MoyaMoya disease (MMD) is a rare, chronic disorder of unknown etiology defined by the gradual occlusion of intracranial vessels, beginning with the supraclinoid carotid arteries and progressing to the anterior, middle, and posterior cerebral arteries. As these vessels become occluded, small collaterals form at the base of the brain, which together give the appearance of a “puff of smoke” on angiographic studies. This disease, which is well documented in Asian populations, has a varying presentation depending on the age of the patient and classically manifests with intracerebral hemorrhage in adults and ischemic stroke in children. The natural history of this disease is also devastating, leading to recurring strokes and subsequent neurocognitive decline.

The treatment prospects for an individual with MMD are limited because no known medical therapy has proven to be effective. Surgical approaches have been developed to directly restore perfusion to oxygen-deprived areas of the brain or indirectly to enable collateral vessel formation. Surgical intervention has been demonstrated to reduce ischemic events and thus has become the only form of effective treatment in symptomatic MMD.
Direct techniques, commonly involving a superficial temporal artery (STA) to middle cerebral artery (MCA) bypass, have been successfully used since the 1970s. Direct revascularization techniques are the most efficacious at reducing ischemic events. However, these techniques also have a myriad of drawbacks.

Direct revascularization carries the risk of hyperperfusion syndrome, which results from a sudden increase in cerebral blood flow; the incidence is as high as 28% and is seen most often in patients with extensive preoperative ischemia. Hyperperfusion syndrome can result in a temporary clinical picture that includes sensorimotor loss, aphasia, and dysarthria. Furthermore, direct procedures can accelerate stenosis of the internal carotid artery (ICA) as well the growth of moyamoya collaterals, which can lead to frontal lobe infarcts and cheiro-oral syndrome. Lastly, the procedure is challenging in the pediatric population because of the patients’ smaller, more delicate cerebral vasculature.

Indirect techniques rely on tissue supplied by the external carotid artery, which is placed on the brain surface and promotes angiogenesis. This approach generally requires less operative time since it is both technically less challenging and less invasive. Importantly, the indirect approaches do not require temporary occlusion of MCA branches, which is required in the STA-MCA bypass. As such, indirect approaches have a better safety profile than direct procedures and are preferred in children and adults with other medical comorbidities. However, in stark contrast to children, collaterals only form in approximately half of the adult patients following the indirect procedures. Even then, collaterals take months to mature, while the direct procedures provide robust reperfusion immediately.

Immediate reperfusion can pose a risk of symptomatic hyperperfusion or postoperative hemorrhage in a chronically ischemic brain. Following indirect procedures, collaterals will only form in the area of the craniotomy field, and a field of insufficient size may lead to persistent frontal lobe ischemia.

Combined procedures have also been employed by some surgeons who have postulated that the technique reduces the incidence of repeat bleeding; however, there is little evidence to show if the outcomes are actually improved or potentially worsened. Thus, the literature does not present a clearly superior revascularization technique in the surgical management of MMD. There have been no randomized clinical trials to facilitate comparison; furthermore, many studies to date combine adult and pediatric data when reporting outcomes. Hence, in this report, we use a decision analytical model to compare clinical outcomes of direct, indirect, and combined revascularization techniques in pediatric and adult patients with MMD.

Methods

We developed a decision analytical model to compare clinical outcomes of direct and indirect revascularization techniques in pediatric and adult patients with MMD. The model projects quality-adjusted life years (QALYs) for the number of postoperative years for which adequate follow-up data are available. Data for the model were derived from a critical review of published reports.

Management Strategies and Outcomes

Direct revascularization involves STA-MCA (or other high-flow arterial) bypasses, whereas indirect bypasses involve placing tissue vascularized by extracranial vessels on the brain surface to promote revascularization. Indirect procedures include encephaloduroarteriosynangiosis, encephaloduroarteriomysynangiosis, and pial synangiosis. Finally, combined approaches involve both direct and indirect procedures in the same patient.

Outcome is measured by surgery’s impact on the patient’s health-related quality of life (QOL). This is customarily measured as utility, a parametric 0–1 scale of a given outcome’s effect on QOL. These are patients’ relative preferences for a given health outcome. For example, an uneventful outcome (no perioperative complications or late-onset strokes) would be scored 1, and death would receive a score of 0. Adverse outcomes would receive intermediate scores. To allow for the possibility that the rate of late strokes would increase with duration of follow-up, we employed QALYs, a combination of both quality and QOL. As an example, 5 years without operative or delayed complications would rate 5 QALYs as would 10 years during which the patient’s QOL was 0.5. We assume that perioperative strokes influence utility for the entire follow-up, whereas late-onset strokes occur, on average, midway through the follow-up period.

