Prior Authorization Review
Panel MCO Policy Submission

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Type of Submission – Check all that apply:
- ☑ New Policy
- ☑ Revised Policy*
- ❌ Annual Review – No Revisions

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 111 Indocyanine Green Angiography**

This CPB has been revised to state that: (i) the use of indocyanine green for sentinel lymph node mapping in cervical and endometrial cancer is considered medically necessary, and (ii) the use of indocyanine green for sentinel lymph node mapping of other cancers (e.g., bladder, breast, colon, kidney, melanoma, ovary, penis, prostate, and stomach; not an all-inclusive list) is considered experimental and investigational.

Name of Authorized Individual (Please type or print):

Dr. Bernard Lewin, M.D.

Signature of Authorized Individual:

[Signature]

www.aetnabetterhealth.com/pennsylvania Revised 08/23/2018
Indocyanine Green Angiography

Policy

I. Aetna considers indocyanine green angiography medically necessary when it is used as an adjunct to fluorescein angiography in the diagnosis and management/treatment of any of the following conditions:

- Acute posterior multi-focal placoid pigment epitheliopathy; or
- Exudative senile macular degeneration; or
- Hemorrhagic detachment of retinal pigment epithelium; or
- Monitoring of foveo-macular vitelliform dystrophy (also known as Best disease); or
- Retinal hemorrhage; or
- Retinal neovascularization; or
- Serous detachment of retinal pigment epithelium.

**Note:** Documentation in the member's medical record should indicate one of the following:

- Evidence of ill-defined subretinal neovascular membrane or suspicious membrane on previous fluorescein angiography; or
- Presence of subretinal hemorrhage or hemorrhagic retinal pigment epithelium. A fluorescein angiography need not have been previously done; or
Clinical Policy Bulletin

Notes

• Retinal pigment epithelium does not show subretinal neovascular membrane on current fluorescein angiography.

The physician’s documentation should support the frequency and medical necessity of this procedure.

II. Aetna considers indocyanine green angiography experimental and investigational in the management of the following conditions (not an all-inclusive list) because it has not been demonstrated to add information that is useful in the management of these conditions:

• Behcet's disease (Behcet's syndrome)
• Choroidal melanoma
• Critical limb ischemia
• Diabetic macular edema
• Drusen differentiation
• Macular schisis
• Parasagittal meningioma
• Pseudo-Moyamoya disease
• Prediction of post-operative thrombosis in the internal jugular vein
• Prediction of wound complications in ventral hernia repair
• Sarcoidosis
• Scleritis and posterior scleritis
• Spinal dural arteriovenous fistula
• Vogt-Koyanagi-Harada disease.

III. Aetna considers indocyanine green angiography-assisted internal limiting membrane peeling in macular hole surgery experimental and investigational because the safety and effectiveness of this approach has not been established.

IV. Aetna considers the intra-operative use of indocyanine green angiography medically necessary for intracranial aneurysm surgery.

V. Aetna considers intra-operative indocyanine green angiography during microsurgical subinguinal varicocelectomy experimental and investigational because the effectiveness of this approach has not been established.
VI. Aetna considers the Spy Elite System (near-infrared angiography with indocyanine green) experimental and investigational for breast reconstruction surgery, evaluation of anastomotic perfusion in colorectal surgery and mapping of sentinel lymph node in cutaneous melanoma, and all other indications because the safety and effectiveness of this approach has not been established.

VII. Aetna considers indocyanine green fluorescence angiography experimental and investigational for intraoperative evaluation of residual parathyroid glands function and prediction of post-operative hypocalcemia risk after total thyroidectomy because the effectiveness of this approach has not been established.

VIII. Aetna considers indocyanine green fluorescence tissue angiography experimental and investigational for the evaluation of the anastomotic leak/perfusion during or after esophagectomy because the effectiveness of this approach has not been established.

IX. Aetna considers the use of indocyanine green for sentinel lymph node mapping in cervical and endometrial cancer medically necessary.

X. Aetna considers the use of indocyanine green for sentinel lymph node mapping of other cancers (e.g., bladder, breast, colon, kidney, melanoma, ovary, penis, prostate, and stomach; not an all-inclusive list) experimental and investigational because its effectiveness for these indications has not been established.

Background

Fluorescein angiography allows visualization of blood flow in retinal and choroidal tissues, permitting diagnostic support in many ocular diseases. In particular, fluorescein angiography has become a very important tool in the diagnosis and treatment of chorio-retinal diseases. However, limitations of fluorescein angiography in imaging the choroidal circulation and associated pathologies prompted the use of alternative dyes to improve choroidal angiography.
Indocyanine green angiography is a diagnostic study where indocyanine green, a fluorescent dye, is injected intravenously, and observations of the retina are made at intervals as increasing intensity of retinal and choroidal circulation is displayed. Indocyanine green angiography is used for the imaging of retinal and choroidal vasculatures. It is effective when used as an adjunct to fluorescein angiography in the diagnosis and treatment of ill-defined choroidal neovascularization (i.e., associated with age-related macular degeneration). It is generally used in evaluating retinal neovascularization, serous detachment of retinal pigment epithelium, hemorrhagic detachment of retinal pigment epithelium, and retinal hemorrhage.

Indocyanine green angiography has been under development for the past 30 years as an imaging method for the choroidal vasculature. Although standard fluorescein angiography is widely used to evaluate exudative and proliferative lesions of the retina, its diagnostic ability in imaging the choroid is limited because of dye scatter by the overlying pigmented structures of the fundus, and also due to leakage of fluorescein through the fenestrated capillaries of the choroid. Improvements in indocyanine green angiography, specifically the development of high resolution digital imaging systems, have permitted the technical feasibility and commercialization of the technology.

The most commonly proposed application of indocyanine green angiography is the detection of choroidal neovascularization, a common component of age related macular degeneration. A series of randomized studies in the 1980s (called the Macular Photocoagulation Study) showed that patients with "classic" choroidal neovascularization could benefit from photocoagulation treatment. Those with diffuse or poorly defined disease or disease involving the foveal avascular zone were considered poor candidates for photocoagulation. With these criteria, it has been estimated that only about about half of patients would be candidates for treatment. In as much as the key to the success of photocoagulation was accurate delineation of choroidal neovascularization, it was hoped that the improved diagnostic capabilities of indocyanine green angiography would lead to the identification of more patients who would be appropriate candidates for treatment.

Given the above discussion, an appropriate outcome for indocyanine green angiography would be its diagnostic capabilities compared to fluorescein angiography in the evaluation of patients with choroidal neovascularization. Yannuzzi and colleagues (1992) performed indocyanine green angiography on 129 patients with age related macular degeneration and ill defined or occult...
neovascularization as identified by a previous fluorescein angiography. In 50 (39%) of the patients, indocyanine green angiography provided additional information such that occult choroidal neovascularization could be reclassified as a classic pattern. A total of 12 patients underwent laser photocoagulation based on the indocyanine green videoangiography (ICGA) findings. Although the exact techniques may vary from study to study, several subsequent reports have also documented improved diagnostic capabilities of indocyanine green angiography compared to fluorescein angiography.

As discussed in the studies above, indocyanine green angiography is used as a second level diagnostic test to further evaluate patients with choroidal neovascularization. Typically all patients will first undergo a fluorescein angiography which will simultaneously evaluate the retinal vasculature, and give initial information regarding the choroidal vasculature. Fluorescein angiography can definitively identify some patients who are not candidates for photocoagulation (i.e. those with neovascularization involving the fovea) and also those who do not have neovascularization. Indocyanine green angiography is then appropriate in those patients with equivocal results with fluorescein angiography, or who require more accurate definition of the neovascularization before proceeding to photocoagulation therapy. Therefore the appropriateness of indocyanine green angiography is contingent upon the results of fluorescein angiography.

In an evidence review on the use of indocyanine green angiography in chorio-retinal diseases, Stanga et al (2003) stated that they do not recommend ICGA for scleritis and posterior scleritis, drusen differentiation, Behcet's disease (Behcet's syndrome), or sarcoidosis, because it has not been demonstrated to add useful clinical information.

Surgical management of macular holes consists of pars plana vitrectomy, removal of the posterior hyaloid facia, and peeling of the epi-retinal membranes (ERM). Additionally, removal of the internal limiting membrane (ILM) may enable an increase in the anatomical and functional success rates. However, recognition of fine ILM is difficult; thus increasing the time that the macula is exposed to intra-operative light. Staining the ILM with indocyanine green (ICG) dye during vitrectomy has been reported to facilitate recognition of the ILM and assures that all adjacent ERM are removed. Therefore, ICG-assisted ILM peeling has gained popularity among vitreo-retinal surgeons. However, there are some concerns about the intra-vitreal ICG application. Reports in the literature described a variety of application
techniques using different concentrations. The post-operative outcomes were controversial reporting heterogeneous anatomical and functional outcomes after ICG application, as well as descriptions of adverse effects related to the dye.

Nakamura et al (2005) examined the duration of post-operative persistence of ICG dye used during vitreous surgery. They found that ICG dye used during macular surgery can persist in the macular region for up to 7 months following surgery, and seems to remain for a longer period of time in cases with macular hole than in cases with other diseases. Caution is needed regarding light exposure by post-operative fundus examinations, daylight, and other natural light. Cheng et al (2005) report 6 cases of ICG-related ocular toxicity after intra-vitreal ICG usage. Five cases had pre-operative diagnosis of macular hole, 1 case had pre-operative rhegmatogenous retinal detachment complicated with proliferative vitreo-retinopathy. All cases received vitrectomy, ICG-assisted ILM peeling and air-fluid exchange. All eyes had residual ICG left at the end of surgery. The authors noted that ocular toxicity caused by ICG may present as pigment epithelial atrophy, which is characteristically larger than the previous area of macular hole and surrounding cuff. Disc atrophy, retinal toxicity, and ocular hypotony were also observed in some cases. In addition, Tognetto et al (2005) reported a case of massive macular edema and visual loss following ICG-assisted macular pucker surgery.

An American Academy of Ophthalmology Preferred Practice Pattern on idiopathic macular hole (AAO, 2003) states that "there are no randomized controlled studies to prove the benefit of ILM peeling and there are many reports of similar results without peeling; current evidence is inconclusive." Regarding the use of ICG, the AAO Preferred Practice Pattern (2003) states: "Some surgeons recommend visualizing the ILM with indocyanine green (ICG) dye staining to aid peeling. There have been reports of damage to the retinal pigment epithelium with the use of ICG dye. The current evidence is inconclusive to recommend for or against the use of ICG during surgery."

In an observational case series (n = 31), Uemoto et al (2005) ascertained the changes in the retinal pigment epithelium (retinal pigment epithelium) and secondary changes in the choroid and fovea following ICG staining of the internal limiting lamina during surgery for an idiopathic macular hole (MH). The authors concluded that the use of ICG dye with illumination may increase the risk of retinal pigment epithelium damage and secondary choroidal and foveal morphological changes.
In a retrospective review, Husson-Danan et al (2006) examined the role of ICG in macular hole surgery. This study included a total of 38 consecutive eyes with macular hole, operated on with ILM, using or not using ICG, diluted in glucose 5% and filtered. Anatomical and functional results were analyzed in each group, using visual field testing, fluorescein fundus angiography and particularly blue filter fundus photographs for the detection of retinal pigment epithelial changes and lesions of optic nerve fibers layer. Fifteen eyes underwent surgery without ICG and 23 eyes with ICG. The mean period of follow-up was 10 months. The duration of surgery was significantly lower in the group with ICG than without (p < 0.001). Overall, 84% of the holes closed without difference between both groups. The improvement in vision at 1, 6 and 12 months was similar in both groups. Fewer defects in the optic nerve fibers layer were observed in the group with ICG than without (p = 0.02). Staining with ICG revealed the presence of an associated ERM in 61% of eyes, whereas it was clinically visible in only 17.5% before surgery. These researchers concluded that using ICG for ILM peeling produced similar visual results to those obtained without ICG. It reduced significantly the duration of surgery and the trauma to the optic nerve fibers layer, without increasing the risk of retinal pigment epithelial damage. However, in light of recent reports concerning the possible toxicity of ICG, its use should be limited in clinical practice to difficult cases.

In a non-randomized comparative study (n = 32), Oie et al (2007) examined the effect of using ICG to stain the ILM during vitrectomy in eyes with retinal detachment resulting from macular hole (MHRD). The medical records of the cases were reviewed retrospectively. During the initial vitrectomy, the ILM was peeled in 22 eyes with ICG (group A) and in 10 eyes without ICG (group B). Main outcome measures included anatomical re-attachment, visual acuity, and optical coherence tomography-determined closure of macular hole. The initial re-attachment rate in group A (86%) was significantly higher than in group B (40%; p = 0.013, Fisher exact test). The post-operative visual acuity at 6 months and the visual improvements at 6 and 12 months in eyes with an initial re-attachment were not significantly different between the 2 groups (p = 0.123, Mann-Whitney rank-sum test; p = 0.17, t test; p = 0.237, t test). The post-operative visual acuity at 12 months with an initial re-attachment in group A was significantly better than in group B (p = 0.039, t test). The macular hole closure rate with an initial re-attachment was 6 of 17 eyes (35%) in group A and 0 of 4 eyes (0%) in group B, and this difference was not significant (p = 0.281, Fisher exact test). The authors concluded that these results show that ICG staining improves the initial reattachment rate and is associated with better post-operative visual acuity at 12 months. Thus, ICG staining
should be used during vitrectomy for MHRD because the complete removal of the ILM with ICG ensures the removal of the tangential traction by an ERM and the inverse traction by the retina that cannot follow the posterior enlargement of a staphyloma. Moreover, these researchers noted that the number of patients in this study was small, and a further prospective, randomized controlled trial is needed to ascertain the effect of ICG. Confirmation of the present findings with a randomized study using a larger sample size and a longer follow-up would be ideal.

Beutel et al (2007) reported on anatomical and visual outcomes after vitrectomy and ILM peeling for idiopathic macular hole repair. A total of 40 patients with stage II to IV idiopathic macular holes were randomly assigned (1:1) in a 2-arm, single-center, randomized controlled. Internal limiting membrane delamination was performed using ICG solution (n = 20) or trypan blue (TB) (n = 20). Two patients did not complete the study, for a total of 19 in each group. Follow-up examinations included Early Treatment of Diabetic Retinopathy Study visual acuity, scanning laser ophthalmoscope micro-perimetry, optical coherence tomography, and fluorescein angiography. Main outcome measure was visual acuity 3 months after surgery. Visual acuity did not show a significant difference between study groups (95% confidence interval [CI]: -2 to 1 lines). The rate of macular hole closures was identical (84%; 95% CI: 60% to 97%). Within-group visual recovery was significant only in the TB group. Central scotomata despite hole closure persisted in 8 patients (42%) in the ICG group and in 5 (26%) in the TB group. The authors concluded that although no statistically significant difference was detected for the primary end point, the better visual recovery in the TB group and the higher rate of persistent central scotomata in the ICG group justify a larger clinical trial.

