The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis

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Abstract

**Background:** Glaucoma is the leading cause of irreversible visual impairment in the world affecting 60.5 million people worldwide in 2010, which is expected to increase to approximately 79.6 million by 2020. Therefore, glaucoma screening is important to detect, diagnose, and treat patients at the earlier stages to prevent disease progression and vision loss. Teleglaucoma uses stereoscopic digital imaging to take ocular images, which are transmitted electronically to an ocular specialist. The purpose is to synthesize literature to evaluate teleglaucoma, its diagnostic accuracy, healthcare system benefits, and cost-effectiveness.

**Methods:** A systematic search was conducted to help locate published and unpublished studies. Studies which evaluate teleglaucoma as a screening device for glaucoma were included. A meta-analysis was conducted to provide estimates of diagnostic accuracy, diagnostic odds ratio, and the relative percentage of glaucoma cases detected. The improvements to healthcare service quality and cost data were assessed.

**Results:** Of 11237 studies reviewed, 45 were included. Our results indicated that, teleglaucoma is more specific and less sensitive than in-person examination. The pooled estimates of sensitivity was 0.832 [95% CI 0.770, 0.881] and specificity was 0.790 [95% CI 0.668, 0.876]. The relative odds of a positive screen test in glaucoma cases are 18.7 times more likely than a negative screen test in a non-glaucoma cases. Additionally, the mean cost for every case of glaucoma detected was $1098.67 US and of teleglaucoma per patient screened was $922.77 US.

**Conclusion:** Teleglaucoma can accurately discriminate between screen test results with greater odds for positive cases. It detects more cases of glaucoma than
in-person examination. Both patients and the healthcare systems benefit from early
detection, reduction in wait and travel times, increased specialist referral rates, and
cost savings. Teleglaucoma is an effective screening tool for glaucoma specifically
for remote and under-services communities.

**Introduction**

Vision impairment represents a serious public health concern since it impacts
social, mental, and physical health of an individual. Visual impairment limits
independence and activities of daily life. Those with visual impairment require
more social support systems, visual aids, and modifications to home life. They are
at a higher risk for injuries, falls, psychological conditions, and are admitted to
nursing homes earlier compared to those without a vision impairment [1].

Glaucoma is the leading cause of irreversible visual impairment in the world
affecting 60.5 million people worldwide in 2010 [2]. In developed countries, half
of glaucoma patients may not experience vision loss until the advanced stages of
the disease and this is expected to be greater in undeveloped countries [3]. Since
there is no cure for glaucoma, glaucoma can progress to blindness if left untreated.
Further, glaucoma accounts for 12% of blind persons worldwide which is
expected to increase to approximately 79.6 million in 2020 [4]. The largest impact
is expected in China and India, which accounts for 40% of all cases together [4].

The burden of the glaucoma has affected both the health care and economic
systems. In Canada, alone, vision loss costs the economy $15.8 billion per year in
which 55% is allocated to direct health care costs [5]. Sixty-five per cent of adults
with partial or full vision loss are unemployed, which translates to $4.06 billion
annually of lost earnings [5]. The direct costs of glaucoma is estimated in the
United States to be $623 for mild, $1915 for moderate, and $2511 for severe forms
of glaucoma and similarly in Europe the costs are €455 per person each year for
mild glaucoma and €969 per person each year for severe glaucoma [4]. Varma et
al. reported as glaucoma progresses to each stage, there is an €86 increase in
treatments costs in European.

Glaucoma screening is important to detect, diagnose, and treat patients at the
erlier stages. Screening and diagnostic tools are significant to prevent glaucoma
from progressing to advanced stages and maintaining health vision. In addition,
glaucoma prevention will minimize future healthcare costs. Screening improves
efficiency of the health care system by increasing the number of patients accessing
ophthalmic services and it reduces the number of false-positive referrals to
ophthalmologists [6].

The standard of care for glaucoma screening is routine optometrist visits every
2–3 years and any suspect glaucoma patient will be referred to an ophthalmologist
for additional diagnostic testing [5]. Those of older ages are at a greater risk of
glaucoma and thus ophthalmologists recommend routine optometrist visits every
2 to 4 years for adults between 40 to 64 years and every 1 to 2 years when aged 65 and older [7]. Patients regularly seen by ophthalmologist for other ocular conditions may also be referred for glaucoma diagnostic testing if signs appear. In-patient care for glaucoma (passive “in-person screening”) is performed at specialized clinics and includes detailed history, slit lamp examination, visual field testing, and fundus photography performed by the optical technician followed by consultation with the ophthalmologist [8].

Teleglaucoma is a relatively new screening and diagnostic tool for targeting remote or under-serviced communities. It uses stereoscopic digital imaging to take ocular images which are transmitted electronically to an ocular specialist. The ocular specialist will then assess the images, identify risk factors and diagnose for glaucoma. If necessary the ocular specialist will refer identified glaucoma cases for medical consultations or to ophthalmologists for follow-up treatment. Unlike other teleophthalmology tools, teleglaucoma requires more sophisticated diagnostic tests. The main tests are optic nerve photographs, Optical Coherence Tomography (OCT), Intraocular Pressure (IOP) measurements, central corneal thickness (CCT) measurements, and visual field tests [9]. The combination of examinations and equipment required can vary based on organizational resources, target goals and populations. However, the more diagnostic tools used during screening for glaucoma the greater the accuracy and effectiveness of the screening process. The equipment required for teleglaucoma are the ophthalmic examination equipment, cameras, and computer imaging software. The A full list of the standard equipment and components of teleglaucoma can be found in Table 1 [9].

The advantages reported in the literature include convenience, decreased travel time to medical clinics, increased access to specialized care for glaucoma, and decreased patient costs [10, 11]. The benefits are mainly seen in remote or underserviced communities such as Aboriginal communities and rural or remote areas where there is limited ocular specialists. Arora et al. reported improved access time (time from patient being referred to the date visit is booked) with teleglaucoma versus standard in-person examinations: 45 days for teleglaucoma versus in-person exam which had 88 days [12]. Teleglaucoma had reduced cycle time (time from registration until patient leaves clinic) of 78 minutes versus in-person exam of 115 minutes [12]. The pioneer teleglaucoma study conducted in Finland reported reduced absence from work by 50% with teleglaucoma versus in-person examination, and in addition reduced traveling (97%), costs (92%), and time (92%) [11].