Decision Analytical Model

Regardless of the surgery chosen, there may be perioperative complications, each with an impact on QOL. During follow-up, delayed ischemic stroke or intracranial hemorrhage may occur. For a given type of surgery, each pathway and outcome is dealt with in the model (Fig. 1). The probabilities and utilities of each outcome are calculated to arrive at an expected utility for each treatment option.

Data Collection and Management

We searched Medline, EMBASE, and the Cochrane Library for articles containing the key word “moyamoya” in conjunction with either the key word “therapy” or “surgery.” We limited our search to articles published in English between 1990 and February 2013. All articles were reviewed by at least 2 authors. The search yielded 695 articles, of which 33 were used in the analysis. These series reported on 4197 surgeries. Reasons for article exclusion are summarized in Fig. 2. Separate searches were done to determine utilities associated with ischemic stroke and intracranial hemorrhage. Pediatric and adult (mean age > 20 years) series were separated for the purpose of analysis. When more then one age group or surgical technique was reported in the same publication, we separated the groups. When this was impossible, the article was excluded from analysis. Table 1 summarizes the articles included in this study. In the absence of any controlled trials, all must be considered Class IV evidence. For both pediatric and adult groups, we separately recorded the following: numbers of sides operated upon in each series, mean ages,
Direct versus indirect revascularization

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sex distribution, perioperative complications and deaths, mean length of follow-up, late ischemic or hemorrhagic strokes or deaths. There was only a single report of combined revascularization in adults, so this category was omitted from the analysis. The patient population did not undergo subgroup analysis for Caucasian and Asian populations due to low numbers in relevant studies.

Statistical Analysis

Probabilities report the likelihood that a hypothetical patient travels along a particular pathway picture in Fig. 1. These represent point estimates of pooled data, which were determined via meta-analysis.\(^{36}\) After testing to exclude heterogeneity,\(^{36}\) an inverse-variance–weighted random-effects model was used to calculate means and distributions. Demographic data, such as mean ages and sex distributions, were pooled in the same fashion. We tested the hypothesis that late stroke and hemorrhage rates were linearly related to length of follow-up. For this, we employed an inverse-variance–weighted random-effects model of meta-regression. These data were used to calculate expected QALYs associated with each of the 3 surgical options. Sensitivity analysis used beta distributions for probabilities, normal distribution for utilities, and a 2D Monte Carlo simulation (100 trials, each made up of 100

### TABLE 1. Articles used in the analysis

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age Group</th>
<th>Bypass Technique</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelson &amp; Scott, 1995</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>34</td>
</tr>
<tr>
<td>Choi et al., 1997</td>
<td>Pediatric</td>
<td>Direct</td>
<td>56</td>
</tr>
<tr>
<td>Darwish &amp; Besser, 2005</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>7</td>
</tr>
<tr>
<td>Duan et al., 2012</td>
<td>Adult</td>
<td>Direct</td>
<td>45</td>
</tr>
<tr>
<td>Duan et al., 2012</td>
<td>Adult</td>
<td>Indirect</td>
<td>1229</td>
</tr>
<tr>
<td>Hankinson et al., 2008</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>12</td>
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<tr>
<td>Hirotsune et al., 1997</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>13</td>
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<tr>
<td>Hyun et al., 2010</td>
<td>Adult</td>
<td>Indirect</td>
<td>228</td>
</tr>
<tr>
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<td>Indirect</td>
<td>5</td>
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<td>Ishikawa et al., 2006</td>
<td>Adult</td>
<td>Combined</td>
<td>11</td>
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<tr>
<td>Isono et al., 2002</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>15</td>
</tr>
<tr>
<td>Jea et al., 2005</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>28</td>
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<tr>
<td>Karasawa et al., 1992</td>
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<td>Combined</td>
<td>104</td>
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<td>Kashiwagi et al., 1997</td>
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<td>Indirect</td>
<td>25</td>
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<tr>
<td>Khan et al., 2012</td>
<td>Adult</td>
<td>Direct</td>
<td>717</td>
</tr>
<tr>
<td>Kim et al., 2000</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>171</td>
</tr>
<tr>
<td>Kim et al., 2002</td>
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<td>Indirect</td>
<td>92</td>
</tr>
<tr>
<td>Kim et al., 2003</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>134</td>
</tr>
<tr>
<td>Kim et al., 2007</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>16</td>
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<tr>
<td>Kim et al., 2010</td>
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<td>410</td>
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<td>Mukawa et al., 2012</td>
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<td>Indirect</td>
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<td>15</td>
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<td>Ohtaki et al., 1998</td>
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<td>16</td>
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<td>Park et al., 2007</td>
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<td>34</td>
</tr>
<tr>
<td>Phi et al., 2011</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>65</td>
</tr>
<tr>
<td>Robertson et al., 1997</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>25</td>
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<tr>
<td>Sainte-Rose et al., 2006</td>
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<td>Indirect</td>
<td>25</td>
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<tr>
<td>Sakamoto et al., 1997</td>
<td>Pediatric</td>
<td>Combined</td>
<td>19</td>
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<tr>
<td>Scott et al., 2004</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>126</td>
</tr>
<tr>
<td>Song et al., 2012</td>
<td>Pediatric</td>
<td>Indirect</td>
<td>36</td>
</tr>
<tr>
<td>Starke et al., 2009</td>
<td>Adult</td>
<td>Indirect</td>
<td>67</td>
</tr>
<tr>
<td>Touho, 2007</td>
<td>Pediatric</td>
<td>Direct</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>Combined</td>
<td>13</td>
</tr>
</tbody>
</table>