In a prospective, non-comparative, interventional case series, Kimura et al (2005) assessed the effectiveness of surgical removal of the ILM in diabetic cystoid macular edema (CME). A total of 21 eyes of 18 consecutive patients with diabetic CME were included in this study. Vitrectomy with separation of the posterior hyaloid and induction of posterior vitreous detachment had been performed previously on 9 eyes. Pars plana vitrectomy for removal of the ILM was performed. CME resolved in eyes that underwent initial vitrectomy and in those with long-standing (greater than 1 year) CME after previous vitrectomy. Post-operative best-corrected visual acuity improved by greater than or equal to 2 lines of a Snellen equivalent in 14 eyes (67%) (p < 0.01). The mean foveal thickness (distance between the inner retinal surface and the retinal pigment epithelium) decreased from 553 microm to 221 microm at 4 weeks (p < 0.001). No recurrences or deterioration of CME was
observed during the entire follow-up period (mean, 17.8 months; range of 8 to 34 months). These investigators concluded that surgical removal of the ILM might be an effective procedure for reducing CME in patients with diabetes. They noted that a prospective, randomized, controlled study is needed to further evaluate the effectiveness of the procedure.

Kwok et al (2005) evaluated the visual outcome and recurrence rate of ERM formation following vitreo-retinal surgery with and without ILM peel. The medical records of 42 consecutive patients who underwent surgery for macular ERM by a single surgeon were reviewed. All patients underwent pars plana vitrectomy and ERM removal with a subset undergoing ILM peel. Recurrence of macular ERM within 18 months and the final visual outcome after surgery were compared between patients with and without ILM removal. Twenty-five patients (59.5%) underwent ERM surgery with ILM peeling and 17 patients (40.5%) underwent ERM surgery without ILM peeling. The mean pre-operative logMAR visual acuity was 0.77 and 0.96 for the ILM peeling and non-ILM peeling groups, respectively. Visual acuity improved significantly in both the ILM and non-ILM peeling groups after ERM surgery ($p < 0.001$ and $p = 0.003$, respectively). Eighteen months after surgery, 3/17 eyes without ILM peeling (17.6%) developed recurrent macular ERM, compared with none of the 25 eyes with ILM peeling (log-rank test, $p = 0.030$). These investigators concluded that ILM removal during macular ERM surgery may minimize the recurrence of ERM, without adverse visual outcome. Moreover, they noted that further controlled prospective studies are needed to determine the role of ILM peeling in ERM surgery.

In a randomized controlled clinical trial, Hillenkamp and colleagues (2007) performed a prospective investigation of the functional and morphological outcome of idiopathic epiretinal membrane (IEM) surgery with or without the assistance of ICG. A total of 60 patients who underwent vitrectomy with removal of IEM combined with cataract surgery were randomly allocated to two groups: (i) 27 patients were operated on with ICG 0.1% in glucose 5%, and (ii) 33 patients without ICG. Functional outcome was assessed 3 to 4 months post-operatively with improvement of best-corrected visual acuity (BCVA), Amsler grid test, and automated and kinetic perimetry. Post-operative residual or recurrent IEM was assessed with biomicroscopy, and macular edema with optical coherence tomography (OCT). Improvement in BCVA was the main outcome measure. BCVA improved in 49 patients, remained unchanged in 5 and decreased in 5. Improvement in BCVA and reduction of macular edema were statistically significant within both groups ($p <$
Improvement in BCVA was not statistically significantly different whether ICG was used or not [0.17 (logarithm of minimum angle of resolution; logMAR) with ICG and 0.24 (logMAR) without ICG] (p = 0.59). There was no statistically significant difference in pre-operative or post-operative BCVA, reduction of macular edema, post-operative Amsler grid test, or incidence of residual or recurrent IEM between the two groups. Visual field defects were detected in 2 patients operated on with ICG. The authors concluded that removal of IEM with or without the assistance of ICG equally improved visual function and macular morphology.

Indocyanine green angiography has been used intra-operatively in the management of intracranial aneurysms. Raabe et al (2005) described the technical integration of ICG near-infrared technology into the optical path of the surgical microscope and reported on the image quality achieved by this method. These researchers hypothesized that ICG angiography permits a simple and quick intra-operative assessment of vessel patency and aneurysm occlusion after clip placement. A special arrangement of filters was designed to allow the passage of near-infrared light required for the excitation of ICG fluorescence (700 to 850 nm) from a modified microscope light source into the surgical field and the passage of ICG fluorescence (780 to 950 nm) from the surgical field back into the optical path of the surgical microscope. Thus, ICG angiography could be completely performed with a surgical microscope. A total of 20 patients with intracranial aneurysms were included in the technical evaluation of the new method. Image quality and spatial resolution were excellent and permitted a real-time assessment of vessel patency and aneurysm occlusion if the structures of interest were visible to the surgeon’s eye under the microscope, including perforating arteries with a diameter of less than 1 millimeter. In 1 patient, vessel occlusion by the clip was found and in 1 case residual filling of the aneurysm was diagnosed. Both cases could be treated by clip correction within 2 mins after primary placement of the clip. In all cases, the intra-operative findings correlated with the post-operative digital subtraction angiography. The authors concluded that ICG angiography using a surgical microscope is valuable for the intra-operative imaging of arterial and venous flow in all visible vessels including small perforating arteries. The simplicity of the method and the speed with which the investigation can be performed indicate that this technique may help to improve the quality and outcome of surgical procedures and reduce the need for intra- or post-operative angiography in selected cases.
de Oliveira et al (2007) described the usefulness of near-infrared ICGA for the intra-operative assessment of blood flow in perforating arteries that are visible in the surgical field during clipping of intracranial aneurysms. In addition, these researchers analyzed the incidence of perforating vessels involved during the aneurysm surgery and the incidence of ischemic infarct caused by compromised small arteries. A total of 60 patients with 64 aneurysms were surgically treated and prospectively included in this study. Intra-operative ICGA was performed using a surgical microscope with integrated ICGA technology. The presence and involvement of perforating arteries were analyzed in the microsurgical field during surgical dissection and clip application. Assessment of vascular patency after clipping was also investigated. Only those small arteries that were not visible on pre-operative digital subtraction angiography were considered for analysis. The ICGA was able to visualize flow in all patients in whom perforating vessels were found in the microscope field. Among 36 patients whose perforating vessels were visible on ICGA, 11 (30 %) presented a close relation between the aneurysm and perforating arteries. In 1 (9 %) of these 11 patients, ICGA showed occlusion of a P1 perforating artery after clip application, which led to immediate correction of the clip confirmed by immediate re-establishment of flow visible with ICGA without clinical consequences. Four patients (6.7 %) presented with post-operative perforating artery infarct, 3 of whom had perforating arteries that were not visible or distant from the aneurysm. The authors concluded that the involvement of perforating arteries during clip application for aneurysm occlusion is a usual finding. Intra-operative ICGA may provide visual information with regard to the patency of these small vessels.

Imizu et al (2008) evaluated the clinical use and the completeness of clipping with total occlusion of the aneurysmal lumen, real-time assessment of vascular patency in the parent, branching and perforating vessels, intra-operative assessment of blood flow, image quality, spatial resolution and clinical value in difficult aneurysms using near infrared ICGA integrated on to an operative Pentero neurosurgical microscope. A total of 13 patients with aneurysms were operated upon. An infrared camera with near infrared technology was adapted on to the OPMI Pentero microscope with a special filter and infrared excitation light to illuminate the operating field which was designed to allow passage of the near infrared light required for excitation of ICG, which was used as the intravascular marker. The intravascular fluorescence was imaged with a video camera attached to the microscope. ICG fluorescence (700 to 850 nm) from a modified microscope light source on to the surgical field and passage of ICG fluorescence (780 to 950 nm)
from the surgical field, back into the optical path of the microscope was used to
detect the completeness of aneurysmal clipping. Incomplete clipping in 3 patients (1
female and 2 males) with unruptured complicated aneurysms was detected using
ICGA. There were no adverse effects after injection of ICG. The completeness of
clipping was inadequately detected by Doppler ultrasound mini-probe and rigid
endoscopy and was thus complemented by ICGA. The authors concluded that the
operative microscope-integrated ICGA as a new intra-operative method for detecting
vascular flow, was found to be quick, reliable, cost-effective and possibly a
substitute or adjunct for Doppler ultrasonography or intra-operative digital
subtraction angiography (DSA), which is presently the gold standard. The simplicity
of the method, the speed with which the investigation can be performed, the quality
of the images, and the outcome of surgical procedures have all reduced the need for
angiography. This technique may be useful during routine aneurysm surgery as an
independent form of angiography and/or as an adjunct to intra-operative or post-
operative DSA.

Dashti et al (2009) evaluated the reliability of ICGA in the evaluation of neck
residuals and patency of branches after micro-neurosurgical clipping of intra-cranial
aneurysms (IAs). During a period of 14 months, 289 patients with intra-cranial
aneurysms were operated on in the authors’ institution. Intra-operative ICGA was
performed during micro-neurosurgical clipping of 239 IAs in 190 patients. Post-
operative computed tomography and computed tomography angiography (CTA)
were performed for all patients. Intra-operative interpretation of ICGA in assessing
the neck residual or the patency of vessels after clipping of each single aneurysm
were recorded and correlated with post-operative CTA and/or DSA. Post-operative
imaging studies revealed no incomplete occlusions of aneurysm domes.
Unexpected neck residuals were observed in 14 aneurysms (6 %). There were no
parent artery occlusions. Unexpected branch occlusions including both major and
minor branching arteries were observed in 15 aneurysms (6 %). The authors
concluded that ICGA is a simple and fast method of blood flow assessment with
acceptable reliability. Indocyanine green videoangiography can provide real-time
information to assess blood flow in vessels of different size as well as the occlusion
of the aneurysm. Intra-operative assessment of blood flow in the perforating
branches is one of the most important advantages. In selected cases such as giant,
complex, and deep-sited aneurysms or when the quality of image in ICGA is not
adequate, other methods of intra-operative blood flow assessment should be
considered.
Wang et al (2009) assessed the effects of surgical microscope-based ICGA in aneurysm surgery and compared the values of ICGA and post-operative DSA. A total of 101 patients with intracranial aneurysm underwent clipping of 113 aneurysms. A microscope-integrated light source containing infrared excitation light illuminated the operating field. The dye ICG was injected intravenously, and the intravascular fluorescence was recorded by a video camera attached to the microscope with optical filtering to block ambient and laser light for collection of only ICG-induced fluorescence. All patients underwent DSA 6-13 days post-operatively. The results of patency of parent, branching, and perforating arteries and documentation of aneurysm obliteration shown by ICGA and DSA were compared. A total of 219 times of ICGA was performed in these 101 patients with excellent image quality and resolution, allowing intra-operative real-time assessment of the cerebral circulation. The ICG angiographic results could be divided into arterial, capillary, and venous phases, comparable to those observed with DSA. In all cases, the post-operative angiographic results corresponded to the intra-operative ICG video angiographic findings. In 3 cases, the information provided by intra-operative ICGA significantly changed the surgical procedure. The authors concluded that simple and repeatable, microscope-based ICGA provides real-time information about vessels and aneurysm sac. This technique may be useful during routine aneurysm surgery as an adjunct to intra-operative microvascular Doppler ultrasonography and DSA.

Li et al (2009) assessed the clinical value of ICG in intracranial aneurysm surgery by comparing the findings with post-operative angiographic results. A total of 120 patients with 148 intracranial aneurysms were included. Indocyanine green angiography was performed before and/or after the aneurysm clipping. A near-infrared excitation light illuminated the operation field, ICG was injected intravenously. The intravenous fluorescence was imaged with a video camera integrated into the microscope. A total of 208 investigations of ICGA were performed. Aneurysm clipping was applied in 120 patients. Incomplete clipping was detected in 4 patients. Parent and/or branching artery stenosis was found in 5 patients. Delayed perfusion of ICG was detected in 1 patient. Post-operative DSA was performed in 108 patients. The post-operative angiographic results were consistent with findings on intra-operative ICG angiograms in 100 patients (92.6 %). In 3 cases, a mild stenosis was seen on DSA, which was not detected intra-operatively using ICG angiogram. In 1 patient, middle cerebral artery stenosis was found. Three patients had small residual aneurysms found by post-operative DSA. The remaining 1 developed a severe cerebral vasospasm. The authors concluded
that ICGA is a simple, reliable and cost-effective method. It provides real-time
information in detecting the patency of parent, branching, perforating arteries and
residual aneurysm. This technique may be a useful adjunct to improve the quality of
intracranial aneurysm surgery.

Ma et al (2009) illustrated the use of intra-operative ICGA in the surgical
management of intracranial aneurysms, including microsurgical clipping and re-
vascularization. This study included a series of 45 patients who were surgically
treated between June 2007 and May 2008 for intracranial aneurysms; 43 had
anterior circulation aneurysms, and 2 had posterior circulation aneurysms. Forty-
one patients were treated with microsurgical clipping; and 4 patients underwent re-
vascularization combined with aneurysm dissection or trapping. Intra-operative
ICGA was used to visualize the aneurysm clipping, patency of parent artery or graft.
The ICGA technique was described, with particular reference to evaluation of the
aneurysm clipping and re-vascularization. A total of 89 ICGA procedures were
performed in 45 patients with intracranial aneurysms. The aneurysms were
completely obliterated for all patients, and the grafts were patented for all except 1
patient. Pre-clipping ICGA showed the relationship of aneurysm and its parent
artery clearly. After aneurysms being clipped, intra-operative ICGA found remnant
of aneurysms, stenosis or occlusion of parent arteries and grafts in 8 cases, which
were revised in the same surgical procedure. The results of ICGA correlated well
with post-operative DSA in 97 % patients. The authors concluded that ICGA can
provide real-time information and guide revision in the same surgical procedure for
the management of intracranial aneurysms.

Hanel and colleagues (2010) stated that identification and complete interruption of
fistulae are essential but not always obvious during the surgical treatment of spinal
dural arterio-venous fistulae (dAVFs). These researchers examined cases in
which they identified and confirmed surgical obliteration of a spinal dAVF with the
aid of microscope-integrated near-infrared ICGA, which was performed during 6
surgical interventions in which 6 intra-dural dorsal AVFs (type I) were interrupted.
An operating microscope-integrated light source containing infrared excitation light
illuminated the operating field and was used to visualize an intravenous bolus of
ICG. The locations of fistulae, feeding arteries, and draining veins and
documentation of occlusion of the fistulae were compared with findings on pre-
operative and post-operative digital subtraction angiography. Indocyanine green
videoangiography identified the fistulous point(s), feeding arteries, and draining
veins in all 6 cases, as confirmed by immediate post-operative selective spinal
angiography. In 1 case, intra-operative ICG ruled out an additional questionable fistula at a contiguous level suspected on the pre-operative angiography. The authors concluded that microscope-based ICGA is simple and provides real-time information about the precise location of spinal dAVFs. During spinal dAVF surgery, this technique can be useful as an independent form of angiography or as an adjunct to intra- or post-operative digital subtraction angiography. They stated that larger series are needed to determine whether use of this modality could reduce the need for immediate post-operative spinal angiography after obliteration of intra-dural dorsal AVFs.