The literature suggests teleglaucoma has comparable diagnostic accuracy. Teleglaucoma technology demonstrated moderate agreement in its ability to diagnose glaucoma (Kappa statistic 0.55% (0.48, 0.62)) [13]. When disc damage had Vertical Cup Disc Ratio (VCDR) greater than 0.7 the Frequency Doubling Technology (FDT) had a substantial agreement with ability to diagnose glaucoma (kappa statistic 0.84) [13]. In addition, a study conducted in rural India compared the ability of teleglaucoma to detect glaucoma compared to standard in-clinic examination and found that there was good agreement in detecting glaucoma.
For glaucoma the kappa scores were 0.61 with standard screening versus 0.59 for teleglaucoma \cite{14}. In comparison to the in-person slit lamp examination, the positive predictive value was 77.5\% for positive teleglaucoma diagnosis and had a negative predictive value of 82.2\% for negative teleglaucoma diagnosis \cite{13}. However, a cohort study conducted by the University of Alberta found 24\% of teleglaucoma photographs were deemed unreadable from media opacities, patient cooperation, and unsatisfactory photographic techniques \cite{13}.

In this study, a systematic review and meta-analysis was conducted on teleglaucoma screening for patients with glaucoma to evaluate the following: the effectiveness of teleglaucoma as a screening device, its diagnostic accuracy, its diagnostic odds ratio, and its cost-effectiveness in comparison to in-person examination. Section 2 will explain the methods, section 3 provides the detailed analysis, and section 4 concludes with a discussion and implications for future research.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
Components & Requirements \\
\hline
Human Resources & Staff: graders, Ophthalmic technicians, nurses, optometrist, physicians, glaucoma specialists/ophthalmologists \\
Information Technology & Secure Diagnostic Imaging (SDI) system \\
& Videoconferencing equipment \\
& Computer systems and software \\
& ISDN installation \\
Screening Equipment & Retinal camera \\
& Tonometer \\
& Devices to measure central corneal thickness \\
& Frequency Doubling Technology (FDT) or Humphrey Visual Field test \\
& Optical Coherence Tomography \\
& Slit lamp \\
& Gonioscope \\
& Retinal camera \\
& Tonometer \\
& Devices to measure central corneal thickness \\
Examinations & Medical & family history \\
& Visual acuity \\
& IOP \\
& CCT \\
& Pupil equal and reactive to light (PERL) or relative afferent pupillary defect (RAPD) \\
& Slit lamp \\
& Gonioscopy \\
& Visual field \\
& Fundus photographs \\
& OCT \\
& Ancillary tests \\
\hline
\end{tabular}
\caption{Standardized teleglaucoma equipment.}
\end{table}

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Methods

Search Strategy

A search methodology was used to assist in locating both published and unpublished studies. Research databases and conference meeting abstracts were searched for articles published from 1999 to current, and included MEDLINE (OVID and PubMed), Cochrane Library (Wiley), BIOSIS (Thomson-Reuters), CINAHL (EBSCO), Web of Science (Thomson-Reuters), and EMBASE (OVID). The grey literature was explored by searching Dissertations and Theses (ProQuest), the Canadian Health Research Collection (Ebrary), as well as the annual meeting abstracts of the European Society of Ophthalmology, Canadian Society of Ophthalmology (CSO), Association for Research in Vision and Ophthalmology (ARVO), and American Academy of Ophthalmology (AAO). The Conference Proceedings Citation Index was also included as part of the Web of Science search. Hand searches of ARVO’s Investigative Ophthalmology & Visual Science journal and Canadian Journal of Ophthalmology associated with CSO were performed. The search strategies employed database specific subject headings and keywords for glaucoma, tele-screening, detection, and their synonyms. Each strategy was structured to accommodate for database and platform specific terminology, and syntax. Supplementary File S1 contains the complete search strategies used for the various databases (Table S1). Alerts were set up for each database to receive publication notifications for new related articles.

Inclusion and exclusion criteria

Articles included were from any country, all in English, published from 1999 to current, and were research articles. The articles included study population that are adults in the general population or populations at risk of glaucoma. The study population included those with or without glaucoma. Articles on teleglaucoma intervention for glaucoma screening were included, both in-comparison to in-person screening and analyzing teleglaucoma on its own. Outcome measures of teleglaucoma articles selected contained efficiency measures, specificity, sensitivity, and its ability to detect glaucoma, as well as patient benefits and cost data. Economic evaluations such as cost-effectiveness analysis and studies with costing data were also included.

The exclusion criteria was articles published prior to 1999 since teleglaucoma is fairly new and to be consistent with the teleglaucoma screening procedure, year 1999 was selected as a cut-off year. Additionally, non-research articles such as methodology papers, editorials, review articles, commentaries, and letters were excluded. Articles on diagnosis or prognosis, genetic screening, and teleophthalmology for ocular conditions other than glaucoma were eliminated.

A total of 11237 articles were retrieved by searching various databases and an additional 526 were retrieved from hand searching and grey literature search which were then imported into EPPI 4.0 reference manager. Based on the inclusion and exclusion criteria, two reviewers independently reviewed all articles.
After removing duplicate articles, 8157 articles were included for screening. Articles were screened by title, abstract, and full text in level 1, 2, and 3 screening respectively. After each level of screening, kappa statistics was calculated to measure reviewer’s agreement. Additionally, if consensus was not reached by the two reviewers’ then a third reviewer intervened to solve disagreements on article eligibility. The agreement between the two reviewers was excellent (kappa = 0.86). The PRISMA diagram demonstrating the selection process is displayed in Figure 1 (Table S3).

Quality Assessment Strategy
Articles were assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines for publication bias, risk of bias, imprecision, inconsistency, and indirectness [15–20]. Articles were graded as either low, moderate, or high quality of evidence. The results indicated that 17 articles were high quality, 13 were moderate quality, and 15 articles were graded as low quality of evidence. Despite the quality of evidence, all articles were included in the analysis.

