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Fluorescence-Guided Surgery and Intervention - An AAPM Emerging Technology Blue Paper

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Abstract

Fluorescence-guided surgery (FGS) and other interventions are rapidly evolving as a class of technologically-driven interventional approaches in which many surgical specialties visualize fluorescent molecular tracers or biomarkers through associated cameras or oculars to guide clinical decisions on pathological lesion detection and excision/ablation. The technology has been commercialized for some specific applications, but also presents technical challenges unique to optical imaging that could confound the utility of some interventional procedures where real-time decisions must be made. Accordingly, the AAPM has initiated the publication of this Blue Paper of The Emerging Technology Working Group (TETAWG) and the creation of a Task Group from the Therapy Physics Committee within the Treatment Delivery Subcommittee. In describing the relevant issues, this document outlines the key parameters, stakeholders, impacts and outcomes of clinical FGS technology and its applications. The presentation is not intended to be conclusive, but rather to inform the field of medical physics and stimulate the discussions needed in the field with respect to a seemingly low-risk imaging technology that has high potential for significant therapeutic impact. This AAPM Task Group is working toward consensus around guidelines and standards for advancing the field safely and effectively.

1. Description of Technology and Application

The technological and logistical implementation of Fluorescence Guided Surgery (FGS) has been evolving for several decades, in parallel research and subspecialty clinical areas.¹ Just in the last few years broadened clinical use has been established, accompanied and supported by growth in commercially available imaging systems.²⁻⁸ The leading commercial enabling factor has been the availability of Indocyanine green (ICG), an FDA-approved fluorescent dye,^{9,10} for blood flow, tissue function and perfusion imaging applications in surgery. Several laboratories and companies have demonstrated this

also for use in various tissue functions and as a lymphatic tracer.¹¹⁻¹³ At the same time FGS capability has been integrated into robotic surgery, which provides a good fit with the use of display-based surgical guidance in a laparoscopic geometry.¹⁴⁻¹⁶ Additionally, substantial investments and innovation have occurred in the development of new fluorescent molecular tracers, which have the potential to generate information beyond passive blood flow or diffusive/convective transport and uptake.¹⁷⁻²³ For instance, therapy monitoring can be carried out intraoperatively using fluorescence imaging, such as during photodynamic therapy where photobleaching can be an indirect measure of dose delivery,^{24,25} or with specially designed protein binding agents which report on receptor availability.²⁶ With the dramatic increase in the number of imaging devices (laparoscopes, endoscopes, wide field open surgical imaging systems, surgical microscopes and retinal cameras) to guide interventional procedures or at various stages of regulatory approval and clinical adoption, it is critical to define objective metrics for their assessment of performance. FGS is one large subset of devices used for guidance, which could also include microscopy systems such as optical coherence tomography, photoacoustic imaging, in-situ microscopy, or more, however, the subject at focus here is macroscopic or wide-field imaging tools which is being adopted by surgeons to view centimeters of tissue at a time. So, this review and discussion will revolve around these latter tools and their utility in surgical and interventional work.

FGS opens opportunities for the use of state-of-the-art imaging in medical specialties that have not traditionally used image guidance technology, such as wound care, battlefield medicine and in major global health challenges where low-cost/hand-held fluorescence imaging could become the norm. As a result, identifying systematic advices for the development and use of devices for FGS is timely for the scientific, translational and clinical communities; hence the purpose of this blue paper. The systems involve both biochemical optical agents administered to patients as well as the use of imaging systems that create images of the distributions of these. There are several factors which dictate the performance and successful use of this approach, which are outlined here and are to be worked on in an AAPM sanctioned workgroup report.

