine, University of Ottawa
Linda Scully	Acting Chief, Division of Gastroentroenterology	Ottawa Hospital
Alan Forster	Senior Scientist	Ottawa Hospital Research Institute
	Professor	Department of Medicine, University of Ottawa

APPENDICES

Appendix 1: Literature Search Strategies

Fibroscan – Transient Elastography – Economics
Final Strategies
2014 Nov 24
Database: Embase Classic+Embase <1947 to 2014 November 21>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:
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1 Fibroscan*.mp. (2186)
2 Elasticity Imaging Techniques/ (10022)
3 ((transient or ultraso* or sonogra*) adj5 (elastogra* or elasto-gra* or elastomet* or elasto-met*)).tw. (4619)
4 (sonoelastogra* or sono-elastrogra*).tw. (575)
5 ((real-time or realtime or RT) adj2 (elastogra* or elasto-gra* or elastomet* or elasto-met*)).tw. (676)
6 (RT-E or RTE).tw. (1981)
7 ((magnetic resonance or MR) adj2 (elastogra* or elasto-gra* or elastomet* or elasto-met*)).tw. (1127)
8 ((shear wave or SW) adj2 (elastogra* or elasto-gra* or elastomet* or elasto-met*)).tw. (501)
9 SWE.tw. (985)
10 (acoustic radiation force impulse or ARFI).tw. (1076)
11 ((noninvasive or non-invasive) adj2 (elastogra* or elasto-gra* or elastomet* or elasto-met*)).tw. (168)
12 (((noninvasive or non-invasive) adj3 (image* or imaging)) and tissue*).tw. (4795)
13 (elasticity adj5 (imaging or sonogra* or ultraso*)).tw. (985)
14 or/2-13 (19292)
15 exp Liver Diseases/ (1208360)
16 Liver Function Tests/ (63417)
17 (liver adj5 (stiffness* or rigidit*)).tw. (2991)
18 LSE.tw. (664)
19 ((liver or hepatic*) adj5 (disease* or disorder* or dysfunction* or fibros*)).tw. (265471)
20 (cirrho* or hepatit* or sarcoidos* or steatohepatitis or steato-hepatitis).tw. (583969)
21 hepatopath*.tw. (5381)
22 fatty liver$1.tw. (34711)
23 or/15-22 (1432428)
24 14 and 23 (4879)
25 1 or 24 (5642)
26 exp Animals/ not (exp Animals/ and Humans/) (8923415)
27 25 not 26 (5477)
28 (comment or editorial or interview or letter or news).pt. (2911792)
29 27 not 28 (5066)
30 Economics/ (238669)
31 exp "Costs and Cost Analysis"/ (451348)
32 Economics, Nursing/ (38048)
33 Economics, Medical/ (42895)
34 Economics, Pharmaceutical/ (8597)
35 exp Economics, Hospital/ (653896)
36 Economics, Dental/ (35890)
37 exp "Fees and Charges"/ (62415)
38 exp Budgets/ (32959)
39 budget*.ti,ab. (45729)
40 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti. (304044)