Polom et al (2011) stated that ever since Kitai first performed fluorescent navigation of sentinel lymph nodes (SLNs) using ICG dye with a charge-couple device and light emitting diodes, the intra-operative use of near infrared fluorescence has served a critical role in increasing the understanding in various fields of surgical oncology. These investigators reviewed the emerging role of the ICG fluorophore and its use in SLN mapping and biopsy in various cancers. In addition, they introduced the novel role of ICG-guided video angiography as a new intra-operative method of assessing microvascular circulation. The authors discussed the promising potential in addition to assessing several challenges and limitations in the context of specific surgical procedures and ICG as a whole. PubMed and Medline literature databases were searched for ICG use in clinical surgical settings. Despite ICG’s significant impact in various fields of surgical oncology, ICG is still in its nascent stages, and more in-depth studies need to be carried out to fully evaluate its potential and limitations.

Vogt-Koyanagi-Harada (VKH) disease is a multi-systemic autoimmune disorder characterized by granulomatous panuveitis with exudative retinal detachments that is frequently associated with neurological and cutaneous manifestations. Bouchenaki and Herbort (2011) reported the management of VKH disease based on ICGA. Subjects with acute episodes of inflammation (inaugural or recurrent) who had received standard ICGA-guided care were studied retrospectively. Standard of care included high-dose systemic corticosteroids at presentation and close ICGA follow-up with addition of immunosuppressive agents and/or intensification of ongoing therapy when recurrent choroidal lesions were detected by ICGA. Visual acuity, number of sub-clinical recurrences, type and duration of therapy, proportion of quiescent patients after therapy, and ICGA findings were recorded. A total of 9 patients (8 females and 1 male) were studied; 5 had inaugural disease and 4 presented with recurrent acute episodes. Visual acuity increased from 0.86 +/- 0.36 to 1.14 +/- 0.34 in the right eyes, and from 0.77 +/- 0.34 to 1.05 +/- 0.33 in the left
eyes. The number of ICGA-detected occult choroidal recurrences amounted to 13. Mean duration of treatment was 30.1 +/- 34.6 months leading to recurrence-free status after discontinuation of therapy in 6 cases with mean duration of 29.5 months. The authors concluded that continuous monitoring and aggressive therapy guided by ICGA in VKH disease prolonged treatment as compared to textbook guidelines but offered the prospect of reaching inflammation-free status after discontinuation of therapy.

Chee and Jap (2013) compared outcomes of ICGA versus clinically monitored immunotherapy in VKH disease. Consecutive patients of Singapore National Eye Centre with VKH receiving high-dose corticosteroids within 4 weeks of onset of symptoms had therapy titrated to clinical signs of activity (controls) or ICGA findings (ICGA). Charts were reviewed for demographics, interval to treatment, duration of therapy and number of systemic immunosuppressants required. Outcome measures were BCVA, disease activity, presence of sun-set glow (SSG) fundus and peri-papillary atrophy (PPA) at 2 years. A total of 52 patients were included (38 controls, 14 ICGA). Duration of treatment was shorter in the control group (17 versus 42 months, p < 0.001) and they required fewer systemic immunosuppressants than the ICGA group (16 % versus 96 %, p < 0.001). The majority (49 eyes, 96.1 %) had 6/12 or better vision and were clinically quiet (43 eyes, 84.3 %) in both groups. Sun-set glow fundus and PPA were similar in both groups. Treatment within 2 weeks of onset was the main factor affecting their occurrence on multi-variate analysis (odds ratio [OR] 0.18, 95 % CI: 0.03 to 0.9, p = 0.047; OR 0.08, 95 % CI: 0.01 to 0.51, p = 0.007, respectively). The authors concluded that ICGA-guided immunotherapy did not result in significantly better outcomes with respect to visual acuity and disease activity in VKH eyes treated within 1 month of onset.

Braun et al (2013) noted that patients requiring lower extremity re-vascularization are increasingly complex. Traditional means of evaluating perfusion before and after re-vascularization are often limited by the presence of medial calcinosis, open wounds, prior toe or fore-foot amputations, and infection. These researchers evaluated the initial application of ICGA to patients with severe lower extremity ischemia to develop quantitative, reproducible parameters to assess perfusion. Indocyanine green angiography uses a charge-coupled device camera, a laser, and intravenous contrast to visually assess skin surface perfusion. From January 2011 to April 2012, they performed ICGA within 5 days of 31 re-vascularization procedures in patients with Rutherford class 5 and 6 ischemia. They also compared
ICGA before and after re-vascularization in a subset of 13 patients. These researchers evaluated multiple, quantitative parameters to assess perfusion. A total of 24 patients underwent ICGA associated with 31 re-vascularization procedures (26 endovascular, 4 open, 1 hybrid) for 26 lower limb wounds; 92% were diabetic and 20% were dialysis-dependent. In 50% of these patients, it was not possible to measure ankle-brachial indexes due to medial calcinosis. Paired analysis of ingress (increase in pixel strength [PxS]), ingress rate (slope of increase in PxS), curve integral (area under the curve in PxS over time), end intensity (PxS at end of study), egress (decrease in PxS from maximum), and egress rate (slope of decrease in PxS) increased significantly (p < 0.05) after re-vascularization. The authors concluded that ICGA provides rapid visual and quantitative information about regional foot perfusion. They believed this is the first report describing quantification of foot perfusion before and after lower extremity re-vascularization for severe limb ischemia. Moreover, they stated that further study is needed to help define the utility of this intriguing new technology to assess perfusion, response to re-vascularization, and potentially, to predict likelihood of wound healing.

The Spy Elite System (LifeCell Corp., Branchburg, NJ) is designed to aid surgeons in identifying and attaching viable tissue during breast reconstruction surgery. The Spy Elite System (using near-infrared light technology) enables surgeons performing breast reconstruction to capture images while in the operating room and allow them to objectively evaluate the quality of blood flow in vessels and tissue. In this regard, the Spy Elite System gives the surgeon real-time confirmation that perfusion of blood to the flap is adequate. Inadequate blood flow into or out of the flap could potentially result in partial or total loss of the flap. The blood flow pattern to the breast skin will be monitored by means of ICGA; the dye highlights areas of tissue with a healthy blood supply, while those areas where circulation is less robust remain darker. Seeing these differences enables surgeons to ascertain which tissue is healthiest and also to evaluate circulation following the procedure.

Newman and associates (2010) stated that skin-sparing mastectomy has been associated with flap ischemia and necrosis. Current clinical methods for assessment of flap viability following mastectomy are largely subjective and lack objective data to guide intra-operative decisions. Intra-operative laser-assisted ICGA (LA-ICGA) was performed on 20 skin sparing mastectomy flaps; LA-ICGA data were retrospectively compared with clinical outcome. Pre-operative, intra-operative, and post-operative digital photographs along with clinical course were evaluated in an effort to identify potential complications. Laser-assisted-ICGA was
performed on 20 breasts in 12 patients. Eleven breasts (55%) demonstrated no wound-healing issues. Nine breasts (45%) experienced wound-healing issues, which were stratified as follows: 1 (5%) mild, 1 (5%) moderate, and 7 (35%) severe. Of these 7 severe wound-healing issues, 5 (25%) required debridement and 2 (10%) required complete removal of the prosthetic device. Retrospective analysis demonstrated a 95% correlation between intra-operative imaging and clinical course with 100% sensitivity and 91% specificity. There was a false-positive rate of 9%. This series suggested LA-ICGA is a useful adjunct to determine mastectomy flap viability. The authors stated that further quantitative advances in this technology may provide objective numerical thresholds to guide intra-operative mastectomy flap debridement when indicated.

Liu et al (2011) noted that in flap reconstruction of complex defects the perfusion of the reconstructive flap is critical to the ultimate success of the reconstruction. This is especially true in perforator-based flaps where it can be difficult to assess the adequacy of perfusion in the operating room. However, the ability to definitively determine the degree of flap perfusion is imperative to clinical decision-making. The authors stated that an emerging technology using near-infrared angiography with ICG dye may significantly improve the immediacy and accuracy of the assessment of flap perfusion.

Phillips et al (2012) noted that intra-operative vascular imaging can assist assessment of mastectomy skin flap perfusion to predict areas of necrosis. No head-to-head study has compared modalities such as LA-ICGA and fluorescein dye angiography with clinical assessment. The authors conducted a prospective clinical trial of tissue expander-implant breast reconstruction with intra-operative evaluation of mastectomy skin flaps by clinical assessment, LA-ICGA, and fluorescein dye angiography. Intra-operatively predicted regions of necrosis were photographically documented, and clinical assessment guided excision. Post-operative necrosis was directly compared with each prediction. The primary outcome was all-inclusive skin necrosis. A total of 51 tissue expander-implant breast reconstructions (32 patients) were completed, with 21 cases of all-inclusive necrosis (41.2%). Laser-assisted ICGA and fluorescein dye angiography correctly predicted necrosis in 19 of 21 cases where clinical judgment had failed. Only 6 of 21 cases were full-thickness necrosis, and 5 of 21 required an intervention (9.8%). Risk factors such as smoking, obesity, and breast weight greater than 1,000 g were statistically significant. Laser-assisted ICGA and fluorescein dye angiography over-predicted areas of necrosis by 72% and 88% (p = 0.002). Quantitative analysis for LA-ICGA
in necrotic regions showed absolute perfusion units less than 3.7, with 90 % sensitivity and 100 % specificity. The authors concluded that LA-ICGA is a better predictor of mastectomy skin flap necrosis than fluorescein dye angiography and clinical judgment. They stated that both methods over-predict without quantitative analysis; LA-ICGA is more specific and correlates better with the criterion standard diagnosis of necrosis.

Sood and Glat (2013) evaluated the use of intra-operative laser angiography using the Spy Elite System for the assessment of perfusion in mastectomy flaps for immediate breast reconstruction. The Spy Elite System uses the contrast ICG, which has an excellent safety profile and pharmacokinetics that allow for repeat evaluations during the same surgical procedure. In recent work, the Spy Elite System has demonstrated high sensitivity and specificity for detection of tissues at risk for ischemia and necrosis during reconstructive surgery. Using a retrospective, chart-review design, the authors compared consecutive cases of immediate breast reconstruction using a prosthesis, before and after implementation of the Spy Elite System. A total of 91 subjects were included in the analysis: 52 prior to Spy (Pre-Spy) and 39 after implementation of Spy (Post-Spy). Baseline characteristics were similar between the groups. Both groups had high rates of co-morbidities, chemotherapy, and radiation therapy. The rate of post-operative complications was 2-fold higher in the Pre-Spy group compared to the Post-Spy group (36.5 % versus 17.9 %); this difference was of borderline significance (p = 0.0631). However, mean number of repeat visits to the OR per patient was significantly higher in the Pre-Spy group (1.21 ± 1.47 versus 0.41 ± 0.71; p = 0.0023). Of the 7 patients with complications in the Post-Spy group, 5 were identified by the Spy Elite System as having poor flap perfusion; none was identified by clinical judgment alone. The authors concluded that the findings of this study suggested that the Spy Elite System can contribute to reduced ischemia-related complications in a population of women undergoing immediate breast reconstruction following mastectomy for breast cancer.

Wu and colleagues (2013) stated that LA-ICGA has been promoted to assess perfusion of random skin, pedicled, and free flaps. Few studies address its potential limitations. In this study, a total of 37 patients who underwent reconstructive procedures with LA-ICGA were studied retrospectively to determine the correlation between clinical findings and LA-ICGA. Indocyanine green angiography underestimated perfusion when areas of less than or equal to 25 % uptake were not debrided and remained perfused. Indocyanine green angiography over-estimated
perfusion when areas with greater than 25% uptake developed necrosis. Of 14 random skin flaps, LA-ICGA under-estimated perfusion in 14% and over-estimated in 14%. In 16 patients undergoing perforator flap breast reconstruction, LA-ICGA correlated with computed tomographic angiogram (CTA) in 85%. Indocyanine green angiography under-estimated perfusion in 7% and over-estimated in 7%. In 8/11 patients undergoing fasciocutaneous flaps, LA-ICGA aided in donor site selection. In 3/6 ALT flaps, a better unilateral blush was found that correlated with Doppler. In all 3, a dominant perforator was found. In 11 patients, there was a 9% under-estimation of flap perfusion. In 3 pedicled flaps, there was a 66% under-estimation and 33% over-estimation of perfusion. The authors concluded that ICGA often confirmed the clinical/radiologic findings in abdominal perforator and fasciocutaneous flaps. It tended to under-estimate perfusion in pedicle and skin flaps. When clinical examination was obvious, LA-ICGA rendered clear-cut findings. When clinical examination was equivocal, LA-ICGA tended to provide ambiguous findings, demonstrating that a distinct cut-off point does not exists for every patient or flap. They stated that ICGA is a promising but expensive technology that would benefit from standardization. They noted that further research is needed before LA-ICGA can become a reliable tool for surgeons.

An UpToDate review on “Breast reconstruction in women with breast cancer” (Nahabedian, 2013) does not mention the use of ICGA/Spy Elite System.

Griffiths et al (2016) stated that fluorescent angiography (FA) has been useful for assessing blood flow and assessing tissue perfusion in ophthalmology and other surgical disciplines for decades. In plastic surgery, indocyanine green (ICG) dye-based FA is a relatively novel imaging technology with high potential in various applications. These investigators reviewed the various FA detector systems currently available and critically appraise its utility in breast reconstruction. They performed a review of the published English literature dating from 1950 to 2015 using databases, such as PubMed, Medline, Web of Science, and Embase. In comparison to the old fluorescein dye, ICG has a superior side effect profile and can be accurately detected by various commercial devices, such as SPY Elite (Novadaq, Canada), FLARE (Curadel LLC, USA), PDE-Neo (Hamamatsu Photonics, Japan), Fluobeam 800 (Fluoptics, France), and IC-View (Pulsion Medical Systems AG, Germany). In breast reconstruction, ICG has established as a safer, more accurate tracer agent, in lieu of the traditional blue dyes, for detection of sentinel lymph nodes with radioactive isotopes ((99m)-Technetium). In prosthesis-based breast reconstruction, intraoperative assessment of the mastectomy skin flap to guide
excision of hypo-perfused areas translates to improved clinical outcomes. Similarly, in autologous breast reconstructions, FA can be utilized to detect poorly perfused areas of the free flap, evaluate microvascular anastomosis for patency, and assess SIEA vascular territory for use as an alternative free flap with minimal donor site morbidity. The authors concluded that ICG-based FA is a novel, useful tool for various applications in breast reconstruction. However, they stated that more studies with higher level of evidence are currently lacking to validate this technology.