Data Extraction Strategy
Qualitative and quantitative data necessary for analysis was obtained from each article. Information on study location, design, effect measures (sensitivity and specificity), percentage of glaucoma diagnosed, service times, image quality, visual acuities, ophthalmic characteristics, and costs were collected. One reviewer extracted data using an excel template. Authors were emailed to obtain missing relevant information. All databases were updated with new information from respective authors. Additional current costing data was provided by ophthalmic equipment vendors INNOVA, Topcon, and Ocular Health Network. Costs were converted to 2014 US dollars [21]. This research study has no financial relationships, investments, or sponsorship related to the cited commercial vendors.

Data Analysis
Data was synthesized and analyzed using STATA 13. When studies reported estimates as range or p-value or multiple estimates, mean and standard deviation (SD) were derived. Hierarchical logistic regression was used to determine the pooled estimates of sensitivity and specificity of teleglaucoma and in-person examination. A graphical representation of the summary estimates was presented in a Hierarchical Summary Receiver Operating Characteristic (HSROC) curve with 95% confidence intervals and 95% prediction regions.

The positive/negative likelihood ratios (LR+/LR−) were calculated using bivariate models to generate estimates of the likelihood of a positive/negative test in a glaucoma/non-glaucoma patient. From this result the diagnostic odds ratio (DOR) was calculated to determine the relative diagnostic effectiveness of
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Figure 1. PRISMA diagram.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

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Table 2. Baseline characteristics of included studies – demographics.

| Author (Year)          | Location | Study Design | Sample Size | Population                                      |
|------------------------|----------|--------------|-------------|-------------------------------------------------|
| Tuulonen et al. (1999) | Finland  | PC           | 70          | Glaucoma patients                               |
| Eikelboom et al. (1999)| Australia| PC           | 27          | Glaucoma patients                               |
| Li et al. (1999)       | USA      | PC           | 32          | Diabetic adults                                 |
| Yogesan et al. (1999)  | Australia| PC           | 27          | Glaucoma clinic patients/suspected of glaucoma  |
| Michelson et al. (2000)| Germany  | PC           | 10          | Glaucoma-diagnosed patients                     |
| Yogesan et al. (2000)  | Indonesia| PC           | 14          | Ophthalmic Clinic patients                      |
| Yogesan et al. (2000)  | Australia| PC           | 43          | Ophthalmic Clinic patients                      |
| Gonzalez et al. (2001) | Spain    | PC           | 139         | Ophthalmic Clinic patients                      |
| Sebastian et al. (2001)| Spain    | CS           | 74          | Glaucoma suspects                               |
| Wegner et al. (2003)   | Germany  | PC           | 1733        | Not stated                                      |
| Labiris et al. (2003)  | Greece   | PC           | 1205        | Glaucoma-diagnosed patients                     |
| Farsi et al. (2003)    | Canada   | PC           | 33          | Glaucoma suspects or diagnosed                  |
| Jin et al. (2003)      | Canada   | CEA          | 339         | Diabetic aboriginals                            |
| Chen et al. (2004)     | Taiwan   | PC           | 113         | Residents of area aged >40 years                |
| de Mul et al. (2004)   | Netherlands| PC          | 1729        | Optometrist patients at-risk for glaucoma       |
| Ianchulev et al. (2005)| USA      | PC           | 33          | Glaucoma suspects or diagnosed                  |
| Paul et al. (2006)     | India    | PC           | 348         | Rural residents at risk for glaucoma            |
| Kumar et al. (2006)    | Australia| PC           | 107         | Patients of the Eye Clinic                      |
| Kumar et al. (2007)    | New Zealand| PC         | 201         | General eye examination clinic Patients          |
| Khouri et al. (2007)   | Not Stated| CS          | 30          | Glaucoma-diagnosed patients                     |
| Pasquale et al. (2007) | USA      | PC           | 350         | Diabetic                                        |
| Khouri et al. (2008)   | USA      | PC           | 28          | Glaucoma-diagnosed patients                     |
| deBont et al. (2008)   | USA      | PC           | 1729        | Optometrist patients at-risk for glaucoma       |
| Sogbesan et al. (2010) | Canada   | CEA/PC       | –           | Optometrist patients at-risk for glaucoma       |
| Anton-Lopez et al. (2011)| Spain | CS         | 1599        | At-risk for glaucoma                            |
| Khurana et al. (2011)  | India    | CS           | 91698       | Ophthalmic Clinic patients                      |
| Staffieri et al. (2011)| Tasmania| PC           | 133         | High risk (First degree relatives of diagnosed POAG) |
| Swierk et al. (2011)   | Germany  | EE           | –           | Ophthalmic Clinic patients                      |
| Amin et al. (2012)     | Canada   | PC           | 72          | Glaucoma suspects or early stages of OAG        |
| Shahid et al. (2012)   | USA      | CS           | 341         | Urban soup kitchen/homeless                     |
| Kassam et al. (2012)   | Canada   | PC           | 257         | At-risk for glaucoma or early-stage glaucoma    |
| Gupta et al. (2013)    | India    | PC           | 247         | Ophthalmic Clinic patients                      |
| Damji et al. (2013)    | Canada   | PC           | 71          | Ophthalmic Clinic patients                      |
| Kiage et al. (2013)    | rural Africa| PC         | 309         | Diabetic adults                                 |
| Verma et al. (2013)    | Canada   | RC           | 247         | Optometrist-referred glaucoma suspects or early OAG |
| Ahmed et al. (2013)    | USA      | RC           | 643         | Diabetic and hypertensive                       |
| Arora et al. (2014)    | Alberta  | PC           | 71          | Glaucoma clinic patients/suspected of glaucoma  |

Legend: CS = Cross-Sectional Study, PC = Prospective Cohort Study, CEA = Cost-effectiveness Analysis, RCS = Retrospective Cohort Study, EE = Economic Evaluation, – = Not Stated.