41 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 (419354)
42 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab. (227250)
43 (value adj2 (money or monetary)).ti,ab. (3385)
44 exp models, economic/ (115693)
45 Quality-Adjusted Life Years/ (20502)
46 (life qualities or life quality or quality adjusted or adjusted life or qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).tw. (107547)
47 exp Models, Economic/ (115693)
48 economic model*.ti,ab. (4608)
49 markov chains/ (68679)
50 markov.ti,ab. (29085)
51 monte carlo method/ (43862)
52 monte carlo.ti,ab. (59651)
53 exp Decision Theory/ (11561)
54 (decision* adj2 (tree* or analy* or model*)).ti,ab. (31719)
55 or/30-54 (1726355)
56 29 and 55 (160)
57 "Quality of Life"/ (390261)
58 quality-adjusted life years/ (20502)
59 (life adj1 (quality or qualities)).ti,ab. (11514)
60 (adjusted adj1 (quality or life)).ti,ab. (21029)
61 (qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).ti,ab. (89265)
62 or/57-61 (428580)
63 29 and 62 (33)
64 56 or 63 (174)
65 64 use prmz (34)
66 Fibroscan*.mp. (2186)
67 elastography/ (10022)
68 ((transient or ultraso* or sonogra*) adj5 (elastogra* or elasto-gra* or elastomet* or elasto-met*)).tw. (4619)
69 (sonoelastogra* or sono-elastrogra*).tw. (575)
70 ((real-time or realtime or RT) adj2 (elastogra* or elasto-gra* or elastomet* or elasto-met*)).tw. (676)
71 (RT-E or RTE).tw. (1981)
72 ((magnetic resonance or MR) adj2 (elastogra* or elasto-gra* or elastomet* or elasto-met*)).tw. (1127)
73 ((shear wave or SW) adj2 (elastogra* or elasto-gra* or elastomet* or elasto-met*)).tw. (501)
74 SWE.tw. (985)
75 (acoustic radiation force impulse or ARFI).tw. (1076)
76 ((noninvasive or non-invasive) adj2 (elastogra* or elasto-gra* or elastomet* or elasto-met*)).tw. (168)
77 (((noninvasive or non-invasive) adj3 (image* or imaging)) and tissue*).tw. (4795)
78 (elasticity adj5 (imaging or sonogra* or ultraso*)).tw. (985)
79 or/67-78 (19292)
80 exp liver disease/ (1208360)
81 liver function test/ (63417)
82 (liver adj5 (stiffness* or rigidit*)).tw. (2991)
83 LSE.tw. (664)
84 ((liver or hepatic*) adj5 (disease* or disorder* or dysfunction* or fibros*)).tw. (265471)
85 (cirrho* or hepatit* or sarcoidos* or steatohepatitis or steato-hepatitis).tw. (583969)
86 hepatopath*.tw. (5381)
87 fatty liver$1.tw. (34711)
88 or/80-87 (1432428)
89 79 and 88 (4879)

90 66 or 89 (5642)
91 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (38721378)
92 exp humans/ or exp human experimentation/ or exp human experiment/ (29509816)
93 91 not 92 (9213233)
94 90 not 93 (5500)
95 (editorial or letter).pt. (2578006)
96 94 not 95 (5105)
97 Economics/ (238669)
98 exp cost/ (451348)
99 exp health economics/ (633712)
100 exp fee/ (62415)
101 budget/ (30581)
102 budget*.ti,ab. (45729)
103 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti. (304044)
104 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 (419354)
105 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab. (227250)
106 (value adj2 (money or monetary)).ti,ab. (3385)
107 statistical model/ (179353)
108 economic model*.ti,ab. (4608)
109 probability/ (108791)
110 markov.ti,ab. (29085)
111 monte carlo method/ (43862)
112 monte carlo.ti,ab. (59651)
113 decision theory/ (2416)
114 (decision* adj2 (tree* or analy* or model*)).ti,ab. (31719)
115 or/97-114 (1730233)
116 96 and 115 (161)
117 exp "quality of life"/ (407204)
118 (life adj1 (quality or qualities)).ti,ab. (11514)
119 (adjusted adj1 (quality or life)).ti,ab. (21029)
120 (qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).ti,ab. (89265)
121 or/117-120 (432766)
122 96 and 121 (33)
123 116 or 122 (178)
124 123 use emczd (140)
125 65 or 124 (174)
126 remove duplicates from 125 (150) [TOTAL UNIQUE RECORDS]
127 126 use prmz (32) [UNIQUE MEDLINE RECORDS]
128 126 use emczd (118) [UNIQUE EMBASE RECORDS]

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Search Name: Fibroscan - Transient Elastography
Date Run: 25/11/14 00:25:39.737
Description: OHRI (KT) - 2014 Nov 24

ID	Search	Hits
#1	Fibroscan*	38
#2	[mh "Elasticity Imaging Techniques"]	103
#3	((transient or ultraso* or sonogra*) near/5 (elastogra* or elasto-gra* or elastomet* or elasto-met*)):ti,ab,kw	88
#4	(sonoelastogra* or sono-elastrogra*):ti,ab,kw	14