Robertson et al (2017) noted that ICG contrast agent has shown some encouraging results in the intraoperative assessment of mastectomy flap perfusion and prediction of subsequent flap necrosis. A large case series from Emory University has looked specifically at ICGA in predicting mastectomy skin flap necrosis (MSFN) in a prospective cohort of 118 patients undergoing skin-sparing mastectomy (SSM) and breast reconstruction. In all, 14 patients experienced post-operative skin flap necrosis. Skin with less than or equal to 25 % perfusion was not viable 90 % of the time, while areas with greater than or equal to 45 % perfusion survived 98 % of the time. This may be a useful adjunct to the prediction and avoidance of MSFN.

Intraoperative indocyanine laser perfusion assessment tools, such as the SPY system (LifeCell Corp., Branchburg, NJ), have been used to identify mastectomy skin flaps at risk of subsequent ischemia and necrosis. Indocyanine green was used to evaluate mastectomy flap perfusion in 39 patients undergoing mastectomy and immediate breast reconstruction with a prosthesis, and this was compared to 52 patients in the pre-SPY era. The post-operative complication rate in this retrospective study was reported as 2-fold higher in the pre-SPY group, but this did not reach statistical significance (p = 0.06). However, the number of repeat visits to theater was significantly higher in the pre-SPY era; 5 of the 7 patients with complications in the post-SPY group were identified by SPY as having poor flap perfusion, but none was identified with clinical judgment alone. The main drawbacks of this study were its small size and retrospective non-randomized design, but it still suggested that the SPY system may be able to contribute peri-operatively to the identification of tissue at risk of ischemia and necrosis. Indocyanine green has also been used to describe specific nipple-areolar complex (NAC) perfusion patterns and may be a helpful adjunct in evaluating higher risk perfusion patterns in nipple-sparing mastectomy (NSM) to try and avoid ischemic complications.

Also, an UpToDate review on “Overview of breast reconstruction” (Nahabedian, 2017) does not mention the use of intraoperative fluorescence angiography.
d’Avella et al (2013) stated that maximal safe resection is the goal of correct surgical treatment of parasagittal meningiomas, and it is intimately related to the venous anatomy both near and directly involved by the tumor. Indocyanine green videoangiography has already been advocated as an intra-operative resourceful technique in brain tumor surgery for the identification of vessels. These researchers investigated the role of ICGV in surgery of parasagittal meningiomas occluding the superior sagittal sinus (SSS). In this study, these investigators prospectively analyzed clinical, radiological and intra-operative findings of patients affected by parasagittal meningioma occluding the SSS, who underwent ICGA assisted-surgery. Radiological diagnosis of complete SSS occlusion was pre-operatively established in all cases. Indocyanine green videoangiography was performed before dural opening, before and during tumor resection, at the end of the procedure. A total of 5 patients were included in this study. In all cases, ICGV guided dural opening, tumor resection, and venous management. The venous collateral pathway was easily identified and preserved in all cases. Radical resection was achieved in 4 cases. Surgery was uneventful in all cases. The authors concluded that despite the small number of patients, the findings of this study showed that ICGA could play a crucial role in guiding surgery of parasagittal meningioma occluding the SSS. Moreover, they stated that further studies are needed to define the role of this technique on functional and oncological outcome of these patients.

Della Puppa et al (2014) noted that there are no doubts about the role that ICGA can play in current vascular neurosurgery. Conversely, in brain tumor surgery, and particularly in meningioma surgery, this role is still unclear. Vein management is pivotal for approaching parasagittal meningiomas, because venous preservation is strictly connected to both extent of resection and clinical outcome. These investigators presented the technical traits and the post-operative outcome of the application of ICGA in patients undergoing parasagittal meningioma surgery. They retrospectively collected demographic, radiological, intraoperative, and follow-up data in 43 patients with parasagittal meningiomas who underwent surgery with the assistance of ICGA between October 2010 and July 2013. Intra-operative ICGA findings at different stages (before dural opening, after dural opening, during resection, after resection) were reviewed. Additional data on functional monitoring, temporary venous clipping, and flow measurements were also recorded. The overall post-operative outcome was evaluated by assessing both the extent of resection and the clinical outcome data. The ICGA studies were performed 125 times in 43 patients, providing helpful data for vein management and tumor resection in all
stages of surgery. In 16% of meningiomas completely occluding the superior sagittal sinus, the ICGA data differed from radiological findings and changed the surgical approach. In 20% of cases the intra-operative ICGA findings directly guided the surgical strategy: venous sacrifice was necessary in 7 cases, without post-operative consequences; temporary clipping with neurophysiological monitoring proved to be predictive of safe venous sacrifice. In 7% of cases the ICGA data needed to be supplemented with flow measurements. Simpson Grade I-II and Grade III resections were achieved in 86% and 14% of cases, respectively, with a 4.6% rate of overall morbidity. The authors concluded that this study showed that ICGA can assist the different stages of parasagittal meningiomas surgery, guiding the vein management and tumor resection strategies with a favorable final clinical outcome. However, in the authors' experience the use of other complementary tools was mandatory in selected cases to preserve functional areas. Moreover, they stated that further studies are needed to confirm that the application of ICGA in parasagittal meningioma surgery may improve the morbidity rate, as reported in this study.

Furthermore, UpToDate reviews on “Meningioma: Clinical presentation and diagnosis” (Park, 2015) and “Systemic treatment of recurrent meningioma” (Wen, 2015) do not mention ICG as a management tool.

Management of Diabetic Macular Edema:

Ogura and colleagues (2015) evaluated the usefulness of ICGA to detect leaking spots and the effectiveness of ICGA-guided focal laser photocoagulation in eyes with diabetic macular edema (DME). A total of 10 eyes (8 patients) with diffuse DME diagnosed using fluorescein angiography (FA) and refractory to a sub-Tenon injection of triamcinolone acetonide (STTA), grid laser photocoagulation, or both were enrolled. Fluorescein angiography and ICGA were performed using the Heidelberg Retina Angiograph 2. Hyper-fluorescent spots on early-phase FA and on early- and late-phase ICGA were super-imposed onto the macular thickness map measured by OCT and counted to calculate the spot density in the area with or without ME; ICGA-guided focal laser photocoagulation was carried out. In 7 eyes, STTA was simultaneously performed. The central macular thickness (CMT) and macular volume (MV) were measured by OCT. On early-phase FA, 4.8 ± 2.3 and 2.3 ± 1.5 hyper-fluorescent spots/disk area were observed inside and outside the ME, respectively. In contrast, the spot density was significantly decreased to 1.8 ± 0.9 inside the ME and was only 0.3 ± 0.4 outside the ME on late-phase ICGA (p < 0.01). The mean follow-up period after ICGA-guided photocoagulation was 19.0
months. The mean BCVA improved significantly from 0.77 ± 0.34 logarithm of the minimum angle of resolution at baseline to 0.52 ± 0.37 at the last visit (p < 0.01). Both CMT and MV significantly decreased (p < 0.01). Recurrence of DME was observed in 4 eyes: 3 eyes were treatable only with STTA and 1 required additional ICGA-guided laser photoocoagulation. The authors concluded that ICGA may be useful to detect leaking spots responsible for DME, enabling less invasive focal laser photoocoagulation even in some of the eyes with diffuse DME. The role of ICGA in the management of DME needs to be further investigated.

Mookiah et al (2015) stated that DME is caused by accumulation of extracellular fluid from hyper-permeable capillaries within the macula. Diabetic macular edema is one of the leading causes of blindness among diabetes mellitus (DM) patients. Early detection followed by laser photoocoagulation can save the visual loss. These investigators discussed various imaging modalities including biomicroscopy, FA, OCT and color fundus photographs used for diagnosis of DME. Various automated DME grading systems using retinal fundus images, associated retinal image processing techniques for fovea, exudate detection and segmentation were presented. The authors also compared various imaging modalities and automated screening methods used for DME grading. The reviewed literature indicated that FA and OCT identify DME related changes accurately; FA is an invasive method, which uses fluorescein dye, and OCT is an expensive imaging method compared to fundus photographs. Moreover, using fundus images DME can be identified and automated. The authors stated that DME grading algorithms can be implemented for tele-screening; fundus imaging based DME grading is more suitable and affordable method compared to biomicroscopy, FA, and OCT modalities; ICGA was not mentioned as a management tool.

Furthermore, an UpToDate review on “Diabetic retinopathy: Screening” (McCulloch, 2015) does not mention ICGA as a management tool.

Prediction of Wound Complications in Ventral Hernia Repair:

Colavita et al (2016) noted that complex ventral hernia repair (VHR) is associated with a greater than 30 % wound complication rate. Perfusion mapping using indocyanine green fluorescence angiography (ICG-FA) has been demonstrated to predict skin and soft tissue necrosis in many reconstructive procedures; however, it has yet to be evaluated in VHR. Patients undergoing complex VHR involving component separation and/or extensive subcutaneous advancement flaps were included in a prospective, blinded study. Patients with active infection were
excluded. Indocyanine green-FA was performed prior to incision and prior to closure, but the surgeon was not allowed to view it. An additional blinded surgeon documented wound complications and evaluated post-operative photographs. The operative ICG-FA was reviewed blinded, and investigators were then un-blinded to determine its ability to predict wound complications. A total of 15 consecutive patients were enrolled with mean age of 56.1 years and average body mass index (BMI) of 34.9, of which 60 % were female. Most (73.3 %) had prior hernia repairs (average of 1.8 prior repairs). Mean defect area was 210.4 cm2, mean operative time was 206 mins, 66.6 % of patients underwent concomitant panniculectomy, and 40 % had component separation. Mean follow-up was 7 months. Two patients developed wound breakdown requiring re-operation, while 1 had significant fat necrosis and another a wound infection, requiring operative intervention; ICG-FA was objectively reviewed and predicted all 4 wound complications. Of the 12 patients without complications, 1 had an area of low perfusion on ICG-FA. This study found a sensitivity of 100 % and specificity of 90.9 % for predicting wound complications using ICG-FA. The authors concluded that in complex VHR patients, subcutaneous perfusion mapping with ICG-FA is very sensitive and has the potential to reduce cost and improve patient quality of life by reducing wound complications and re-operation. These preliminary findings need to be validated by well-designed studies.

**Prediction of Post-Operative Thrombosis in the Internal Jugular Vein:**

Yoshimatsu et al (2015) noted that although rare, thrombosis does occur in the internal jugular vein (IJV), which often leads to detrimental results. These researchers evaluated the feasibility of intra-operative ICGA for prediction of IJV thrombosis. From December of 2013 to August of 2014, these investigators performed ICGA intra-operatively on patients who underwent free-flap reconstruction with head and neck cancer. A total of 10 flaps from 8 of these patients were chosen where 1 pedicle artery of a flap was anastomosed to the superior thyroid artery in an end-to-end fashion, and 1 pedicle vein of the flap was anastomosed to the IJV in an end-to-side fashion. For each case, the time it took for the dye to enter the pedicle artery and exit the pedicle vein into the IJV was measured in seconds (ICG time). These data were compared in 2 groups: group 1, which showed signs of congestion post-operatively and group 2, which showed no signs of congestion. Signs of congestions were defined as purple or blue flap color, rapid capillary refill, swollen flap, and brisk bleeding with dark blood after prick with 23-gauge needle. Of the 10 flaps, 1 flap demonstrated signs of congestion post-operatively and was found with a thrombus in the IJV. The ICG time in this case was significantly longer than the
means of ICG time in flaps with no thrombosis (18 ± 0 seconds versus 6.0 ± 1.0). The authors concluded that intra-operative ICGA may predict post-operative IJV thrombosis with accuracy. The findings of this feasibility study need to be validated in well-designed studies.

The Spy Elite System:

Evaluation of Anastomotic Perfusion in Colorectal Surgery:

Protyniak et al (2015) stated that the essentials for any bowel anastomosis are: adequate perfusion, tension free, accurate tissue apposition, and minimal local spillage. Traditionally, perfusion is measured by assessing palpable pulses in the mesentery, active bleeding at cut edges, and lack of tissue discoloration. However, subjective methods lack predictive accuracy for an anastomotic leak. These researchers used intra-operative ICG-FA to objectively assess colon perfusion before a bowel anastomosis. A total of 77 laparoscopic colorectal operations, between June 2013 and June 2014, were retrospectively reviewed. The perfusion to the colon and ileum was clinically assessed, and then measured using the SPY Elite Imaging System. The absolute value provided an objective number on a 0 to 256 gray-scale to represent differences in ICG fluorescence intensity. The lowest absolute value was used in data analysis for each anastomosis (including small bowel) to represent the theoretical least perfused/weakest anastomotic area. The lowest absolute value recorded was 20 in a patient who underwent a laparoscopic right hemi-colectomy for an adenoma, with no post-operative complications; 4 low anterior resection patients had additional segments of descending colon resected. There was 1 mortality in a patient who underwent a laparoscopic right hemi-colectomy. The authors concluded that the findings of this study illustrated an initial experience with the SPY system in colorectal surgery. They stated that the SPY provided an objective, numerical value of bowel perfusion. However, they noted that the evidence is scant as to the significance of these numbers; and large-scale randomized controlled trials (RCTs) are needed to determine specific cut-off values correlated with surgical outcomes, specifically anastomotic leak rates.

Mapping of Sentinel Lymph Node in Cutaneous Melanoma:

Korn et al (2014) noted that sentinel lymph node biopsy is the standard of care for intermediate-depth and high-risk thin melanomas. Recently, ICG and near-infrared imaging have been used to aid in sentinel node biopsy. These researchers determined the feasibility of sentinel lymph node biopsy with ICG SPY Elite
navigation and evaluated the technique compared with the standard modalities. A retrospective review of 90 consecutive cutaneous melanoma patients who underwent sentinel lymph node biopsy was performed. Two cohorts were formed: group A, which had sentinel lymph node biopsy performed with blue dye and radioisotope; and group B, which had sentinel lymph node biopsy performed with radioisotope and ICG SPY Elite navigation. The cohorts were compared to assess for differences in localization rates, sensitivity and specificity of sentinel node identification, and length of surgery. The sentinel lymph node localization rate was 79.4 % using the blue dye method, 98.0 % using the ICG fluorescence method, and 97.8 % using the radioisotope/hand-held gamma probe method. Indocyanine green fluorescence detected more sentinel lymph nodes than the vital dye method alone (p = 0.020). A trend toward a reduction in length of surgery was noted in the SPY Elite cohort. The authors concluded that sentinel lymph node mapping and localization in cutaneous melanoma with the ICG SPY Elite navigation system was technically feasible and may offer several advantages over current modalities, including higher sensitivity and specificity, decreased number of lymph nodes sampled, decreased operative time, and potentially lower false-negative rates. These preliminary findings from a feasibility study need to be validated by well-designed studies.