FIG. 1. Decision analytical tree outlining possible pathways and outcomes after surgery for MMD. After surgery, a patient can have an unremarkable recovery, or suffer perioperative stroke, intracranial hemorrhage, or even death. These same 4 possible outcomes can occur during follow-up.
meta-analytical pooling and meta-regressions were done with Stata (version 12.1, StataCorp LP). Analyses of the model employed TreeAge Pro 2012 (Tree Age Software, Inc.). Statistical comparisons employed one-way ANOVA; pairwise comparisons used the Bonferroni correction for multiple comparisons. We considered differences whose \( p < 0.05 \) to be significant.

### Results

The utility of a generic ischemic stroke is \( 0.599 \pm 0.364 \); that of intracranial hemorrhage is \( 0.868 \pm 0.169 \).

#### Pediatric MMD

Table 2 presents mean ages and sex distributions for the 3 pediatric surgical cohorts. There were no significant differences among the 3 groups, nor were there any significant differences between any 2 pairs.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Mean Age</th>
<th>SD</th>
<th>Difference</th>
<th>Proportion Female</th>
<th>SD</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct</td>
<td>10.037</td>
<td>4.868</td>
<td>F = 1.888, ( p = 0.168 )</td>
<td>0.579</td>
<td>0.198</td>
<td>F = 1.003, ( p = 0.379 )</td>
</tr>
<tr>
<td>Indirect</td>
<td>8.599</td>
<td>1.965</td>
<td>( p = 0.067 )</td>
<td>0.589</td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>7.439</td>
<td>1.264</td>
<td>( p = 0.019 )</td>
<td>0.641</td>
<td>0.119</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct</td>
<td>29.7</td>
<td>2.020</td>
<td>( p = 0.334 )</td>
<td>0.607</td>
<td>0.151</td>
<td>( p = 0.914 )</td>
</tr>
<tr>
<td>Indirect</td>
<td>34.7</td>
<td>6.362</td>
<td>( p = 0.1544 )</td>
<td>0.624</td>
<td>0.1544</td>
<td></td>
</tr>
</tbody>
</table>

Pooled values of probabilities for the model are presented in Table 3. Meta-regression showed no significant increased rate of stroke or hemorrhage with length of follow-up. Accordingly, the pooled values of these parameters were used. So few studies reported mortality rates during follow-up that this aspect was excluded from the analysis. It is expected that perfect treatment, without perioperative or late complications, would result in a number of QALYs equal to the length of the follow-up.

The model calculated the expected QALYs in the 3 pediatric groups after 5- and 10-year follow-up periods (Table 4). These differences were highly significant (\( F = 209.04, p < 0.001 \)). Although there is no significant difference between the combined and indirect approaches at 5 or 10 years (\( p = 0.383 \) and \( p = 0.261 \), respectively), both were superior to direct revascularization (\( p < 0.001 \)).