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| Author (Year) | Teleglaucoma Equipment | Comparator |
|--------------|------------------------|------------|
| Tuulonen et al. (1999) [11] | Canon CR5-45NM non-mydriatric fundus camera, slit-lamp, Panasonic video camera, HF II perimeter | In-person examination |
| Eikelboom et al. (1999) [31] | Nidek Nm-100 Handheld fundus camera | Teleglaucoma only |
| Li et al. (1999) [35] | Non-mydriatric retinal camera. Digital images | Image Quality of Teleglaucoma |
| Yogesan et al. (1999) [36] | Portable fundus camera, Nidek NM100 | Teleglaucoma only |
| Michelson et al. (2000) [37] | Self-tonometry portable device called Ocuton, PaIPIlot, IOP curve | Teleglaucoma only |
| Yogesan et al. (2000) [38] | Handheld fundus camera (NM100) | Teleglaucoma only |
| Yogesan et al. (2000) [39] | DIO digital indirect ophthalmoscope, handheld fundus camera Nidek NM100, stereo fundus camera (Nidek 3D-x) | Teleglaucoma only |
| Gonzalez et al. (2001) [40] | Non-mydriatric fundus camera (canon CR6-45M) | In-person examination |
| Sebastian et al. (2001) [41] | C-20-5 FDT, Humphrey-Zeiss, & Topcon optic nerve head photographs | Teleglaucoma only |
| Wegner et al. (2003) [42] | Goldman applanation tonometer and mobile HRT | Teleglaucoma only |
| Labiris et al. (2003) [43] | Slt lamp, Octopus perimeter visual field, fundus camera, Optotype, air tonometer | In-person examination |
| Fansi et al. (2003) [44] | – | Healthy vs Glaucoma eyes |
| Jin et al. (2003) [45] | Tonometry | In-person examination |
| Chen et al. (2004) [46] | Digital 35-degree colour fundus images, non-mydriatric digital fundus camera (CR6-45, Canon) | In-person examination |
| de Mul et al. (2004) [47] | Nerve fibre analyser, GDx | In-person examination |
| Ianchulev et al. (2005) [32] | Peristat: self-test | In-person examination |
| Paul et al. (2006) [48] | – | Teleglaucoma only |
| Kumar et al. (2006) [33] | I-care tonometry | Teleglaucoma only |
| Kumar et al. (2007) [49] | – | In-person examination |
| Khouri et al. (2007) [50] | Digital stereo fundus camera - Nidek 3-Dx | Image Quality of Teleglaucoma |
| Pasquale et al. (2007) [51] | Topcon TRC NW-5S non-mydriatric retinal camera (Paramus) interfaced to a standard color video camera (Sony 970-MD) | Teleglaucoma only |
| Khouri et al. (2008) [52] | Non-mydriatric 45-deg camera, Canon Japan. DICOM image format | Image Quality of Teleglaucoma |
| deBont et al. (2008) [53] | Nerve fibre analyser, GDx | Image Quality of Teleglaucoma |
| Sogbesan (2010) [54] | – | In-person examination |
| Anton-Lopez et al. (2011) [55] | HRT, nerve-fibre analyzer (GDX-VCC), I-Care (rebound tonometry) | In-person examination |
| Khurana et al. (2011) [56] | – | Teleglaucoma only |
| Staffieri et al. (2011) [57] | – | Teleglaucoma only |
| Swierk et al. (2011) [58] | – | In-person examination |
| Amin et al. (2012) [59] | Slit lamp, IOP, CCT, visual field, anterior and stereo posterior segment photos and OCT | In-person examination |
| Shahid et al. (2012) [6] | 8.2 megapixel non-mydriatric retinal camera | Teleglaucoma only |
| Kassam et al. (2012) [9] | Remote service - slit lamp, fundus photographs, | In-person examination |
| Gupta et al. (2013) [14] | Fundus Camera (Portcam II) | In-person examination |
| Damji et al. (2013) [60] | – | In-person examination |
| Kiage et al. (2013) [13] | Topcon 777 | In-person examination |
| Verma et al. (2013) [61] | – | In-person examination |
| Ahmed et al. (2013) [62] | Topcon TRC non-mydriatric retinal camera, Tonopen | Teleglaucoma only |
| Arora et al. (2014) [12] | – | In-person examination |

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teleglaucoma. DOR is the ratio of the odds of a positive screen test in a glaucoma case relative to the odds of a negative screen test in a non-glaucoma case [22].

Due to the variability of study effectiveness measures, not one article had a complete set of data. Missing data was treated as statistically missing values and not included in the analysis. Only articles with complete data were included in each analysis. Publication bias was assessed using funnel plots.

**Results**

A total of 45 studies were included in this meta-analysis. Table 2 and Table 3 display the baseline characteristics of each study. Studies were conducted in fourteen different countries with representation in each continent. All articles were published between 1999 and 2014. The cumulated individuals of all studies were 101,512 participants. All studies were observational studies, as there were no randomized controlled trials conducted. Three studies contained economic evaluations or cost-effectiveness analysis. Of the 45 studies, 16 compared teleglaucoma to in-person examination. The other 29 studies analyzed teleglaucoma without comparison or was an evaluation of different teleglaucoma equipment. There was minimal variation in study populations; they included either glaucoma patients or patients who were at risk of glaucoma (based on diabetes status, family history of glaucoma, age, or ethnicity). Table 4 displays additional study details on demographics and study methods (glaucoma definition, pupil dilation, and number of field tests examined). Although there was some variation, less than 10% of studies reported these details. The main outcome measures were specificity and sensitivity (Table 5). Other included outcome measures (percentage of glaucoma diagnosed, referral rate, and proportion of images with poor quality) are displayed in table 5.

Costing data was given by nine studies and the quality of analysis of costing is displayed in table 6. Teleglaucoma costs vary by the capacity of the service and the type and amount of equipment. The current vendor estimate shows that the total costs for standard glaucoma equipment range from 89,703.53 to 123,164.55 US dollars (Table 6) [23, 24]. Additionally, to transfer images and patient test results securely to ophthalmologists electronically a service exists costing $62.13 US/month [21, 25]. This service allows teleglaucoma technicians and ophthalmologists to login electronically to attach, send, view and assess retinal images and patient test results.

Costing data from the literature shows the cost per detected case of glaucoma ranged from $13.03–2020.96 US after conversion to US dollars and adjusted for inflation to 2014 costs (Table 7) [26]. The mean cost is $1098.67 US for every case of glaucoma detected (n=3) (Table 7). The mean cost of teleglaucoma per patient screened was $922.77 US (n=2) (Table 7).