Evaluation of Anastomotic Perfusion in Colorectal Surgery:

James et al (2015) examined the literature on the use of FA in laparoscopic rectal surgery. A PubMed search was undertaken using terms “fluorescence angiography” and “rectal surgery”. The search was expanded using the related articles function. Studies were included if they used FA specifically for rectal surgery. Outcomes of interest including anastomotic leak rate, change of operative strategy and time taken for FA were recorded. A total of 11 papers detailing the use of FA in rectal surgery were outlined demonstrating that this technique may change operative strategy and lead to a reduction in anastomotic leak rate. These investigators discussed assessment of colorectal blood supply using FA and how this technique holds great potential to detect insufficiently perfused bowel. In so doing, the operator can adjust their operative strategy to mitigate these affects with the aim of reducing the complications of anastomotic leak and stenosis. However, the authors concluded that there is a clear need for RCTs in order to determine this definitively.

Degett et al (2016) noted that anastomotic leakage following gastro-intestinal (GI) surgery remains a frequent and serious complication associated with a high morbidity and mortality. Indocyanine green fluorescence angiography is a newly developed technique to measure perfusion intra-operatively. These researchers
systematically reviewed the literature concerning ICG-FA to assess perfusion during the construction of a primary GI anastomosis in order to predict anastomotic leakage. The following 4 databases PubMed, Scopus, Embase, and Cochrane were independently searched by 2 authors. Studies were included in the review if they assessed anastomotic perfusion intra-operatively with ICG-FA in order to predict anastomotic leakage in humans. Of 790 screened papers, 14 studies were included in this review; 10 studies (n = 916) involved patients with colorectal anastomoses and 4 studies (n = 214) patients with esophageal anastomoses. All the included studies were cohort studies. Intra-operative ICG-FA assessment of colorectal anastomoses was associated with a reduced risk of anastomotic leakage (n = 23/693; 3.3 % (95 % CI: 1.97 to 4.63 %) compared with no ICG-FA assessment (n = 19/223; 8.5 %; 95 % CI: 4.8 to 12.2 %). The anastomotic leakage rate in patients with esophageal anastomoses and intra-operative ICG-FA assessment was 14 % (n = 30/214). None of the studies involving esophageal anastomoses had a control group without ICG-FA assessment. The authors concluded that no RCTs have been published. They stated that ICG-FA appeared to be a promising method to assess perfusion at the site intended for anastomosis. However, there is insufficient evidence to determine that the method can reduce the leak rate.

Boni et al (2016) evaluated the feasibility and the usefulness of intra-operative assessment of vascular anastomotic perfusion in colorectal surgery using ICG-enhanced fluorescence. Between May 2013 and October 2014, all anastomosis and resection margins in colorectal surgery were investigated using FA intra-operatively to evaluate colonic perfusion before and after completion of the anastomosis, both in right and left colectomies. A total of 107 patients undergoing colorectal laparoscopic resections were enrolled: 40 right colectomies, 10 splenic flexure segmental resections, 35 left colectomies, and 22 anterior resections. In 90 % of cases, the indication for surgery was cancer and high ligation of vessels was performed. Based on the fluorescence intensity, the surgical team judged the distal part of the proximal bowel to be anastomosed insufficiently perfused in 4/107 patients (2 anterior, 1 sigmoid, and 1 segmental splenic flexure resections for cancer), and consequently, further proximal "re-resection" up to a "fluorescent" portion was performed. None of these patients had a clinical leak. The overall morbidity rate was 30 %; 1 patient undergoing right colectomy had an anastomotic leakage, apparently unrelated to ischemia; there were no clinical evident anastomotic leakages in colorectal resections including all low anterior resections. The authors concluded that ICG-enhanced FA provided useful intra-operative information about the vascular perfusion during colorectal surgery and may lead to a change in the site
of resection and/or anastomosis, possibly affecting the anastomotic leak rate. Moreover, they stated that larger further randomized prospective trials are needed to validate this new technique.

Intraoperative Flap Evaluation:

Lohman and colleagues (2015) stated that over the last decade, micro-surgeons have used a greater variety of more complex flaps. At the same time, micro-surgeons have also become more interested in technology, such as ICGA, dynamic infrared thermography (DIRT), and photo-spectrometry, for pre-operative planning and post-operative monitoring. These technologies are now migrating into the operating room, and are used to optimize flap design and to identify areas of hypoperfusion or problems with the anastomoses. Although relatively more has been published about ICGA, information is generally lacking about the intra-operative role of these techniques. These researchers performed a systematic analysis of articles discussing intra-operative ICGA, DIRT, and photo-spectrometry to better define the sensitivity, specificity, expected outcomes, and potential complications associated with these techniques. For intra-operative ICGA, the sensitivity was 90.9 % (95 % CI: 77.5 to 100) and the accuracy was 98.6 % (95 % CI: 97.6 to 99.7). The sensitivity of DIRT was 33 % (95 % CI: 11.3 to 64.6), the specificity was 100 % (95 % CI: 84.9 to 100), and the accuracy was 80 % (95 % CI: 71.2 to 89.7). The sensitivity of intra-operative photo-spectrometry was 92 % (95 % CI: 72.4 to 98.6), the specificity was 100 % (95 % CI: 98.8 to 100), and the accuracy was also 100 % (95 % CI: 98.7 to 100). The authors concluded that these technologies for intra-operative perfusion assessment have the potential to provide objective data that may improve decisions about flap design and the quality of microvascular anastomoses. However, they stated that more work is needed to clearly document their value.

Monitoring of Foveo-Macular Vitelliform Dystrophy (Best Disease):

In a review on “Best disease” (also known as vitelliform macular dystrophy), Altaweel (2016) stated that “Fluorescein angiogram reveals blockage of choroidal fluorescence by the vitelliform lesion. The angiogram is otherwise normal at this stage. In the atrophic stage, a transmission defect is noted … If a choroidal neovascular membrane develops, then a corresponding area of hyperfluorescence with leakage will be found in fluorescein or indocyanine green angiography".
Intra-Operative ICGA During Microsurgical Subinguinal Varicocelectomy:

Shibata and colleagues (2015) stated that microsurgical subinguinal varicocelectomy is one of the best treatment modalities for varicoceles. However, the difficulty in identifying testicular arteries that should be spared is a limitation of this technique. In a pilot study, these researchers evaluated the effectiveness of intra-operative ICGA during microsurgical subinguinal varicocelectomy in 3 cases. These investigators performed microsurgical subinguinal varicocelectomy using a surgical microscope for observing infrared fluorescence in patients with infertility or chronic pain associated with varicoceles. After the exposure of the spermatic cord blood vessels, ICG was injected intravenously to identify and isolate the testicular artery. Thereafter, the varicose veins were repeatedly ligated, while preserving a few lymphatic vessels and the spermatic duct. The testicular artery could be clearly identified by ICGA and were able to separate under ICGA. The preserved arteries were confirmed by ICGA at the end of microsurgical operation; all the internal spermatic veins could be safely ligated while sparing the testicular arteries and lymphatic vessels. The authors concluded that microsurgical subinguinal varicocelectomy using intra-operative ICGA facilitated safe and quick surgery by enabling the visualization of the spermatic cord blood vessels. They stated that this was the first report to indicate the usefulness of vessel visualization by ICGA during microsurgical subinguinal varicocelectomy.

Indocyanine Green Angiography for Coronary Artery Bypass Graft Surgery:

Takahashi and associates (2004) stated that off-pump coronary artery bypass grafting (CABG) has been rapidly increased, because of its less invasiveness with low complications. However, graft patency rate highly depends on the operators’ capability due to technical difficulties. The SPY system, based on the fluorescence of ICG, is an innovative device that permits validation of graft patency intra-operatively. Real time images of grafts are obtained with no need for catheterization, X-rays or iodine contrast medium. High-quality images could be obtained in all 290 grafts of 72 off-pump CABG cases (mean of 4.0 grafts per patient). Four anastomoses (1.4 %), including 2 proximal and 2 distal, were revised because of defects detected by SPY images. In 1 case, the SPY system revealed no blood flow in a radial sequential graft, although transit-time flow meter measurements showed a diastolic dominant pattern. SPY images provide critical information to surgeons to detect non-patent grafts, allowing them to be revised while the patient is still on the operating table. The authors concluded that using the SPY system, technical failures could be completely resolved during surgery. They
stated that the use of the SPY system for intra-operative graft validation during off-pump CABG may become the gold standard for surgical management in the near future.

This technology had several drawbacks. First, it did not provide an exact graft flow quantity measurement. Quantitative graft flow measurement software is currently being investigated. Second, the laser light source is of relatively low power to ensure safe clinical use. However, this limited the penetration of the light through tissue to about 1 mm. Thus, clear images could not be obtained when the coronary artery has a deep intra-myocardial location. The pedicled conduits with significant amounts of overlying tissue were also less well visualized. However, these investigators believed that full skeletonization of the arterial conduits is a very useful and important technique for complete arterial revascularization of all the coronary vascular regions.

Desai and colleagues (2006) noted that early CABG failures may be preventable if identified intra-operatively. These researchers compared the diagnostic accuracy of 2 intra-operative graft assessment techniques -- transit-time ultrasound flow measurement and ICG fluorescent-dye graft angiography. Patients undergoing isolated CABG with no contraindications for post-operative angiography were enrolled in the study. Patients were randomly assigned to be evaluated with either ICG angiography (ICGA) and then transit-time ultrasonic flow measurement or transit-time flow then ICGA. Patients underwent X-ray angiography on post-operative day 4. The primary end-point of the trial was to determine the sensitivity and specificity of the 2 techniques versus reference standard X-ray angiography to detect graft occlusion or greater than 50 % stenosis in the graft or peri-anastomotic area. Between February 2004 and March 2005, a total of 106 patients were enrolled and X-ray angiography was performed in 46 patients. In total, 139 grafts were reviewed with all 3 techniques and 12 grafts (8.2 %) were demonstrated to have greater than 50 % stenosis or occlusion by the reference standard. The sensitivity and specificity of ICGA to detect greater than 50 % stenosis or occlusion was 83.3 % and 100 %, respectively. The sensitivity and specificity of transit-time ultrasonic flow measurement to detect greater than 50 % stenosis or occlusion was 25 % and 98.4 %, respectively. The p value for the overall comparison of sensitivity and specificity between ICGA and transit-time flow ultrasonography was 0.011. The difference between sensitivity for ICGA and transit-time flow measurement was 58
% with a 95% confidence interval (CI) of 30% to 86%, p = 0.023. The authors concluded that ICGA provided better diagnostic accuracy for detecting clinically significant graft errors than did transit-time ultrasound flow measurement.

In a “Letter to the Editor” regarding the afore-mentioned study by Desai et al, Kulik and colleagues (2007) stated that “We have identified limitations in their analysis and other logistical challenges that may constitute important barriers to the generalizability of their conclusions”.

In a pilot study, Waseda and associates (2009) evaluated the intra-operative fluorescence imaging (IFI) system in the real-time assessment of graft patency during off-pump CABG. Patients undergoing off-pump CABG received IFI analysis, intra-operative transit time flowmetry, and post-operative X-ray angiography. In off-line IFI analysis, the graft washout was classified based on the number of heart beats required for ICG washout: fast washout (less than or equal to 15 beats) and slow washout (greater than 15 beats). A total of 507 grafts in 137 patients received IFI analysis. Of all the IFI analyses, 379 (75%) grafts were visualized clearly up to the distal anastomosis. With regard to anastomosis location, anterior location was associated with a higher percentage of fully analyzable images (90%). More than 80% of images were analyzable, irrespective of graft type; 6 grafts with acceptable transit time flowmetry results were diagnosed with graft failure by IFI, which required on-site graft revision. All revised grafts’ patency was confirmed by post-operative X-ray angiography. Conversely, 21 grafts with unsatisfactory transit time flowmetry results demonstrated acceptable patency with IFI. Graft revision was considered unnecessary in these grafts, and 20 grafts (95%) were patent by post-operative X-ray angiography. Compared with slow washout, fast washout was associated with a higher pre-operative ejection fraction, use of internal mammary artery grafts, and anterior anastomosis location. The authors concluded that the IFI system enabled on-site assessment of graft patency, providing both morphologic and functional information. They stated that this technique may help reduce procedure-related, early graft failures in off-pump bypass patients.

This study had several drawbacks. First, this was a pilot study from a single-center experience, which potentially limited the generalizability of findings. Second, this was not a randomized study and the decision to revise the grafts was based on IFI results. Thus, these researchers were unable to calculate sensitivity and specificity of the IFI system. Third, the results of the IFI system were only semi-quantitatively
analyzed due to lack of brightness standardization. Fourth, in this case-series, grafts were fully skeletonized for better visualization by the IFI system. Incomplete skeletonization or pedicled conduits may interfere with image acquisition.

In an editorial that accompanied the afore-mentioned study by Waseda et al, Ward and colleagues (2009) stated that “Intraoperative fluorescence imaging uses the fluorescence properties of indocyanine green dye to image the newly constructed grafts and the native coronary circulation. Indocyanine green may be administered via a central venous line or directly into the bypass graft (better image quality). The maximum penetration of the laser beam is 1 to 2 mm of soft tissue. Intraoperative fluorescence imaging has 3 important drawbacks: First, it requires direct illumination of the graft (potentially difficult on the back of the heart); second, the entire graft cannot be imaged in the same sequence by a single central venous injection; and third, it requires at least partial “skeletonization” of pedicled grafts and native coronary arteries to adequately visualize the distal anastomosis. Because of these drawbacks, Waseda et al found that only 75 % of grafts were completely visualized. Nine grafts that had been deemed to have acceptable flow by IFI were later found to be occluded by X-ray angiography (3.1 % false negative rate). Although IFI appears to have an advantage over TTFM in sensitivity, it is also more cumbersome, time-consuming, and expensive … Waseda et al focus on the use of IFI technology in the specific circumstance of OP-CABG surgery. They state, “the clinical benefits of OP-CABG are partly offset by a mildly higher rate of early graft occlusion”. In fact, several prospective randomized controlled trials and a meta-analysis suggest that grafts performed during OP-CABG have a significantly lower patency rate and have less complete revascularization than grafts constructed ON-CABG. These results reflect the technical demands of OP-CABG procedures and may account for the surprising 27 % utilization of the intra-aortic balloon pump in the report by Waseda et al. One group even suggested the need for informed consent if OP-CABG techniques are to be used. Conversely, a recent publication asserts, “numerous retrospective as well as randomized prospective studies have demonstrated that OP-CABG is associated with decreased risk-adjusted morbidity and mortality compared with ON-CABG”. The disparate results described here may be explained by surgical technical ability and dedication to OP-CABG techniques. However, the results quoted are not necessarily mutually exclusive. To resolve the issue, we need long-term follow-up of graft patency and outcomes". 
The Canadian Agency for Drugs and Technologies in Health’s guidelines on “Intraoperative assessment of coronary artery bypass grafts” (CADTH, 2011) noted that no evidence-based guidelines were identified regarding the intra-operative assessment of the integrity and patency of coronary artery bypass grafts.