#5 (("real-time" or realtime or RT) near/2 (elastogra* or elasto-gra* or elastomet* or elasto-met*)):ti,ab,kw 22
#6 ("RT-E" or RTE):ti,ab,kw 27
#7 (("magnetic resonance" or MR) near/2 (elastogra* or elasto-gra* or elastomet* or elasto-met*)):ti,ab,kw 11
#8 (("shear wave" or SW) near/2 (elastogra* or elasto-gra* or elastomet* or elasto-met*)):ti,ab,kw 8
#9 SWE:ti,ab,kw 7
#10 ("acoustic radiation force impulse" or ARFI):ti,ab,kw 15
#11 ((noninvasive or "non-invasive") near/2 (elastogra* or elasto-gra* or elastomet* or elasto-met*)):ti,ab,kw 3
#12 (((noninvasive or "non-invasive") near/3 (image* or imaging)) and tissue*):ti,ab,kw 13
#13 (elasticity near/5 (imaging or sonogra* or ultraso*)):ti,ab,kw 153
#14 {or #2-#13} 256
#15 [mh "Liver Diseases"] 10260
#16 [mh "Liver Function Tests"] 1025
#17 (liver near/5 (stiffness* or rigidit*)):ti,ab,kw 40
#18 LSE:ti,ab,kw 16
#19 ((liver or hepatic*) near/5 (disease* or disorder* or dysfunction* or fibros*)):ti,ab,kw 4678
#20 (cirrho* or hepatit* or sarcoidos* or steatohepatitis or steato-hepatitis):ti,ab,kw 15175
#21 hepatopath*:ti,ab,kw 68
#22 (fatty next liver*):ti,ab,kw 641
#23 {or #15-#22} 20860
#24 #14 and #23 78
#25 #1 or #24 91

DSR – 2
DARE – 21
CENTRAL – 51
HTA – 11
NHS EED – 6 (Econ)

Appendix 2: Further Analysis—Test Positive and Test Negative

Table A1: Test Positive and Test Negative—TE Versus Liver Biopsy for the Diagnosis of Liver Fibrosis, by METAVIR Stage

Strategy	F ≥ 2			F ≥ 3			F = 4		
	ΔCDF	ΔTP	ΔTN	ΔCDF	ΔTP	ΔTN	ΔCDF	ΔTP	ΔTN
Hepatitis B									
Liver biopsy					Reference				
TE	–23	–15	–8	–22	–12	–10	–15	–3	–12
Hepatitis C									
Liver biopsy					Reference				
TE	–19	–11	–8	–11	–4	–7	–9	–2	–7
ALD									
Liver biopsy					Reference				
TE	NA	NA	NA	–19	–10	–9	–16	–6	–9
NAFLD									
Liver biopsy					Reference				
TE	NA	NA	NA	–16	–3	–13	–11	–2	–9

Abbreviations: ALD, alcoholic liver disease; CDF, correctly diagnosed fibrosis; NAFLD, nonalcoholic fatty liver disease; TE, transient elastography; TN, true negative; TP, true positive.
Note: Results are presented per 100 individuals requiring the diagnostic test.

Table A2: Test Positive and Test Negative—TE Versus Liver Biopsy for the Diagnosis of Liver Steatosis, by Steatosis Stage

Strategy	S ≥ 1			S ≥ 2			S = 3		
	ΔCDS	ΔTP	ΔTN	ΔCDS	ΔTP	ΔTN	ΔCDS	ΔTP	ΔTN
All Chronic Liver Disease									
Liver biopsy					Reference				
TE	–21	–10	–11	–19	–4	–15	–21	–2	–19

Abbreviations: ALD, alcoholic liver disease; CDs, correctly diagnosed steatosis; NAFLD, nonalcoholic fatty liver disease; TE, transient elastography; TN, true negative; TP, true positive.
Note: Results are presented per 100 individuals requiring the diagnostic test.

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Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: EvidenceInfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4606-6900-6 (PDF)