The expertise and knowledge required to develop and implement FGS are diverse, involving not only medical physics and engineering but also biochemistry, pharmacology, medicinal chemistry, materials science, imaging science, optical biophysics, and computer vision. The complexity is further compounded by the wide range of surgical and medical sub-specialties in which these procedures are being adopted.^{11,27} Accordingly, the agent and device combinations vary considerably. Figure 1 illustrates the dual expertise base needed in both hardware design and performance (a) as well as optical probes and pharmaceutical science (b). Even with these two obvious parts of system/procedure development and approval, there is considerable nuance to making systems work optimally. Hence, this document will focus largely on the technical issues that need consideration, as an introduction to the field, and the specific implementations and applications will be discussed as branches of this main effort.

As listed in Table I, the key issues related to optical agents include things like: (i) their intended use; (ii) their detection efficiency in each clinical setting; (iii) potential inaccuracies or artefacts during either approved or off-label applications within the clinical workflow; and (iv) guidelines for use in different standard-of-care settings.²⁸⁻³⁰ Because of these issues, different systems can have dramatically different performance based on factors such as the optical filtering, excitation light and field homogeneity, the detector type and the dynamic range of the camera(s), as well as the performance achieved when imaging different tissues and correction for biophysical effects such as spectrally-dependent light attenuation by tissue and surface contours that can distort the images or make quantitation challenging.^{31,32} Understanding these issues is critical to ensuring that, as new technological solutions are introduced for FGS, the relevant regulatory bodies, developers and users are aware of these unique issues and that clinical data generated by different imaging systems can be related to each other.

The areas of rapid development and potentially divergent specifications due to differing applications occur along the lines of 1) device design, 2) optical agents, 3) tissue optics, 4) image processing and display, 5) performance testing, and 6) guidelines, regulations and approval processes. Each of these key areas is identified below. It is worth noting that several of the key enabling technology

elements are themselves evolving rapidly, driven by advances in other fields, including photonics (devices) and genomics/molecular biology (agents).

Each of these specific issues requires detailed expert consideration to put in place informative guidance for developers, manufacturers (instrumentation and pharmaceutical), and operators to hasten clinical realization and ensure optimum impact of FGS.

2. Predicted Clinical and Research Impact

FGS is scientifically, technologically, clinically complex, and so development and implementing appropriate guidelines require multidisciplinary expertise, as well as a multi-step process for convergence on consensus goals. This field of medical intervention has aspects of radiation therapy, interventional radiology and surgery combined. The potential clinical benefits are substantial to create better tools that will allow surgeons to make conclusively accurate decisions while in the setting of their procedure. Some of the interventional procedures can be transformative for identifying structural, functional and biomarker-related features such as blood flow, vessel patterns, secretory ducts, nerves, lymph ducts & nodes, excretory function, cancer extent and biomarker expression, pathogen detection and identification, as well as retinal diseases. Interventional procedures based upon molecular expression have considerable potential to become a reality in the coming years and could become central themes in personalized medicine with custom targeted agents based upon the molecular profile of the pathology targeted in the procedure. This is much longer term, but is in clinical trial work now, and each agent requires uniquely designed devices for the optical probe spectra and concentration expected in a given anatomic location.

Currently, system costs and market penetration are changing rapidly, with the wide range of uses, such as intraoperative workstations, monitoring devices, systems for registration with other imaging tools, and remote telemedicine applications. Transformative systems such as the da Vinci® robot (Intuitive Surgical, Inc.) and neurosurgical guidance systems have incorporated fluorescence channels and are changing the paradigm of how surgery is performed.¹⁴⁻¹⁶ This evolution will likely continue; however, evidence of clinical success in applying molecular-specific probes in human procedures will be essential

for the approach to have maximum impact in healthcare. Nevertheless, several untargeted fluorescent agents are already in clinical use (ICG, fluorescein), as is aminolevulinic acid (ALA) which induces endogenous production of Protoporphyrin IX (PpIX) in cancer and pre-cancer tissues with a degree of molecular specificity across a spectrum of different cancers (skin, bladder, lung, brain, etc.).³³⁻³⁶ A range of both visible as well as near-infrared probes are being developed and tested in clinical trials. Their use can be quite different, with visible dyes sometimes utilized by direct visualization of the emission. Often, both types of probes are visualized with electronic imaging and enhanced/augmented display features.