Another necessary costing aspect is the ophthalmologist fee for glaucoma consultation. The ophthalmologist may be compensated for each teleglaucoma referral or time spent on teleophthalmology consultations. Compensation varies
Table 4. Additional Details on Baseline Characteristics of Included Studies.

| Author (Year)         | Study Population Ethnicity | Glaucoma definition                                                                 | Dilated pupil | # Field tests |
|-----------------------|----------------------------|--------------------------------------------------------------------------------------|---------------|---------------|
| Eikelboom et al. (1999) [31] | –                          | –                                                                                    | Yes           | –             |
| Yogesan et al. (1999) [36]      | –                          | –                                                                                    | Yes           | –             |
| Yogesan et al. (2000) [38]      | –                          | –                                                                                    | Yes           | –             |
| Yogesan et al. (2000) [39]      | –                          | –                                                                                    | Yes           | –             |
| Ianchulev et al. (2005) [32]    | 15% White, 9% African American, 76% Hispanic | –                                                                                    | No            | –             |
| Chen et al. (2004) [46]         | 100% Asian                 | “The diagnosis of glaucoma was made according to the anatomical findings from the patient’s optic nerve disc, and functional visual field examination by frequency-doubling perimeter (FDP). Intracocular pressure (IOP) was also evaluated. An elevated IOP was defined as over 17 mmHg (1 mmH = 133 Pa). Severe glaucoma was defined as an optic cup: disc ratio over 0.7 with an FDP defect or elevated IOP. Mild glaucoma was defined as an optic cup: disc ratio between 0.7 and 0.5, or disc asymmetry of over 20%, with an FDP defect or elevated IOP.” | –             | –             |
| Kumar et al. (2006) [33]        | 96% Caucasian, 4% Asian    | IOP of 21 mmHg was threshold for suspected glaucoma                                  | –             | –             |
| Paul et al. (2006) [48]         | 100% Indian                | –                                                                                    | –             | –             |
| Kumar et al. (2007) [49]        | –                          | In accordance with glaucoma screening protocol of Lions Eye Institute: Vertical cup disc ratio (VCDR) > 0.5, IOP > 21 mmHg, abnormal visual field related to glaucoma, and or disk asymmetry > 0.2. | Yes           | –             |
| Pasquale et al. (2007) [51]     | 16% African American (of glaucoma suspects) 14% African American (Of non-glaucoma suspects) | “VF’s were considered glaucomatous if the pattern deviation plot showed a nasal step, nasal depression, arcuate defect, paracentral loss that respected the horizontal meridian, or temporal wedge defects based on previously published criteria… Patients were designated as “no glaucoma” if the CDR was < 0.6 in both eyes and CDR asymmetry was < 0.1 in the absence of reliable glaucomatous VFs. Patients were designated as having “glaucoma-suspicious optic discs” if the CDR was > 0.6 in either eye or CDR asymmetry was > 0.1 with or without reliable glaucomatous VFs. Patients with more subtle optic nerve changes were labeled as having glaucoma-suspicious optic discs if VFs were available and reliable and showed change consistent with glaucomatous loss.” | –             | Three         |
| Staffieri et al. (2011) [57]    | –                          | “Subjects were classified as having definite glaucoma on the basis of characteristic optic nerve head changes (cup: disc ratio [CDR] outside the 97.5 percentile for the normal population or rim width less than 0.1 CDR at the superior and inferior poles of the disc) and definite visual field defect consistent with glaucoma. Individuals with stereoscopic disc photos consistent with structural damage but in whom field testing was unreliable or unobtainable were classified as glaucoma suspect.” | Yes           | –             |
| Khurana et al. (2011) [56]      | 100% Indian                | –                                                                                    | –             | –             |
| Anton-Lopez et al. (2011) [55]  | –                          | “2/3 Criteria were considered suspects and referred for glaucoma consultation: (1) global Moorefield’s Regression Analysis borderline or outside normal limits, (2) Nerve Fibre Index > 30, and tonometry > 21 mmHg.” | –             | –             |
| Shahid et al. (2012) [6]        | 78% African American, 10% Caucasian, 6.7% Hispanic, 4.8% Other | –                                                                                    | Yes           | One           |
Table 4. Cont.

| Author (Year)          | Study Population Ethnicity | Glaucoma definition                                                                                   | Dilated pupil | # Field tests |
|------------------------|----------------------------|--------------------------------------------------------------------------------------------------------|---------------|---------------|
| Kiage et al. (2013)    | 100% African               | Category 1 diagnosis (structural and functional evidence): 2 out of 3 of the following: VCDR ≥0.7, focal glaucoma disc changes, VCDR asymmetry (≥0.2). Category 2 diagnosis (structural evidence with unproved field loss): 2 out of 3 of the following: VCDR ≥0.8, focal glaucoma disc changes, VCDR asymmetry ≥0.3. Category 3 diagnosis (optic disc not clearly seen): 1 of the following visual acuity <3/60 and IOP > 21 mmHg or visual acuity <3/60 and evidence of glaucoma surgery or medical records confirming glaucoma morbidity. Glaucoma suspect: one of the following IOP ≥23 mmHg, 1/3 of the glaucomatous optic neuropathy listed in category 2, glaucoma visual field defect only. | Yes           | Three         |
| Gupta et al. (2013)    | 100% Indian                | Glaucoma diagnosis based on disc findings VCDR of ≥0.7 or focal neuroretinal rim defect.               | Yes           | –             |

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Table 5. Study relevant outcome measures.