The American College of Cardiology Foundation/American Heart Association guideline on “Coronary artery bypass graft surgery” (Hills et al, 2011) stated that “Over the past 20 years, the patency rate of all graft types has improved gradually, so that the present failure rate of LIMA grafts at 1 year is about 8 % and of SVGs roughly 20 %. Many patients being referred for CABG nowadays have far advanced CAD, which is often diffuse and exhibits poor vessel runoff. Technical issues at the time of surgery may influence graft patency, and intraoperative imaging may help to delineate technical from nontechnical issues. Because coronary angiography is rarely available intraoperatively, other techniques have been developed to assess graft integrity at this time, most often the transit-time flow and intraoperative fluorescence imaging. The transit-time flow is a quantitative volume-flow technique that cannot define the severity of graft stenosis or discriminate between the influence of the graft conduit and the coronary arteriolar bed on the mean graft flow. Intraoperative fluorescence imaging, which is based on the fluorescent properties of indocyanine green, provides a “semiquantitative” assessment of graft patency with images that provide some details about the quality of coronary anastomoses. Although both methods are valuable in assessing graft patency, neither is sufficiently sensitive or specific to allow identification of more subtle abnormalities. It is hoped that such imaging may help to reduce the occurrence of technical errors”.

Indocyanine Green Fluorescence Imaging in Colorectal Surgery:

Ris and colleagues (2014) noted that anastomotic leakage is a devastating complication of colorectal surgery. However, there is no technology indicative of in-situ perfusion of a laparoscopic colorectal anastomosis. These researchers detailed the use of near-infrared (NIR) laparoscopy (PinPoint System, NOVADAQ, Canada) in association with fluorophore [ICG, 2.5 mg/ml] injection in 30 consecutive patients who underwent elective minimally invasive colorectal resection using the simultaneous appearance of the cecum or distal ileum as positive control. The median (range) age of the patients was 64 (40 to 81) years with a median (range) BMI of 26.7 (20 to 35.5) kg/m(2); 24 patients had left-sided resections (including 6 low anterior resections) and 6 had right-sided resections. Of the total, 25 operations were cancer resections and 5 were for benign disease [either diverticular strictures (n = 3) or Crohn’s disease (n = 2)]. A high-quality intra-operative ICG angiogram
was achieved in 29/30 patients. After ICG injection, median (range) time to perfusion fluorescence was 35 (15 to 45) s. Median (range) added time for the technique was 5 (3 to 9) mins. Anastomotic perfusion was documented as satisfactory in every successful case and encouraged avoidance of defunctioning stomas in 3 patients with low anastomoses. There were no post-operative anastomotic leaks. The authors concluded that perfusion angiography of colorectal anastomosis at the time of their laparoscopic construction was feasible and readily achievable with minimal added intra-operative time. They stated that further work is needed to determine optimum sensitivity and threshold levels for assessment of perfusion sufficiency, in particular with regard to anastomotic viability.

In a prospective, multi-center, open-label, singl-arm, clinical trial, Jafari and associates (2015) examined the feasibility and utility of fluorescence angiography (FA) for intra-operative perfusion assessment during left-sided colectomy and anterior resection at 11 centers in the United States. A total of 147 patients were enrolled, of whom 139 were eligible for analysis. Diverticulitis (44 %), rectal cancer (25 %), and colon cancer (21 %) were the most prevalent indications for surgery. The mean level of anastomosis was 10 ± 4 cm from the anal verge. Splenic-flexure mobilization was performed in 81 % and high ligation of the inferior mesenteric artery in 61.9 % of patients. There was a 99 % success rate for FA, and FA changed surgical plans in 11 (8 %) patients, with the majority of changes occurring at the time of transection of the proximal margin (7 %). Overall morbidity rates were 17 %. The anastomotic leak rate was 1.4 % (n = 2). There were no anastomotic leaks in the 11 patients who had a change in surgical plan based on intra-operative perfusion assessment with FA. The authors concluded that PinPoint was a safe and feasible tool for intra-operative assessment of tissue perfusion during colorectal resection. There were no anastomotic leaks in patients in whom the anastomosis was revised based on inadequate perfusion with FA. They stated that a randomized controlled clinical trial is planned to further evaluate the true clinical significance of this new technology compared with the more standard assessment of the proximal transection line.

This study had several drawbacks. As a prospective single-arm study of moderate size, inherent biases exist; this study did not include an internal comparison group. There was no standardization with regard to technique of operation and anastomosis or pre-operative or post-operative care. Although total operative time was recorded, the total imaging time was not recorded. Importantly, there was no standardization of the “standard of care” assessment of proximal bowel viability.
based on normal visual assessment or assessment of bleeding at the transection line. Participants were a heterogeneous group undergoing low pelvic and relatively high-risk anastomoses. This heterogeneous population and the sample size did not allow the authors to draw any specific conclusions regarding the consequence that patient characteristics may have on interpretation of data.

In a case-matched, retrospective study, Kin and co-workers (2015) examined if intra-operative angiography decreases colorectal anastomotic leaks. The investigators found no significant difference in incidence of anastomotic leak in subjects managed with intra-operative fluorescence angiography compared to those managed without. Patients who underwent colectomy or proctectomy with primary anastomoses were included; they were matched 1:1 with respect to sex, age, level of anastomosis, presence of a diverting loop ileostomy, and pre-operative pelvic radiation therapy. The intra-operative use of FA to assess perfusion of the colon for anastomosis was studied. Anastomotic leak within 60 days and whether FA changed surgical management were the main outcomes measured. Case matching produced 173 pairs. The groups were also comparable with respect to BMI, smoking status, diabetes mellitus, surgical indications, and type of resection. In patients who had intra-operative FA, 7.5 % developed anastomotic leak, whereas 6.4 % of those without FA did (p value not significant). Univariate analysis revealed that pre-operative pelvic radiation, more distal anastomosis, surgeon, and diverting loop ileostomy were positively associated with anastomotic leak. Multivariate analysis demonstrated that level of anastomosis and surgeon were associated with leaks. Poor perfusion of the proximal colon seen on FA led to additional colon resection before anastomosis in 5 % of patients who underwent intra-operative FA. The authors concluded that the use of intra-operative FA to assess the perfusion of the colon conduit for anastomosis was not associated with colorectal anastomotic leak. Perfusion was but one of multiple factors contributing to anastomotic leaks. They stated that additional studies are needed to determine whether this technology is beneficial for colorectal surgery. The main drawbacks of this study were its retrospective design with the use of historical control subjects, selection bias, and small sample size.

Keller and colleagues (2017) stated that ICG fluorescence imaging is a surgical tool with increasing applications in colorectal surgery. This tool has received acceptance in various surgical disciplines as a potential method to enhance surgical field visualization, improve lymph node retrieval, and decrease the incidence of anastomotic leaks. In colorectal surgery specifically, small studies have shown that
intra-operative fluorescence imaging is a safe and feasible method to assess anastomotic perfusion, and its use might affect the incidence of anastomotic leaks. Controlled trials are ongoing to validate these conclusions. The number of new indications for ICG continues to increase, including innovative options for detecting and guiding management of colorectal metastasis to the liver. These advances could offer great value for surgeons and patients, by improving the accuracy and outcomes of oncological resections.

In a systematic review on “ICG fluorescence-guided surgery in metastatic colorectal cancer”, Liberale and associates (2017) concluded that ICG fluorescence-guided imaging is a promising technique in the detection of small infra-clinic lymph node, hepatic, and peritoneal metastatic deposits that may allow better staging and more complete surgical resection with a potential prognostic benefit for patients.

van den Bos and co-workers (2018) determined the feasibility of near-infrared fluorescence (NIRF) angiography in anastomotic colorectal surgery and determined the effectiveness of the technique in improving imaging and quantification of vascularization, thereby aiding in decision-making as to where to establish the anastomosis. A total of 10 studies were included; 8 of these studies made a statement about the ease of use. In none of the studies complications due to the use of the technique occurred. The technique changed the resection margin in 10.8% of all NIRF cases. The anastomotic leak rate was 3.5% in the NIRF group and 7.4% in the group with conventional imaging; 2 of the included studies used an objective quantification of the fluorescence signal and perfusion, using ROIs (Hamamatsu Photonics) and IC-Calc, respectively. The authors concluded that although the feasibility of the technique appeared to be agreed on by all current research, large clinical trials are needed to further evaluate the added value of the technique.

Indocyanine Green Fluorescence Angiography for Intraoperative Evaluation of Residual Parathyroid Glands Function and Prediction of Post-Operative Hypocalcemia Risk after Total Thyroidectomy:

Lavazza and co-workers (2016) stated that identification of the parathyroid glands during thyroid surgery may prevent their inadvertent surgical removal and thus provide a better post-operative quality of life (QOL). Nevertheless, the most common "technique" for intra-operative evaluation of perfusion of parathyroid gland tissues during thyroid surgery is visual inspection of the physical condition of tissues, e.g., their color and bleeding edges. Another technique is measurement of intact
parathyroid hormone (PTH). Recently, ICG-enhanced fluorescence has been used in various surgical techniques, particularly laparoscopic surgery, to improve visualization and to provide detailed anatomical information. Fluorescent optical guidance helps surgeons to avoid inadvertent tissue injury while enhancing procedural efficiency. The authors concluded that this technique has potential use for evaluating perfusion of the parathyroid gland in real-time intra-operative angiography. Moreover, they stated that further large randomized prospective trials are needed to validate this new technique. Primary end-points of future studies should include evaluation of the effectiveness of ICG-enhanced fluorescence for estimating parathyroid gland perfusion before wound closure and for identifying changes in the previously identified gland at the end of surgery. Secondary end-points of future studies should include identification of potential technique-related failures or complications such as inability to record fluorescence, allergic or other adverse reaction to ICG injection, overall cost of the technique, and the incidence of postoperative hypocalcemia (PH).

Lang and associates (2017) stated that because the fluorescent light intensity on an indocyanine green fluorescence angiography (ICGFA) reflects the blood perfusion within a focused area, the fluorescent light intensity in the remaining in-situ parathyroid glands may predict post-operative hypocalcemia risk after total thyroidectomy. A total of 70 patients underwent intra-operative ICGFA after total thyroidectomy. Any parathyroid glands with a vascular pedicle was left in-situ while any parathyroid glands without pedicle or inadvertently removed was auto-transplanted. After total thyroidectomy, an intravenous 2.5 mg ICGFA was given and real-time fluorescent images of the thyroid bed were recorded using the SPY imaging system. The fluorescent light intensity of each ICGFA as well as the average and greatest fluorescent light intensity in each patient were calculated. Post-operative hypocalcemia was defined as adjusted calcium of less than 2.00 mmol/L within 24 hours. The fluorescent light intensity between discolored and normal-looking ICG fluorescence angiographies was similar (p = 0.479). No patients with a greatest fluorescent light intensity greater than 150 % developed PH while 9 (81.8 %) patients with a greatest fluorescent light intensity less than or equal to 150 % did. Similarly, no patients with an average fluorescent light intensity greater than 109 % developed PH while 9 (30 %) with an average fluorescent light intensity less than or equal to 109 % did. The greatest fluorescent light intensity was more predictive than day-0 PH (p =0.027) and % PTH drop day-0 to 1 (p < 0.001). The authors concluded that ICGFA is a promising operative adjunct in determining residual parathyroid glands function and predicting PH risk after total thyroidectomy.
Jitpratoom and Anuwong (2017) noted that ICG-enhanced fluorescence imaging is recent innovation as the "real-time intraoperative imaging" technique. Many clinical studies have been reported in the literature that use different devices and techniques that employ various doses and usages of ICG as a non-specific contrast agent. Several groups have performed studies in endocrine surgery, especially with regards to parathyroid-related outcomes after thyroid and parathyroid surgery. However, there is no consensus on the technical details that should be applied. These investigators reviewed the current literature on potential use of intra-operative ICGA for evaluating parathyroid gland preservation. The authors concluded that this study reviewed the current status of ICG-enhanced fluorescence imaging and parathyroid preservation in both thyroid and parathyroid surgery. They stated that although there still are questions regarding its utility, current data suggested that a correlation does exist with regards to the relationship between parathyroid perfusion and post-operative parathyroid function. They stated that additional studies are needed for the further validation of ICGA as an intra-operative tool in assessing real-time parathyroid preservation.

DeLong and colleagues (2018) evaluated the ease and utility of using ICGFA for intraoperative localization of the parathyroid glands; ICGFA was performed during 60 parathyroidectomies for primary hyperparathyroidism during a 22-month period. Indocyanine green was administered intravenously to guide operative navigation using a commercially available fluorescence imaging system. Video files were graded by 3 independent surgeons for strength of enhancement using an adapted numeric scoring system. There were 46 (77 %) female patients and 14 (23 %) male patients whose ages ranged from 17 to 87 (average of 60) years old. Of the 60 patients, 43 (71.6 %) showed strong enhancement, 13 (21.7 %) demonstrated mild-to-moderate vascular enhancement, and 4 (6.7 %) exhibited little or no vascular enhancement. Of the 54 patients who had a pre-operative sestamibi scan, a parathyroid adenoma was identified in 36, while 18 failed to localize. Of the 18 patients who failed to localize, all 18 patients (100 %) had an adenoma that fluoresced on ICG imaging. The operations were performed safely with minimal blood loss and short operative times. The authors concluded that ICG has the potential to assist surgeons in identifying parathyroid glands rapidly with minimal risk.

Indocyanine Green fluorescence Tissue Angiography for Evaluation of the Anastomotic Leak/Perfusion During or after Esophagectomy:

http://qawww.aetna.com/cpb/medical/data/100_199/0111_draft.html 08/26/2018
Karampinis and colleagues (2017) stated that optimal perfusion of the gastric conduit during esophagectomy is critical for the anastomotic healing since poor perfusion has been associated with increased morbidity due to anastomotic leaks. Until recently surgical experience was the main tool to assess the perfusion of the anastomosis. In a retrospective, case-control study, these researchers hypothesized that anastomoses located in the zone of optimal ICG perfusion of the gastric conduit ("optizone") have a reduced anastomotic leakage rate after esophagectomy. Indocyanine green fluorescence tissue angiography was used to evaluate the anastomotic perfusion in 35 patients undergoing esophagectomy with gastric conduit reconstruction. The transition point of the "optizone" to the mal-perfused area of the conduit was defined macroscopically and with the use of ICGA during the operation. The anastomosis was performed in the optizone whenever possible. The results of the ICG patients were retrospectively reviewed and compared with 55 patients previously operated without ICGA. The visual assessment of the conduit perfusion concurred with the ICGA in 27 cases. In 8 cases (22.8 %) the ICGA deviated from the visual aspect; 1 case of anastomotic leakage was observed in the group of patients in which the anastomosis could be performed in the optizone (1/33; 3 %) compared with 10 cases in the control group (18 %; p = 0.04). In 2 cases these investigators had to perform the anastomosis in an area of compromised ICG perfusion. Both patients developed an anastomotic leakage. The authors concluded that ICG tissue angiography represented a feasible and reliable technical support in the evaluation of the anastomotic perfusion after esophagectomy. In this retrospective analysis these researchers observed a significant decrease in anastomotic leakage rate when the anastomosis could be placed in the zone of good perfusion defined by ICG fluorescence. Moreover, they stated that a prospective trial is needed in order to provide higher level evidence for the use of ICG fluorescence in reducing leakage rates after esophagectomy.