While the focus of this study is intentionally around the technological aspects of the imaging systems, this must be done with appreciation of the optical probes that the systems are to be paired with. The evolution of optical probes is likely be significantly slower than the evolution of optical imaging systems, as can be seen today with indocyanine green, where with just the one agent, there are nearly a dozen commercial imaging systems cleared for imaging it. Since the injected optical agents are in more intimate biological contact than the imaging systems, their approvals will be slower and based around the toxicity/benefit of the procedure planned. It is very likely that many more hardware systems will be developed for each agent approved in the coming years. However, it is this fact that makes the standardization and guidelines around optical systems even more relevant.

3. Impact on the Vested Professionals

Optical procedures are already ubiquitous in medicine, through the use of many different diagnostic and therapeutic systems, from simple pulse oximeters to endoscopes, a multiplicity of ophthalmological and dermatological systems, to complex multimodal operating microscopes and laparoscopes as well as medical lasers. Fluorescence-based imaging has had less penetrance to date but is of increasing use, not only by clinical specialists who are familiar with optical technologies but also surgical sub-specialties where integration of optical techniques with new technologies is changing practice. ICG-based fluorescence imaging already has important applications in cardiology, hepatology and ophthalmology and is becoming more widely used in surgical oncology procedures. Isosulphan blue

imaging is used widely in oncologic surgery for lymph node detection, while ALA-PpIX fluorescence imaging is used in neurosurgery, therapeutic endoscopy and dermatology.

Little discussion of the role of technically-trained experts in FGS has occurred to date, in part because the development has been largely industry driven and serviced. The current industry-driven approach follows the endoscopy/laparoscopy model where physical specialists are the users and provide medical guidance, but the producing companies provide most of the technical direction and maintenance. However, as the paradigm of molecular agent-device combinations becomes more of a reality, it will become more important to involve multidisciplinary expertise that is not traditionally found in “instrument” companies. At the same time, optical physicists and engineers have traditionally been found in academic bioengineering departments and a few large research institutions, rather than in the clinical activity of hospitals. On the research side, biomedical optics has emerged over the past 20 years largely in the context of the development of photonics, which is a large and diverse field, rather than in the context of traditional medical physics, and has its own professional bodies (journals and conferences) that are separate from medical physics as represented by organizations like AAPM. It may be easier to integrate these highly specialized disciplines in hospitals where medical physics and biomedical engineering divisions are combined, which is more common in the European than North American settings. Nuclear medicine, where radiochemists and medical physicists collaborate, is another example of the type of joint expertise that will be required to implement and support optical instrumentation and optical agents. However, the need for expertise at the confluence of devices, agents, tissue optics, image display, performance testing and regulatory requirements is growing.

4. Regulatory Ramifications: Safety and Essential Performance

Existing standards designed to facilitate evaluation of safety and effectiveness are largely self-produced by each company and approved through their own manufacturing controls processes. These may or may not be part of their regulatory clearance or approval, or best practices for use – and so may not be sufficient given that there is no higher oversight or professional guidance beyond the industry and their

safety approvals. Yet the creation of FGS-specific standards has not occurred to any significant extent. Lack of standardization of fluorescence imaging systems will lead to unreliable clinical results as well as impact the design and magnitude of clinical and animal studies required to demonstrate efficacy. Furthermore, the current research paradigm where comparisons between imaging systems are rarely performed and performance results provided in different studies are not readily comparable, is detrimental to technological progress. Examples of the type of tests required to rigorously assess the performance of a fluorescence imaging system are shown in Figure 2(a), which include well established characteristics such as spatial resolution and contrast resolution, but also some less conventional factors such as albedo, tissue optical factors, scatter from the tissue and depth dependence of the signal. In most cases, corrections for these responses are not included, but the signal response to these tissue optical effects is important. This lack of standardization will become increasingly problematic as FGS continues to expand, mature and penetrate clinical practice.