| Author (Year)          | Specificity (%) | Sensitivity (%) | Percentage Glaucoma diagnosed | Percentage Referral Rate | Percentage of Image of Poor Quality |
|------------------------|-----------------|-----------------|-------------------------------|--------------------------|------------------------------------|
| Li et al. (1999)       | –               | –               | –                             | –                        | 18.8                               |
| Yogesan et al. (1999)  | 84.5            | 82.5            | –                             | –                        | –                                  |
| Eikelboom et al. (1999)| 71.5            | 67              | –                             | –                        | –                                  |
| Yogesan et al. (2000)  | 87              | 100             | –                             | –                        | –                                  |
| Gonzalez et al. (2001) | –               | –               | 7.9                           | –                        | 13                                 |
| Sebastian et al. (2001)| –               | –               | 2.7                           | –                        | 4                                  |
| Wegner et al. (2003)   | –               | –               | –                             | –                        | 9.4                                |
| de Mul et al. (2004)   | 58              | 82              | 4.6                           | 11                       | –                                  |
| Ianchulev et al. (2005)| 95.5            | 81.5            | –                             | –                        | –                                  |
| Kumar et al. (2006)    | 98.8            | 38.1            | –                             | –                        | –                                  |
| Kumar et al. (2007)    | 93.6            | 91.1            | –                             | –                        | –                                  |
| Pasquale et al. (2007) | 96              | 59              | –                             | –                        | –                                  |
| de Bont et al. (2008)  | –               | –               | –                             | 11                       | 11                                 |
| Staffieri et al. (2011)| –               | –               | 5                             | –                        | –                                  |
| Anton-Lopez et al. (2011)| –             | –               | 1.9                           | 7.7                      | –                                  |
| Khurana et al. (2011)  | –               | –               | 1.06                          | 12.5                     | –                                  |
| Shahid et al. (2012)   | –               | –               | –                             | 32                       | –                                  |
| Ahmed et al. (2013)    | –               | –               | –                             | 19.4                     | 5                                  |
| Gupta et al. (2013)    | 81.82           | 72.1            | –                             | –                        | –                                  |
| Kiage et al. (2013)    | 89.6            | 41.3            | 14                            | –                        | 24                                 |
| Verma et al. (2013)    | –               | –               | 31                            | 31                       | –                                  |
| Arora et al. (2014)    | –               | –               | 44                            | –                        | –                                  |

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Table 6. Quality of analysis for costing.

| Author (Year)           | Object                                      | Costs ($) | Currency |
|-------------------------|---------------------------------------------|-----------|----------|
| Tuulonen et al. (1999)  | Fixed Costs                                 |           |          |
|                         | Fundus camera (1 unit)                      | 200       | FIM      |
|                         | ISDN installation (3 units)                 | 6.5       | FIM      |
|                         | Server computer (2 units for 5 years)       | 50        | FIM      |
|                         | Software application (2 units for 5yrs)     | 50        | FIM      |
|                         | Video slit-lamp (1 unit)                    | 40        | FIM      |
|                         | Write-off 10 years (3%)                     | 40.62     | FIM      |
|                         | Use of teleophthalmology equipment          | 24.372    | FIM      |
|                         | Video conference equipment                  | 84        | FIM      |
|                         | Write-off 5 years                           | 18.342    | FIM      |
|                         | Automated perimetry – Humphrey              | 132       | FIM      |
|                         | Write-off 10 years (3%)                     | 15.474    | FIM      |
|                         | Other fixed costs                           |           |          |
|                         | Service and updating                        | 5         | FIM      |
|                         | Line costs per month                        | 3.672     | FIM      |
|                         | Premise                                     | 1.608     | FIM      |
|                         | Utilities                                   | 1.608     | FIM      |
|                         | Other costs                                 | 7.133     | FIM      |
| Yogesan et al. (2000)   | Satellite phone                             | 30000     | EUR      |
|                         | Mobile phone                                | 3250      | EUR      |
| Jin et al. (2003)       | Total expenditure capital                   | 160260    | CAN      |
|                         | Operating costs per 1 year                  | 348665    | CAN      |
|                         | Projected 2005 Costs                        | 385226    | CAN      |
|                         | Operating costs amortized over 5 years       | 32052     | CAN      |
|                         | Operating costs amortized over 5 years per diabetic case | 1231     | CAN      |
|                         | Professional and Lab Fees                   | 291       | CAN      |
|                         | Costs per patient                           | 1231      | CAN      |
|                         | Travel costs                                | 805       | CAN      |
|                         | Escort travel expenses                      | 340       | CAN      |
| Chen et al. (2004)      | Costs per detected case                     | 10        | US       |
| Ianchulev et al. (2005) | Costs per targeted glaucoma screening       | 60        | US       |
|                         | Costs per detected case                     | 1000      | US       |
| Sogbesan (2010)         | Patient savings                             | 2527      | CAN      |
| Anton-Lopez et al. (2011) | Incremental Costs                         | 24150     | EUR      |
|                         | Costs per detected case                     | 1420      | EUR      |
|                         | Primary Care visit                          | 15        | EUR      |
|                         | General Ophthalmic Visit                   | 18        | EUR      |
|                         | Ophthalmic Visit with tests                 | 52        | EUR      |
|                         | Glaucoma Consultation                       | 26        | EUR      |
| Swierk et al. (2011)    | Medical Care                                | 291.21    | EUR      |
|                         | Accommodation costs                         | 280       | EUR      |
|                         | Costs per patient                           | 288.72    | EUR      |
| Ahmed et al. (2013)     | Equipment costs (digital retinal camera, Tonopen and computer) | 46000 | US |
by states and/or provinces, government legislation, and available private grants. In the United States, Medicare and Medicaid provide several reimbursement programs for physicians delivering telemedicine consultations [27, 28]. In Ontario, Canada, the compensation for the fee-for-service model, is $16.00 CAN per ophthalmic referral [29]. The physician liable for teleglaucoma consultations must be a licensed ophthalmologist in both the area of the service and the patient. Physicians must hold liability coverage appropriate to state/provincial laws. In Canada, the Canadian Medical Protective Association provides ophthalmologists with liability coverage for teleophthalmology [30].

Ten studies had complete data necessary to conduct the analysis for teleglaucoma diagnostic accuracy. The summary estimate for sensitivity was 0.833 [95% CI 0.77, 0.88] and specificity was 0.79 [95% CI 0.668, 0.875] for glaucoma screening using optic nerve examinations (Figure 2). The summary estimates indicate that teleglaucoma correctly detects 83.3% of glaucoma cases and correctly classifies 79% of those without glaucoma as glaucoma-negative. Figure 3 displays each study estimate and the summary estimate with its associated confidence intervals and the generated HSROC curve. The distribution of the studies in the

| Author (Year) | Object | Costs ($) | Currency |
|--------------|--------|-----------|----------|
| Vendor Estimates (2014) [23, 24] | OCT | 48,000–49,000 | CAN |
| Slit Lamp | 7,420–19,990 | CAN |
| Slit lamp mounted | 1,400–2,400 | CAN |
| Non-contact | 8,995 | CAN |
| Retinal Camera | 27,900–27, 995 | CAN |
| Visual Field Analyser | 16,340–32,420 | CAN |
| **TOTAL RANGE:** | **89,703.53–123,164.55** | US |
| Ocular Health Network (2014) [25] | Imaging Transfer Service | 70/Month | CAN |