Schlottmann and Patti (2017) noted that anastomotic leakage is a determining factor of morbidity and mortality after an esophagectomy. An adequate blood supply of the gastric conduit is vital to prevent this complication. These investigators determined the feasibility and usefulness of ICG fluorescence imaging to evaluate the gastric conduit perfusion during an esophagectomy. Patients with distal esophageal cancer or esophago-gastric junction cancer scheduled for esophagectomy were enrolled in this study. After pulling up the gastric conduit into the chest and before performing the anastomosis, 5 mg of ICG was injected as a bolus. Visual assessment of the blood supply of the gastric conduit was compared with the ICG fluorescence imaging pattern of perfusion. A total of 5 patients were included in this study. Hybrid Ivor-
Lewis esophagectomy (laparoscopic abdomen and right thoracotomy) was performed in all cases. In all patients, visual assessment of the perfusion of the stomach determined that the conduit was well perfused. In 2 patients (40%), ICG fluorescence showed an inadequate blood supply of the conduit's tip. Resection of the de-vitalized portion of the conduit was performed in these 2 patients. No anastomotic leaks were recorded, and all patients had an uneventful post-operative course. The authors concluded that visual assessment of the gastric conduit may under-estimate perfusion and inadequate blood supply; ICG fluorescence imaging is a promising tool to determine the gastric conduit perfusion during an esophagectomy. They stated that prospective studies with larger series are needed to confirm the usefulness of ICG fluorescence imaging during esophagectomy.

**Sentinel Lymph Node Mapping for Cervical and Endometrial Cancer:**

Buda and co-workers (2016) compared the detection rate (DR) and bilateral optimal mapping (OM) of sentinel lymph nodes (SLNs) in women with endometrial and cervical cancer using ICG versus the standard technetium-99m radio-colloid ((99m)Tc) radiotracer plus methylene or isosulfan blue, or blue dye alone. From October 2010 to May 2015, a total of 163 women with stage I endometrial or cervical cancer (118 endometrial and 45 cervical cancer) underwent SLN mapping with (99m)Tc with blue dye, blue dye alone, or ICG; DR and bilateral OM of ICG were compared respectively with the results obtained using the standard (99m)Tc radiotracer with blue dye, or blue dye alone. SLN mapping with (99m)Tc radiotracer with blue dye was performed on 77 of 163 women, 38 with blue dye only and 48 with ICG. The overall DR of SLN mapping was 97, 89, and 100 % for (99m)Tc with blue dye, blue dye alone, and ICG, respectively. The bilateral OM rate for ICG was 85 %—significantly higher than the 58 % obtained with (99m)Tc with blue dye (p = 0.003) and the 54 % for blue dye (p = 0.001); 31 women (19 %) had positive SLNs. Sensitivity and negative predictive value (NPV) of SLN were 100 % for all techniques. The authors concluded that SLNs mapping using ICG demonstrated higher DR compared to other modalities. In addition, ICG was significantly superior to (99m)Tc with blue dye in terms of bilateral OM in women with early stage endometrial and cervical cancer. The higher number of bilateral OM may consequently reduce the overall number of complete lymphadenectomies, reducing the duration and additional costs of surgical treatment.

Ruscito and colleagues (2016) noted that historically, blue dyes, (99)Tc or a
combination of the 2 tracers have been used for SLN mapping in cervical and endometrial cancer patients; ICG has been recently introduced in this setting. These investigators evaluated the differences in overall and bilateral detection rates as well as in false-negative rates (FNRs) among the different tracers. The electronic databases PubMed, Medline, and Scopus were searched in January 2016 by searching the terms "sentinel lymph node" and "dye" and "indocyanine green", and "cervical cancer" or "endometrial cancer". Series comparing different tracers injected intracervically and reporting the DR and/or SLN FNR were selected. A total of 45 studies were retrieved; 6 studies including 538 patients met selection criteria. Compared with blue dyes, ICG SLN mapping had higher overall (OR 0.27; 95 % CI: 0.15 to 0.50; p < 0.0001) and bilateral DRs (OR 0.27; 95 % CI: 0.19 to 0.40; p < 0.00001). No differences were found between ICG and (99)TC, although these results were based on data of a single series. No differences in overall and bilateral DRs were found between ICG and the combination of blue dyes and (99)TC. The pooled analysis of FNRs data showed no difference in FNRs between tracers. The authors concluded that in cervical and endometrial cancer, ICG SLN mapping appeared to be equivalent to the combination of blue dyes and (99)TC in terms of overall and bilateral DRs. Its safety profile and ease of use may favor its employment respect to conventional tracers.

Soliman and associates (2017) discussed their prospective validation study of SLN mapping for high-risk endometrial cancer. These researchers stated that SLN mapping continues to evolve in the surgical staging of endometrial cancer. These investigators identified the sensitivity, FNR and FN predictive value (FNPV) of SLN compared to complete pelvic and para-aortic lymphadenectomy (LAD) in women with high-risk endometrial cancer. Women with high-risk endometrial cancer (grade 3, serous, clear cell, carcinosarcoma) were enrolled in this prospective surgical trial. All patients underwent pre-operative PET/CT and intra-operative SLN biopsy followed by LAD. Patients with peritoneal disease on imaging or at the time of surgery were excluded. Patients were evaluable if SLN was attempted and complete LAD was performed. A total of 123 patients were enrolled between April 2013 and May 2016; 101 were evaluable. At least 1 SLN was identified in 89 % (90); bilateral detection 58 %, unilateral pelvic 40 %, para-aortic only 2 %; ICG was used in 61 %, blue dye in 28 %, and blue dye and technetium in 11 %; 23 patients (23 %) had greater than or equal to 1 positive node. In 20/23, greater than or equal to 1 SLN was identified and in 19/20 the SLN was positive. Only 1 patient had bilateral negative SLN and positive non-SLNs on final pathology. Overall, sensitivity of SLN was 95 % (19/20), FNR was 5 % (1/20) and FNPV was 1.4 % (1/71). If side-
specific LAD was performed when a SLN was not detected, the FNR decreased to 4.3% (1/23). The authors concluded that their trial demonstrated that SLN biopsy plus side-specific LAD, when SLN was not detected, was a reasonable alternative to a complete LAD in high-risk EC.

In a multi-center, retrospective, observational study, Di Martino and colleagues (2017) compared SLN mapping in women with cervical cancer stage greater than IB1 (tumor size greater than 2 cm) using ICG versus the standard technique using radioisotope Tc99m radiotracer with or without blue dye. A total of 95 women with stage IB1 cervical cancer who underwent SLN mapping with Tc99m with or without blue dye or ICG and radical hysterectomy were included in this trial. The DR and bilateral mapping rate were compared between ICG and standard Tc99m radiotracer with or without blue dye. Lymphadenectomy was performed, and the FNR was assessed; 47 patients underwent SLN mapping with Tc99m with or without blue dye, and 48 did so with ICG. All patients underwent radical hysterectomy with or without bilateral salpingo-oophorectomy between 2008 and 2016. The overall DR of SLN mapping was 91.5% for Tc99m with or without blue dye and 100% for ICG. A 91.7% rate of bilateral migration was achieved for ICG, significantly higher than the 66% obtained with Tc99m with or without blue dye (p = 0.025); 9 of the 23 SLN-positive patients (39.1%) were diagnosed exclusively as a result of the ultra-staging used to identify micro-metastases or isolated tumor cells only. The authors concluded that in advanced cervical cancer (stage IB1 greater than 2 cm), the DR and bilateral migration rate on real-time fluorescent SLN mapping were higher with ICG than with Tc99m radiotracer with or without blue dye.

Papadia and associates (2017) noted that SLN mapping in endometrial cancer is rapidly gaining acceptance in the clinical community. As compared to a full lymphadenectomy in every patient, to a selective lymphadenectomy after frozen section of uterus in selected patients with intra-uterine risk factors or to a strategy in which a lymphadenectomy is always omitted, SLN mapping appeared to be a reasonable and oncologically safe middle ground. Various protocols can be used when applying an SLN mapping. These investigators reviewed the characteristics, toxicity and clinical impact of (Tc-99m, of the blue dyes (methylene blue, isosulfan blue and patent blue) and of ICG. These researchers stated that ICG has an excellent toxicity profile, has higher overall and bilateral DRs as compared to blue dyes and higher bilateral DRs as compared to a combination of Tc-99m and blue dye. The detrimental effect of BMI on the detection rates was attenuated when ICG was used as a tracer. The authors concluded that the ease of use of the ICG SLN
mapping was perceived by the patients as a better quality of care delivered. The authors stated that whenever possible, ICG should be favored over the other tracers for SLN mapping in patients with endometrial cancer.

How and co-workers (2018) performed a systematic review of the literature to determine pooled estimates for SLN DR and diagnostic accuracy, while exploring impact of the SLN on adjuvant therapy and oncologic outcomes. These researchers performed a systematic search utilizing Medline, Embase, and Web of Science electronic databases for all studies published in the English language until October 31, 2017. Studies were included for review and potential aggregate analyses if they contained at least 30 endometrial cancer patients with undergoing SLN mapping and reported on detection rates (overall, bilateral or para-aortic) or diagnostic accuracy (sensitivity and NPV). Pooled estimates were calculated via meta-analyses utilizing a random-effects model. Studies reporting on the impact of SLN on adjuvant therapy, as well as studies comparing SLN mapping to completion lymphadenectomy were qualitatively reviewed and analyzed as well. These investigators identified 48 eligible studies, which included 5,348 patients for review and inclusion in the meta-analysis for SLN detection or diagnostic accuracy. The pooled SLN DRs were 87 % (95 % CI: 84 to 89 %, 44 studies) for overall detection, 61 % (95 % CI: 56 to 66 %, 36 studies) for bilateral detection, and 6 % (95 % CI: 3 to 9 %, 31 studies) for para-aortic detection. The use of ICG improved overall (94 %, 95 % CI: 92 to 96 %, 19 studies) SLN DRs compared to blue tracer (86 %, 95 % CI: 83 to 89 %, 31 studies) or technetium-99 (86 %, 95 % CI: 83 to 89 %, 25 studies). This trend was similarly observed in terms of bilateral DRs (74 % versus 59 % versus 57 %, respectively). There was no difference in para-aortic SLN detection rate between each tracer. The pooled estimates for diagnostic accuracy for 34 studies were 94 % (95 % CI: 91 to 96 %) for sensitivity and 100 % (95 % CI: 99 to 100 %) for NPV. Diagnostic accuracy of SLN mapping was not negatively affected in patients with high-grade endometrial histology. Patients with SLN mapping were more likely to receive adjuvant therapy and did not have inferior survival or recurrence outcomes compared to those undergoing completion lymphadenectomy. The authors concluded that SLN mapping is a feasible and accurate alternative to stage patients with endometrial cancer. Utilizing ICG resulted in the highest SLN DRs.

Furthermore, National Comprehensive Cancer Network (NCCN)’s clinical practice guideline on “Uterine neoplasms” (Version 2.2018) states that “Indocyanine green (ICG) recently emerged as a useful imaging dye that requires near-infrared camera
for localization, provides a very high SLN detection rate, and is commonly used in many practices at the present time … Recent findings also suggest that ICG may be preferable to blue dyes. Attention to detail and experience are critical to ensure optimal outcomes”.

**Sentinel Lymph Node Mapping for Breast Cancer / Melanoma:**

Niebling and co-workers (2016) systematically reviewed different SLN biopsy (SLNB) techniques and performed a meta-analysis for corresponding identification and FNRs. A systematic review of the literature on SLNB in patients with early stage breast carcinoma and melanoma was performed. Only original study groups were included. The SLN identification rate and FNR were pooled for patients with breast carcinoma or melanoma according to radio-colloid tracer, blue dye, ICG, or a combination of a radio-colloid tracer with blue dye or ICG. Between 1992 and 2012, a total of 154 studies (88 breast carcinoma and 66 melanoma) were reported that met the eligibility criteria. These studies included a total of 44,172 patients. The pooled SLN identification rate in breast carcinoma and melanoma patients using solely blue dye was 85 % (range of 65 to 100 %) and 84 % (range of 59 to 100 %), while for radio-colloid alone it was 94 % (range of 67 to 100 %) and 99 % (range of 83 to 100 %), respectively. Using a combination of radio-colloid and blue, identification rates were 95 % (range of 94 to 95 %) and 98 % (range of 98 to 98 %). The authors concluded that the current meta-analysis provided data that favored the use of radio-colloid or radio-colloid combined with a blue dye for SLN identification. Performing SLNB with radio-colloid alone was the technique of choice for experienced surgeons, since blue dye has multiple disadvantages. Moreover, they stated that SLNB using ICG as a fluorescent dye appeared a promising technique for the near future.

Sugie and colleagues (2017) noted that SLN biopsy using ICG fluorescence is safe and has a high DR for SLNs. However, the results of this novel technique are heterogeneous. In a meta-analysis, these researchers evaluated the diagnostic performance of the ICG fluorescence method compared with the standard radioisotope (RI) method in early-stage breast cancer. All eligible studies were identified from 2005 through 2015. A proportion meta-analysis was performed using a fixed effects and/or random effects model based on the study heterogeneity. A total of 12 studies met the inclusion criteria and included 1,736 women. There was no significant difference between ICG fluorescence and RI for SLN detection using either the fixed effects model (OR 1.29, 95 % CI: 0.87 to 1.90) or the random effects
model (OR 1.32, 95 % CI: 0.54 to 3.18). There were 7 studies reporting the DR for tumor-positive SLN. The ICG fluorescence method was significantly better than the RI method in the fixed effects model (OR 1.87, 95 % CI: 1.00 to 3.49) for staging axilla. However, there was no difference in the random effects model (OR 1.90, 95 % CI: 0.74 to 4.86). There was study outcome heterogeneity for the detection of SLN but not for tumor-positive SLN. There was no publication bias observed in the studies included. The authors concluded that the ICG fluorescence method has valid diagnostic performance for SLN detection and showed a trend toward better axilla staging compared with the RI method; ICG fluorescence is a useful alternative to RI for SLN biopsy.