Development of standards, however, will be particularly challenging, given that the specifications and performance of fluorescence imaging instruments vary widely and are much more diverse than traditional radiological imaging systems. Furthermore, the potential contrast agents are also chemically and biologically diverse, and potential photochemical damage mechanisms are not well characterized and quantified. Thus, additional research may be needed before standard safety evaluation methods can be identified/developed, and standards may be limited to indicating key performance characteristics and suggesting test methods rather than highly proscriptive, quantitative guidelines and thresholds. Use of standards as part of the premarket regulatory process is a topic of considerable interest, which again depending upon the application, will be important to guide accurate real time clinical decision making.

The range of tissue variables and FGS-specific effects that influence clinical performance will likely need to be addressed to some degree in the regulatory process. For example, reliable and accurate quantification of tracer amounts from fluorescent imaging requires accurate correction for the types of effects shown in Figure 2(a).^{37,38} As a result, procedures using FGS systems or methods, in which appropriate accommodation for tissue optical effects are not implemented, could have mixed results, from

inconsistent usage or incorrect interpretation of the resulting images. This is an area of high importance for consensus discussion, where the field of FGS needs better evidenced-based standardization and calibration metrics and processes.

As illustrated in Figure 2(b), regulation of FGS by the FDA in the United States or via the CE marking process in Europe, covers clinical evaluation studies and marketing of clinical imaging devices used with contrast agents. FGS systems have been going through the 510(k) clearance process in the US as a Class II device (medium but significant risk), but some parts or additions to a system could be found to be Class I (minimal potential for harm), depending upon the exact procedure targeted and the level of involvement that the device/agent has in the procedure. The regulatory process focuses on establishment of product safety and effectiveness, which can encompass a wide variety of issues, including preclinical safety and performance testing, biocompatibility, validation and verification of computational models, clinical trial design, biostatistics, software, human factors, and quality assurance procedures. FGS falls under the category of “combination products” since it involves the combined use of a device and a drug, and is thus covered by a unique set of regulations. It is likely that future combination systems would make use of existing molecular agent approvals or device approvals, such that the introduction of a new device or a new agent is made easier through only changing one of the two components. A good example of this was the recent, June 2017, FDA approval of 5-aminolevulinic acid HCL (5-ALA).³⁹ The agent was indicated for use as an adjunct for the visualization of malignant tissue during surgery in patients with glioma tumors.⁴⁰⁻⁴³ Agent approval was not tied to a specific imaging system, but rather for use with surgical operating microscopes having exposure and spectral characteristics as specified in the drug labeling [NDA 208630 Labeling]. Currently, approvals are based upon the integrated package of the device and the diagnostic compound performance, and will be treated as a new clearance or approval, sometimes separately and sometimes as a combination depending upon the risk/benefits of the system and agent. However, regulatory policy on combination products is evolving, particularly with the recent passing of laws such as the 21st Century Cures Act and the FDA Reauthorization Act (Section 706) which

mandate changes in procedures that may lead to more streamlined processes for individualized clearance of agents and devices.

Objective, quantitative test methods to evaluate essential performance characteristics can facilitate device development and regulatory assessment, especially if FDA recognizes a consensus standard to enable consistent measurements during clinical use and provide quality control during manufacturing. As with established imaging modalities (e.g. US, CT, MRI), biologically-relevant phantoms designed and validated for determination of critical figures of merit will likely play key roles. The AAPM has had a major role in establishment of these phantoms and guidelines in radiological procedures, to ensure system performance and patient safety, and should ideally use this expertise to expand into FGS where similar challenges and goals are present. Standards that address potential FGS safety issues have the potential to reduce the burden of animal and clinical testing. Novel safety issues may include drug-device phototoxicity for novel fluorescence agents or established agents used at higher agent or light doses, additive photo-thermal effects of exogenous chromophores, and photothermal effects of light on organs and tissues. The parallel roles of professional society guidance, standards and governance are illustrated in Figure 2(b), as part of the technological development process.