Table 7. Teleglaucoma estimated 2014 unit costs.

| Author (Year) | Cost per detected case ($US) (Adjusted for inflation to 2014 costs) | Inflation Rate (%) | Cost per patient ($US) (Adjusted for inflation to 2014 costs) | Inflation Rate (%) |
|--------------|---------------------------------------------------------------|-------------------|---------------------------------------------------------------|-------------------|
| Jin et al. (2003) [45] | – | – | 1434.63 | 25.49 |
| Chen et al. (2004) [46] | 13.03 | 30.32 | – | – |
| Ianchulev et al. (2005) [32] | 1262.02 | 26.2 | – | – |
| Anton-Lopez et al. (2011) [55] | 2020.96 | 5.89 | – | – |
| Swierk et al. (2011) [58] | – | – | 410.91 | 5.89 |
| **Mean costs** | **1098.67** | | **922.77** | |
Refining starting values:

Iteration 0: log likelihood = -78.600767 (not concave)
Iteration 1: log likelihood = -75.982129
Iteration 2: log likelihood = -75.554028
Iteration 3: log likelihood = -75.340131

Performing gradient-based optimization:

Iteration 0: log likelihood = -75.340131
Iteration 1: log likelihood = -75.338524
Iteration 2: log likelihood = -75.338524

Meta-analysis of diagnostic accuracy

Log likelihood = -75.338524 Number of studies = 8

|            | Coef.     | Std. Err. | z       | P > |z|   | [95% Conf. Interval] |
|------------|-----------|-----------|---------|-----|----|---------------------|
| Bivariate  |           |           |         |     |    |                     |
| E(\logitSe) | 1.603718  | .2012079  |         |     |    | 1.209357 1.998078   |
| E(\logitSp) | 1.327128  | .3199906  |         |     |    | .6999575 1.954298   |
| Var(\logitSe) | .2967446  | .1757148  |         |     |    | .0929718 .947141   |
| Var(\logitSp) | .9162078  | .5546539  |         |     |    | .279007 3.001197   |
| Corr(\logits) | .485518   | .3151724  |         |     |    | -.271123 .8712955  |
| HSROC      |           |           |         |     |    |                     |
| Lambda     | .3.127015 | .4806803  |         |     |    | 2.184899 4.069131   |
| Theta      | .5623328  | .3130932  |         |     |    | -.0513186 1.175984  |
| beta       | .5636856  | .3954614  | 1.43    | 0.154 |    | -.2114045 1.338776  |
| s2alpha    | .154916   | .8267713  |         |     |    | .5442752 4.409345   |
| s2theta    | .1341308  | .0918339  |         |     |    | .035054  .5132295   |
| Summary pt.|           |           |         |     |    |                     |
| Se         | .8325373  | .0280522  |         |     |    | .7701852  .8805951  |
| Sp         | .7903651  | .0530186  |         |     |    | .6681784  .8759145  |
| DOR        | 18.74346  | 8.251661  |         |     |    | 7.908883 44.42062  |
| LR+        | 3.971368  | 1.064445  |         |     |    | 2.348511 6.715643  |
| LR-        | .2118802  | .0431373  |         |     |    | .1421647  .3157831  |
| 1/LR-      | .4.719649 | .960887  |         |     |    | 3.166731 7.034096  |

Covariance between estimates of E(\logitSe) & E(\logitSp)  .0254672

Figure 2. Hierarchical logistic regression results.

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The diagnostic tools of the included studies varied slightly (Table 8). Eight out of the ten studies analyzed for sensitivity and specificity used at minimum optic nerve examinations as part of the screening process (Table 8). The other two studies reported using IOP or visual field defects as the methods to detect glaucoma suspects (Table 8). For these studies which did not include fundus photographs, the sensitivity and specificity were 81.5% and 95.5% respectively for glaucoma screening using only visual field and 38.1% and 98.8% respectively for glaucoma screening using IOP and Orbscan Topography (Table 5) [32, 33].

The study populations used to assess diagnostic accuracy were those at-risk of glaucoma (based on diabetes status, family history, age, ethnicity, etc.), optometrist and ophthalmic clinic patients, and patients who were glaucoma suspects (Table 1). One study reported its study population as glaucoma patients only (Table 1) and contrary, this study had one of the lower reported scores for diagnostic accuracy: specificity was 71.5% and sensitivity was 67% (Table 5) [31].

The plot demonstrates the variability of both specificity and sensitivity amongst studies. Six studies fall outside of the 95% confidence interval of the summary estimate. The 95% prediction region is the estimate of future observations. The results demonstrate a fairly wide prediction region for both true predictions of specificity and sensitivity, with greater variability expected for specificity.
Three studies reported sensitivity and specificity of in-person examination. The weighted mean of sensitivity was 74.9 ± 27.6% (n = 3) and specificity was 88.8 ± 10.3% (n = 3) for in-person examination. The summary estimates indicate that in-person examination correctly detects 74.9% of glaucoma cases and correctly classifies 88.8% of those without glaucoma as glaucoma-negative. The positive likelihood ratio was 3.97 [95% CI: 2.3–6.7] while the negative likelihood ratio was 0.21 [95% CI: 0.14–0.32] (Figure 2). This demonstrates that the likelihood of a positive screen test in a glaucoma case is greater than the likelihood of a negative screen test in a non-glaucoma case. In addition, the positive likelihood ratio is greater than one and thus the positive screen test is associated with glaucoma. Since the negative likelihood ratio is less than one, the negative screen test is associated with the absence of disease [22]. The effectiveness of the diagnostic accuracy of teleglaucoma was given by the DOR, which was 18.7 [95% CI: 7.9–44.4] (Figure 2). The relative odds of a positive screen test in glaucoma cases are 18.7 times more likely than a negative screen test in a non-
glaucoma case. Since the DOR was greater than one the test is discriminating between true positives and true negatives correctly [22].

There was insufficient data to conduct hierarchical logistic regression on the percentage of glaucoma diagnosed. Three of the 45 studies reported percentage of glaucoma diagnosed in both teleglaucoma and in-person examination necessary for analysis. The mean percentage of glaucoma diagnosed was 13.4% for teleglaucoma and 7.8% for in-person examination which suggests that teleglaucoma is capable of detecting more cases of glaucoma.