Guo and associates (2017) stated that recent studies showed that near-infrared (NIR) fluorescence imaging using ICG has the potential to improve the performance of SLN mapping. The current cohort study was designed to examine the value of the combination of ICG and methylene blue (MB) dye in breast cancer patients undergoing SLN biopsy. Between 2010 and 2013, a total of 198 consecutive early breast cancer patients eligible for SLN biopsy were enrolled and 200 biopsy procedures were performed by injection of both ICG and MB. SLNs were searched and removed under the guidance of fluorescence and/or blue dye. The mapping characteristics, the DR of SLNs and positive SLNs, and the number of SLNs of ICG, MB, and ICG + MB were compared. Injection safety of ICG and MB was evaluated. Fluorescence imaging of lymphatic flow, which was helpful to locate the incision site, could be seen in 184 of 200 procedures. The nodal detection rate of ICG, MB, and ICG + MB samples was 97, 89, and 99.5 % (χ² = 26.2, p < 0.001), respectively, with the combination method yielding a superior identification result. The addition of ICG to the MB method resulted in the identification of more lymph nodes (median 3 versus 2) and more positive axillas (22.7 % involved axillas were discovered by fluorescence only) than either method alone. No acute or chronic allergic reaction was observed in this study. However, 23 patients (23/82) who received breast-conserving therapy reported temporary skin staining, and 5 patients had permanent tattooing. Palpable subcutaneous nodules at the injection sites were reported in 9 patients. There were no reports of skin necrosis. The authors concluded that lymphatic navigation by ICG fluorescence detected SLNs at a high DR and improved the mapping performance when added to the MB method. They stated that the novel ICG + MB dual tracing modality, without involvement of radioactive isotopes, exhibited great potential as an alternative to traditional standard mapping methods.

However, NCCN’s clinical practice guidelines on “Breast cancer” (Version 1.2018)
and “Melanoma” (Version 2.2018) do not mention indocyanine green SLN mapping.

**Sentinel Lymph Node Mapping for Colon Cancer:**

Chand and colleagues (2018) stated that in colon cancer, appropriate tumor excision and associated lymphadenectomy directly impact recurrence and survival outcomes. Currently, there is no standard for mesenteric lymphadenectomy, with a lymph node yield of 12 acting as a surrogate quality marker. In a pilot study, these researchers determined the safety and feasibility of ICG fluorescence imaging to demonstrate lymphatic drainage in colon cancer in a dose-escalation study. A prospective study of colon cancer patients undergoing curative laparoscopic resection was performed. At surgery, peri-tumoral sub-serosal ICG injection was done to demonstrate lymphatic drainage of the tumor. A specialized fluorescence system excited the ICG and assessed lymphatics in real time. The primary outcome was the feasibility of ICG fluorescent lymphangiography for lymphatic drainage in colon cancer; secondary outcomes were the optimal protocol for dose, injection site, and ICG lymphatic mapping timing. A total of 10 consecutive patients were evaluated (6 men, mean age of 69.5 years). In all, lymphatic channels were seen around the tumor to a varying extent; 8 (80 %) had drainage to the sentinel node. In all cases where the lymphatic map was seen, there was no further spread 10 mins after injection. In 2 patients (20 %), additional lymph nodes located outside of the proposed resection margins were demonstrated. In both cases the resection was extended to include the nodes and in both patients these nodes were positive on histopathology. Factors contributing to reduced lymphatic visualization were inadequate ICG concentrations, excess India ink blocking drainage, and inflammation from tattoo placement. The authors concluded that ICG can be safely injected into the peri-tumoral sub-serosal and demonstrated lymphatic drainage in colon cancer. They stated that this proof of concept and proposed standards for the procedure can lead to future studies to optimize the application of image-guided precision surgery in colon cancer. Furthermore, this technique may be of value in indicating the need for more extended lymphadenectomy.

Moreover, NCCN’s clinical practice guidelines on “Colon cancer” (Version 2.2018) does not mention indocyanine green SLN mapping.

**Sentinel Lymph Node Mapping for Gastric Cancer:**

Takeuchi and Kitagawa (2015) stated that clinical application of SLN mapping in
patients with early-stage gastric cancer has been a controversial issue for years. However, a recent meta-analysis and a prospective multi-center trial of SLN mapping for early-stage gastric cancer have shown acceptable SLN DRs and accuracy of determination of lymph node status. A dual-tracer method that uses radioactive colloids and blue dyes is currently considered the most reliable method for the stable detection of SLNs in patients with early-stage gastric cancer.

However, the new technologies such as ICG infrared or fluorescence imaging might revolutionize the SLN mapping procedures in gastric cancer. For early-stage gastric cancer, the establishment of individualized, minimally invasive treatments based on SLN concept may retain the patients’ quality of life.

Ohdaira and colleagues (2017) described the retrospective feasibility study of ICG fluorescence SLN mapping in back-table for early gastric cancer using PINPOINT (NOVADAQ, Canada); SLN mapping were performed as following; the day before surgery, 0.5 ml ICG was injected endoscopically in 4 quadrants of the submucosa surrounding the gastric cancer using an endoscopic puncture. Intra-operatively, the gastro-colic ligament was divided to visualize all possible directions of lymphatic flow from the stomach. PINPOINT was used to illuminate regional lymph nodes from the serosal side. Positive staining was confirmed by at least 3 surgeons and an endoscopist during surgery. Lymph node dissection and gastrectomy were performed according to the criteria of gastric cancer treatment guidelines of Japanese Gastric Cancer Association. All 6 patients had gastrectomy with laparoscopic approach; ICG-positive lymphatic flow and lymph nodes were able to be observed in all the patients. Final pathological diagnosis was all Stage I and curative resection. All the patients had ICG-positive lymphatic area in left gastric artery (LGA) area; 2 patients with tumor located in L area had ICG positive flow to right gastro-epiploic artery (RGEA) area. The mean of ICG positive lymph nodes was 8.6; 1 patient had a metastatic lymph node in station No.4, which was positive for ICG. The authors concluded that this method made identification of ICG-positive lymph nodes easy in SLN mapping in back-table under room light. Moreover, they stated that although further accumulation and analysis are necessary, they may be able to apply this method for intra-operative SLN mapping of laparoscopic gastric cancer surgery.

Moreover, NCCN’s clinical practice guidelines on “Gastric cancer” (Version 2.2018) does not mention indocyanine green SLN mapping.

**Sentinel Lymph Node Mapping for Ovarian Cancer:**
Buda and colleagues (2017) noted that SLN mapping has increased its feasibility in both early-stage cervical and endometrial cancer. There are few SLN studies regarding the ovary because of the risk of tumor dissemination and perhaps because the ovary represents an inconvenient site for injection. In this preliminary study, these researchers examined the feasibility of SLN mapping of the ovary with ICG during laparoscopic retroperitoneal aortic surgical staging. The 10 women who were included in this study underwent aortic with pelvic laparoscopic staging, which included SLN biopsy, extra-fascial total hysterectomy, and bilateral salpingo-oophorectomy in case of an ovarian tumor. The fluorescent dye was injected on the dorsal and ventral side of the proper ovarian ligament and the suspensory ligament, close to the ovary and just underneath the peritoneum. In all cases except 1, SLNs were detected soon after the injection in the aortic compartment and in 3 cases also in the common iliac region. Only 1 intra-operative complication occurred: a superficial lesion of the vena cava that was recovered with a laparoscopic suture.

The authors concluded that laparoscopic ovarian SLN mapping performed by means of an injection of ICG fluorescent tracer in the ovarian ligaments appeared feasible and promising. Moreover, they stated that further investigation are needed to evaluate the possible applications of this new technique for staging patients with early-stage ovarian cancer.

Moreover, NCCN’s clinical practice guidelines on “Ovarian cancer” (Version 2.2018) does not mention indocyanine green SLN mapping.

**Sentinel Lymph Node Mapping for Urological Cancers (e.g., Bladder, Kidney, Penis, and Prostate):**

Aoun and colleagues (2018) stated that bilateral pelvic lymph node dissection (PLND) represents the most accurate and reliable staging procedure for the detection of lymph node invasion in prostate cancer and bladder cancer. However, the procedure is not without complications. In this field, ICG fluorescence-guided SLN identification is an emerging and promising technique, as accurate staging of urologic cancer could be enhanced by a thorough evaluation of the SLNs. These researchers reviewed available evidence and performed a meta-analysis on ICG-guided SLN detection for urologic malignancies. They carried out a systematic review to examine the clinical value of ICG for the identification of sentinel lymphatic drainage for bladder, prostate, kidney and penile cancers was undertaken, with a meta-analysis to generate pooled DR concerning patients (clinical sensitivity) and
nodes basin (technical sensitivity) separately. Studies reporting on the use of ICG for the detection of SLNs from the bladder, prostate and penile cancers were included. A total of 10 clinical trials were included. Using the fixed effects model and the random effects model, the pooled patient DRs and their 95% CI were 0.88 (0.82 to 0.92) and 0.92 (0.84 to 0.96), respectively. The pooled nodes DRs were 0.71 (95% CI: 0.68 to 0.74) using the fixed effect model and 0.75 (95% CI: 0.56 to 0.87) using the random effect model. Significant heterogeneities existed among studies for patients and for nodes ($I^2 = 0.66, p < 0.001$ and $I^2 = 0.96, p < 0.001$, respectively). Significant publication bias was found in patient DR ($p < 0.001$) and in nodes DR ($p < 0.001$). The authors concluded that SLN mapping in bladder and prostate cancer is a method with a high DR, although its specificity to predict LN invasion remains poor. Moreover, they stated that large well-constructed trials are needed to evaluate the impact of ICG-fluorescence-guided SLN dissection on uro-oncologic surgery.


**CPT Codes / HCPCS Codes / ICD-10 Codes**

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td></td>
<td><strong>CPT codes covered if selection criteria are met:</strong></td>
</tr>
<tr>
<td></td>
<td>92240 Indocyanine-green angiography (includes multi-frame imaging) with interpretation and report</td>
</tr>
<tr>
<td></td>
<td>92242 Fluorescein angiography and indocyanine-green angiography (includes multiframe imaging) performed at the same patient encounter with interpretation and report, unilateral or bilateral</td>
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<tr>
<td></td>
<td><strong>Other CPT codes related to the CPB:</strong></td>
</tr>
<tr>
<td>+38900</td>
<td>Intraoperative identification (eg, mapping) of sentinel lymph node(s) includes injection of non-radioactive dye, when performed (List separately in addition to code for primary procedure)</td>
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<tr>
<td>55530</td>
<td>Excision of varicocele or ligation of spermatic veins for varicocele; (separate procedure)</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>55535</td>
<td>Excision of varicocele or ligation of spermatic veins for varicocele; abdominal approach</td>
</tr>
<tr>
<td>55540</td>
<td>Excision of varicocele or ligation of spermatic veins for varicocele; with hernia repair</td>
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</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

**C69.30 - C69.32**  
Malignant neoplasm of choroid [not covered for choroidal melanoma]

**H30.141 - H30.149**  
Acute posterior multifocal placoid pigment epitheliopathy

**H30.90 - H30.93**  
Unspecified chorioretinal inflammation

**H31.8**  
Other specified disorders of choroid

**H35.051 - H35.059**  
Retinal neovascularization, unspecified

**H35.09**  
Other intraretinal microvascular abnormalities

**H35.3210 - H35.3293**  
Exudative age-related macular degeneration

**H35.3529**  
Dystrophies primarily involving the retinal pigment epithelium

**H35.60 - H35.63**  
Retinal hemorrhage [subretinal hemorrhage or hemorrhagic retinal pigment epithelium]

**H35.711 - H35.719**  
Central serous chorioretinopathy

**H35.721 - H35.729**  
Serous detachment of retinal pigment epithelium

**H35.731 - H35.739**  
Hemorrhagic detachment of retinal pigment epithelium

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

**C70.0**  
Malignant neoplasm of cerebral meninges [parasagittal meningioma]

**D32.0**  
Benign neoplasm of cerebral meninges [parasagittal meningioma]

**D86.0 - D86.9**  
Sarcoidosis
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<th>Code</th>
<th>Code Description</th>
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<tr>
<td>Code</td>
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<tr>
<td>H15.001 - H15.129</td>
<td>Scleritis and episcleritis</td>
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<td>H20.821 - H20.829</td>
<td>Vogt-Koyanagi syndrome</td>
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<tr>
<td>H30.811 - H30.819</td>
<td>Harada's disease</td>
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<tr>
<td>H31.101 - H31.109</td>
<td>Unspecified choroidal degeneration [hereditary drusen]</td>
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<tr>
<td>H33.101 - H33.199</td>
<td>Retinoschisis and retinal cysts</td>
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<tr>
<td>H35.361 - H35.369</td>
<td>Drusen (degenerative) of macula</td>
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<tr>
<td>H47.321 - H47.329</td>
<td>Drusen of optic disc</td>
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<td>I77.0</td>
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<td>K43.0 - K43.9</td>
<td>Ventral hernia</td>
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<tr>
<td>M35.2</td>
<td>Behcet's disease</td>
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<tr>
<td>Q28.8</td>
<td>Other specified congenital malformations of circulatory system</td>
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</table>

Non-ophthalmic:

HCPCS codes covered for indications listed in the CPB:

<table>
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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C9733</td>
<td>Non-ophthalmic fluorescent vascular angiography [Spy Elite System]</td>
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</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>A52.05</td>
<td>Other cerebrovascular syphilis [syphilitic ruptured cerebral aneurysm]</td>
</tr>
<tr>
<td>E89.0</td>
<td>Postprocedural hypothyroidism [total thyroidectomy or esophagectomy]</td>
</tr>
<tr>
<td>I60.00 - I60.9</td>
<td>Nontraumatic subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>---------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>I67.1</td>
<td>Cerebral aneurysm, nonruptured</td>
</tr>
<tr>
<td>Q28.3</td>
<td>Other malformations of cerebral vessels [cerebral arteriovenous aneurysm, congenital]</td>
</tr>
<tr>
<td>Z90.49</td>
<td>Acquired absence of other specified parts of digestive tract [total thyroidectomy or esophagectomy]</td>
</tr>
<tr>
<td>Z98.890</td>
<td>Other specified postprocedural states [total thyroidectomy or esophagectomy]</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


47. Nahabedian M. Breast reconstruction in women with breast cancer. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed October 2013.
51. Park JK. Meningioma: Clinical presentation and diagnosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed April 2015.
52. Wen PY. Systemic treatment of recurrent meningioma. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed April 2015.
57. McCulloch DK. Diabetic retinopathy: Screening. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed October 2015.


Amendment to
Aetna Clinical Policy Bulletin Number:
0111 Indocyanine Green Angiography

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania revised 08/23/2018