5. Unique Educational/Curriculum Requirements

Education appears to occur within the physician sub-specialties where the procedures are performed, and little interaction with medical physics or biomedical engineering expertise takes place, except in major research centers. Procedure-based education is largely supplied by vendors today with the early adopting practices, and knowledge and standards are appropriately shared between physicians as part of their peer-to-peer or vendor-to-peer education approaches. However, given the growth of procedures and associated devices, compounded by the large research growth in molecular FGS systems and agents, and divergent areas of use, there is a need to augment vendor-user training with in-hospital expertise, especially in applications where the complexity of use can induce potential liability or ineffective procedures. A major limitation to this development is the lack of a clear professional

organization which bridges the gap between the scientific and clinical use of FGS. The AAPM is one society which has expertise to help establish an educational, best-practices and standardization framework for FGS, and can work with adopting physicians to improve appropriate planning a quality audit.

In order to ensure success of this initiative, the AAPM would be required to reach out to clinical organizations beyond radiation therapy, radiology and nuclear medicine. These radiation focused specialties/departments are the ones to which it has primarily engaged to date yet outreach to surgery specialties as well as scientific/technical/molecular organizations in biophotonics/biomedical optics will be required for this initiative, since these are where the core enabling expertise resides. One parallel society addressing similar issues with a more biochemical or biological focus is the World Molecular Imaging Society, which has developed an Optical Navigation Surgical Interest Group (OSN-IG). Other parallel surgical societies are the International Society for Computer Aided Surgery and parallel interest groups or societies in sub-specialties such as neurosurgery and orthopedics. As systems and procedures become established, the flow of educational information flow will be critical between relevant individual research groups, professional societies, funding agencies and regulatory/standards bodies involved in the procedures. The technical expertise base and history of the AAPM taking a lead role in via work group reports makes this body the most likely to forge a successful plan for establishing expert guidance in this complex and changing technological area of medicine.

6. Conclusions

This blue paper outlines a skeleton of the clinical, scientific, technical and organizational issues associated with FGS in the broad areas of device design, optical tracers, tissue optics, image processing and display, performance analysis, standards, and regulatory issues, as listed in Table 1. Each technical domain involves one or more specific challenges that require the attention of the membership of the AAPM to help analyze problem areas and guide best clinical practices. The current guidance in this field is driven by government regulatory clearances around existing indications and growth is industry driven, with training being peer-to-peer or industry-to-user, without significant professional society guidance but

with an approach driven by local best practice principles. Technical societies such as the AAPM have a role to fill in helping ensure that standards are established and met, and the future interventional procedures continue to be done with safe, effective systems. It is hoped that this brief Blue Paper will provide a start to development of a deeper informed discussions that create a working document with guidance on the development, commercialization, and safe/effective application of FGS systems, which is in process within an AAPM sanctioned Task Group on this topic.