#### Adult MMD

Table 2 also presents mean ages and sex distributions for the 2 adult surgical cohorts. The Student t-test shows no significant differences between the groups. Pooled values of probabilities for the model are presented in Table 3. As in the case of children, meta-regression showed no significant increased rate of stroke or hemorrhage with length of follow-up. We used pooled values here as well. Late death occurred in 0.8% (± 0.01) of adults.

Because so few reports involved follow-up exceeding 4 years postsurgery, we compared procedures at that point. Table 4 shows that indirect revascularization resulted in over one-half QALY more than the direct option during the 4-year follow-up period. This difference was highly significant (\( p < 0.001 \)).

### Discussion

In this study, we applied decision analysis methodology to compare the effectiveness of surgical revascularization techniques to treat MMD. To date, there have been no clinical trials comparing surgical revascularization techniques for MMD. Were an adequately powered, well-run, randomized, controlled trial practical, it would be preferable to a comparative effectiveness study such as ours. However, the large numbers of subjects needed, the lack of clinical equipoise among neurosurgeons, the great variety of surgical techniques, and clinical presentation in MMD make such a trial very unlikely. Thus, our results currently offer the best comparison of the two approaches. The present study shows that in pediat-
ric patients, there was no significant difference between the combined and indirect approaches, but both are superior to direct revascularization at 5- and 10-year follow-up periods. In adults, indirect revascularization yielded 50% more QALYs than the direct approach at the 4-year follow-up point.

This apparent superiority of indirect procedures may be due to the sheer technical difficulty of the direct procedures and the learning curves associated with performing them well. Though direct procedures may be more effective in reducing the incidence of future stroke, the added risk of the procedure’s technical difficulty (especially in children), hyperperfusion syndrome, and increasing the rate of stenosis appear to outweigh this benefit. The reduced operative time and invasiveness, as well as the relative ease of the indirect procedures, may contribute to the well-documented decrease in adverse effects. Moreover, it is also possible that the risk of perioperative stroke from the delayed formation of collaterals following indirect procedures may be overstated. It is also important to note that appropriate propensity matching is not possible given that the patient populations may differ.

Our study noted that pediatric patients tolerated the combined procedure well and did not suffer from an increased rate of adverse events as compared with adult patients undergoing the direct procedure. However, the current study is a review rather than a study designed to test noninferiority. It would be necessary to conduct further analysis to compare the indirect and combined procedure in the pediatric population to determine truly if the outcomes were similar. If the two procedures were determined to have equal efficacy, it stands to reason that the choice would be the less invasive approach.

Our decision model is limited by its simplifying assumptions. Our small numbers precluded us from confirming that the incidence of late-onset postoperative ischemic stroke increases over time. Additionally, particular surgeons are certainly more facile at direct anastomoses than others, and certain indirect procedures may well be superior to others. The model developed in the present study cannot make allowances for this. Furthermore, we limited surgical complications to ischemic stroke and intracranial hemorrhage. However, it should be noted that other recorded complications tended to be transient or mild with little effect on overall outcome.

An important limitation in a retrospective analysis such as this is the unknown, potentially confounding factors that influenced selections of surgical approach in the studies that were analyzed and used to create our decision model. Hence, we were unable to control for various vascular factors that might have influenced a surgeon’s decision making, and likewise, we could not ensure that these factors were the same among the various studies reviewed. This may have introduced selection bias and thus have restricted the validity of our results. Finally, many studies of outcome after revascularization have only focused on ischemic events, whereas other adverse outcomes such as seizures and neurocognitive decline are also critical considerations.

Conclusions

We performed a comparative analysis of direct, indirect, and combined revascularization techniques for MMD in adults and children. In both patient populations, we found significantly inferior outcomes with direct revascularization compared with the other two surgical approaches.
References


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Stein, Macyszyn, Ali. Acquisition of data: Macyszyn, Attiah, Faught, Hossain, Man, Patel, Sobota. Analysis and interpretation of data: Macyszyn, Ali, Drafting the article: Macyszyn, Attiah, Ali, Zager. Critically revising the article: Stein, Macyszyn, Ali, Zager. Reviewed submitted version of manuscript: Stein, Macyszyn, Ma, Ali. Approved the final version of the manuscript on behalf of all authors: Stein. Statistical analysis: Macyszyn, Ali. Administrative/technical/material support: Stein, Macyszyn, Attiah. Study supervision: Stein, Macyszyn, Zager.

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