Other effectiveness measures of teleglaucoma were analyzed such as variables of healthcare service quality. The mean percentage of patients referred to specialist for consultation was $12.5 \pm 7.8\%$ ($n=6$). The mean percentage of images that were of poor quality was $10.4 \pm 6.7\%$ ($n=7$). It took a mean time of $75.6 \pm 87.7$ seconds ($n=4$) to process the teleglaucoma images. Timing associated with teleglaucoma service is another measure of quality. The mean time for screening was $8.8 \pm 5.1$ minutes ($n=3$). The time reported for ophthalmologist to make diagnosis was $34$ minutes ($n=1$). The mean reporting time was $7.6 \pm 2.6$ minutes ($n=6$). Teleglaucoma gave a reduction for patient travel time of 61.23 hours ($n=1$). Teleglaucoma had a mean access time (time from patient being referred to the date visit is booked) of $59.7 \pm 9.9$ minutes ($n=4$) in comparison to $73.7 \pm 29.8$ minutes ($n=4$) for in-person examination. The mean cycle time (time from registration until patient leaves clinic) for teleglaucoma was $81.7 \pm 6$ minutes ($n=2$), which was less than that of in-person examination, $116 \pm 2.5$ minutes ($n=2$). The mean proportion of patient satisfaction with teleglaucoma was $47.3 \pm 8.8\%$ ($n=2$) while only $42\%$ ($n=1$) were satisfied with in-person examination.

**Discussion**

Telemedicine has demonstrated good use for offering glaucoma services to people of remote areas. Teleglaucoma is beneficial to remote areas as the physician is not required to see patients in person, which reduces wait times and shortens the length of ophthalmic consultations. Teleglaucoma avoids long distance travel and time wasted on commute. The results of the pooled estimates for diagnostic accuracy have shown teleglaucoma to be more sensitive and less specific than in-person examinations. Teleglaucoma is advantageous at detecting true positive cases of glaucoma, but has a higher rate of false positives in comparison to in-person examination. With very high DOR estimates, it is suggested that teleglaucoma can accurately discriminate screen tests. Teleglaucoma has demonstrated capability to detect glaucoma cases that may not have been detected during in-person examination. Glaucoma progresses without patient awareness and it is usually detected at the advanced stages. Thus teleglaucoma serves as a tool for early detection of glaucoma. If caught earlier and with treatment, glaucoma can be effectively managed and can result in the preservation of vision.
Telemedicine for glaucoma can have several combinations of examinations and measurements used for glaucoma screening. Examination of fundus photographs are commonly used for teleglaucoma screening. Four of the ten studies analyzed used only fundus examinations while another four studies included IOP, CCT, visual field loss, and visual acuity, in addition to fundus photograph examinations (Table 8). Two studies did not use fundus photograph examination but rather visual acuity, IOP, CCT, and ACT (Table 8). However, this is based on studies who explicitly stated the terms for ophthalmic examination. Some studies reported “comprehensive eye examinations” were performed, but did not explicitly state which examinations were performed, thus assumptions cannot be made. The use of different tests for glaucoma screening can potentially bias the results as the more diagnostic tools used during screening results in a greater probability of correct diagnosis naturally. However, the results did not show any significant differences in accuracy with studies which reported using multiple diagnostic tools. Interestingly, the specificity and sensitivity values reported ranged independent of the number and the type of examination used for teleglaucoma (Table 4 and Table 8).

The combinations of examinations are dependent on financial and resource limitations of the hosting organization and can vary from small programs to very large programs. It is dependent on the target goals and target populations of the organization. However, the standard examinations recommended for glaucoma screening are those that can evaluate visual field defects, IOP, and the biological structure and function of the optic nerve. These include HRT, OCT, optic disc photography, RNFL photography, as well as FDT, tonometry, and perimetry [34]. There were limitations within the study. Insufficient data reported was a major limitation of the meta-analysis, although authors were contacted for additional information. Nevertheless, the key goal was to systematically review the literature on tele-glaucoma and in-person screening and perform the meta-analysis. With small samples sizes there was not enough power to show statistical or clinical significance. Different comparators were reported by studies and to ensure internal validity, only studies with exact comparators were analyzed together. This was one of the reasons for reduced sample sizes for the analysis. However, our analysis does provide information on diagnostic accuracy of teleglaucoma, its capability to detect glaucoma, and to detect negative and positive cases correctly. It demonstrates teleglaucoma has the potential as a screening device to detect a greater amount of cases than in-person examination. Since teleglaucoma is an active screening, it suggests glaucoma cases are detected at earlier stages. However the significance of this difference is limited by the number of comparative studies. The majority of the studies were non-comparative which, in addition, limits the significance of the relative effectiveness to in-person examination.

Teleglaucoma has been evaluated in many different ways: diagnostic accuracy, cost reduction, technological capabilities (image quality, image transmission speed, etc.), reduction of patient and health care provider time, and convenience. Thus many studies focus on only part of the effectiveness. As a result, there is insufficient data when summarizing all of the studies together. This has proven
the need for more research literature on the diagnostic accuracy of teleglaucoma and its ability to detect glaucoma in comparison to in-person examination. There is a need for research on the follow-up of detected cases and long-term effects of teleglaucoma. In addition, better quality of evidence through randomized controlled trials is recommended. There are implications for cost-effectiveness analyses. Although, costing data suggests cost savings for patients’ time and travel with teleglaucoma, a thorough costing of current health care expenditure is required to determine its overall cost-effectiveness from the scope of the healthcare system.

Teleglaucoma is beneficial to offering services in underserviced regions and rural areas. It considerably reduces patient access times and cycle times. The time required for service is shorter than in-person examination and physician commitments are reduced. As a result teleglaucoma saves costs to patients and costs to the health care system as a whole.

Supporting Information

Table S1. Systematic review search strategy.
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Table S2. PRISMA checklist.
doi:10.1371/journal.pone.0113779.S002 (DOCX)

Table S3. Excluded full-text articles.
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Author Contributions

Conceived and designed the experiments: SMT WGH MMM JC CH. Performed the experiments: SMT MJ WGH MMM JC CH. Analyzed the data: SMT MMM WGH. Wrote the paper: SMT MMM WGH JC CH.

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