7. References

- 1 Polom, K. *et al.* Current trends and emerging future of indocyanine green usage in surgery and oncology: a literature review. *Cancer* **117**, 4812-4822, doi:10.1002/cncr.26087 (2011).
- 2 Kogon, B. *et al.* The role of intraoperative indocyanine green fluorescence angiography in pediatric cardiac surgery. *Ann Thorac Surg* **88**, 632-636, doi:S0003-4975(09)00439-1 [pii]10.1016/j.athoracsur.2009.03.010 (2009).
- 3 Miyashiro, I. *et al.* Laparoscopic detection of sentinel node in gastric cancer surgery by indocyanine green fluorescence imaging. *Surg Endosc* **25**, 1672-1676, doi:10.1007/s00464-010-1405-3 (2011).
- 4 Tsuzuki, S. *et al.* Application of indocyanine green (ICG) fluorescence for endoscopic biopsy of intraventricular tumors. *Childs Nerv Syst* **30**, 723-726, doi:10.1007/s00381-013-2266-6 (2014).
- 5 Daskalaki, D. *et al.* Indocyanine Green (ICG) Fluorescent Cholangiography During Robotic Cholecystectomy: Results of 184 Consecutive Cases in a Single Institution. *Surg Innov*, doi:1553350614524839 [pii]10.1177/1553350614524839 (2014).
- 6 Imai, K. *et al.* Detection of pleural lymph flow using indocyanine green fluorescence imaging in non-small cell lung cancer surgery: a preliminary study. *Surg Today* **43**, 249-254, doi:10.1007/s00595-012-0237-2 (2013).
- 7 Yoshida, M. *et al.* Indocyanine green injection for detecting sentinel nodes using color fluorescence camera in the laparoscopy-assisted gastrectomy. *J Gastroenterol Hepatol* **27 Suppl 3**, 29-33, doi:10.1111/j.1440-1746.2012.07067.x (2012).
- 8 AV, D. S., Lin, H., Henderson, E. R., Samkoe, K. S. & Pogue, B. W. Review of fluorescence guided surgery systems: identification of key performance capabilities beyond indocyanine green imaging. *J Biomed Opt* **21**, 80901, doi:10.1117/1.JBO.21.8.080901 (2016).
- 9 Abe, H. *et al.* Indocyanine green fluorescence imaging system for sentinel lymph node biopsies in early breast cancer patients. *Surg Today* **41**, 197-202, doi:10.1007/s00595-009-4254-8 (2011).
- 10 Alander, J. T. *et al.* A review of indocyanine green fluorescent imaging in surgery. *Int J Biomed Imaging* **2012**, 940585, doi:10.1155/2012/940585 (2012).

- 11 Marano, A. *et al.* Application of fluorescence in robotic general surgery: review of the
literature and state of the art. *World J Surg* **37**, 2800-2811, doi:10.1007/s00268-013-
2066-x (2013).
- 12 Tsujino, Y., Mizumoto, K., Matsuzaka, Y., Niihara, H. & Morita, E. Fluorescence
navigation with indocyanine green for detecting sentinel nodes in extramammary Paget's
disease and squamous cell carcinoma. *J Dermatol* **36**, 90-94, doi:10.1111/j.1346-
8138.2009.00595.xJDE595 [pii] (2009).
- 13 Marshall, M. V. *et al.* Near-Infrared Fluorescence Imaging in Humans with Indocyanine
Green: A Review and Update. *Open Surg Oncol J* **2**, 12-25,
doi:10.2174/1876504101002010012 (2010).
- 14 Manny, T. B. & Hemal, A. K. Fluorescence-enhanced robotic radical cystectomy using
unconjugated indocyanine green for pelvic lymphangiography, tumor marking, and
mesenteric angiography: the initial clinical experience. *Urology* **83**, 824-829,
doi:10.1016/j.urology.2013.11.042S0090-4295(14)00015-6 [pii] (2014).
- 15 Pessaux, P. *et al.* Robotic duodenopancreatectomy assisted with augmented reality and
real-time fluorescence guidance. *Surg Endosc* **28**, 2493-2498, doi:10.1007/s00464-014-
3465-2 (2014).
- 16 Bjurlin, M. A. *et al.* Near-infrared fluorescence imaging: emerging applications in robotic
upper urinary tract surgery. *Eur Urol* **65**, 793-801, doi:10.1016/j.eururo.
2013.09.023S0302-2838(13)01010-5 [pii] (2014).
- 17 van Dam, G. M. *et al.* Intraoperative tumor-specific fluorescence imaging in ovarian
cancer by folate receptor-alpha targeting: first in-human results. *Nat Med* **17**, 1315-1319,
doi:10.1038/nm.2472 nm.2472 [pii] (2011).
- 18 Ito, A. *et al.* New whole-body multimodality imaging of gastric cancer peritoneal
metastasis combining fluorescence imaging with ICG-labeled antibody and MRI in mice.
Gastric Cancer **17**, 497-507, doi:10.1007/s10120-013-0316-0 (2014).
- 19 Snoeks, T. J. *et al.* Towards a successful clinical implementation of fluorescence-guided
surgery. *Mol Imaging Biol* **16**, 147-151, doi:10.1007/s11307-013-0707-y (2014).
- 20 Sevik-Muraca, E. M. Translation of near-infrared fluorescence imaging technologies:
emerging clinical applications. *Annu Rev Med* **63**, 217-231, doi:10.1146/annurev-med-
070910-083323 (2012).
- 21 Chen, K. *et al.* A Cy5.5-labeled phage-displayed peptide probe for near-infrared
fluorescence imaging of tumor vasculature in living mice. *Amino Acids* **42**, 1329-1337,
doi:10.1007/s00726-010-0827-5 (2012).
- 22 Nakajima, T. *et al.* Targeted, activatable, in vivo fluorescence imaging of prostate-
specific membrane antigen (PSMA) positive tumors using the quenched humanized J591
antibody-indocyanine green (ICG) conjugate. *Bioconjug Chem* **22**, 1700-1705,
doi:10.1021/bc2002715 (2011).
- 23 Pogue, B. W. *et al.* Review of Neurosurgical Fluorescence Imaging Methodologies. *IEEE*
J Sel Top Quantum Electron **16**, 493-505, doi:10.1109/JSTQE.2009.2034541 (2010).
- 24 Jarvi, M. T., Patterson, M. S. & Wilson, B. C. Insights into photodynamic therapy
dosimetry: simultaneous singlet oxygen luminescence and photosensitizer
photobleaching measurements. *Biophys J* **102**, 661-671, doi:S0006-3495(11)05474-9
[pii] 10.1016/j.bpj.2011.12.043 (2012).

- 25 Wilson, B. C., Patterson, M. S. & Lilge, L. Implicit and explicit dosimetry in
photodynamic therapy: a New paradigm. *Lasers Med Sci* **12**, 182-199,
doi:10.1007/BF02765099 (1997).
- 26 Tichauer, K. M. *et al.* Microscopic lymph node tumor burden quantified by macroscopic
dual-tracer molecular imaging. *Nat Med* **20**, 1348-1353, doi:10.1038/nm.3732 nm.3732
[pii] (2014).
- 27 Polom, W., Markuszewski, M., Rho, Y. S. & Matuszewski, M. Usage of invisible near
infrared light (NIR) fluorescence with indocyanine green (ICG) and methylene blue
(MB) in urological oncology. Part 1. *Cent European J Urol* **67**, 142-148,
doi:10.5173/ceju.2014.02.art5 00346 [pii] (2014).
- 28 Zhu, B., Rasmussen, J. C. & Sevic-Muraca, E. M. A matter of collection and detection
for intraoperative and noninvasive near-infrared fluorescence molecular imaging: to see
or not to see? *Med Phys* **41**, 022105, doi:10.1118/1.4862514 (2014).
- 29 Pogue, B. W. *et al.* Vision 20/20: Molecular-guided surgical oncology based upon tumor
metabolism or immunologic phenotype: Technological pathways for point of care
imaging and intervention. *Med Phys* **43**, 3143, doi:10.1118/1.4951732 (2016).
- 30 Elliott, J. T. *et al.* Review of fluorescence guided surgery visualization and overlay
techniques. *Biomed Opt Express* **6**, 3765-3782, doi:10.1364/BOE.6.003765 243885 [pii]
(2015).
- 31 Zhao, Q. *et al.* A handheld fluorescence molecular tomography system for intraoperative
optical imaging of tumor margins. *Med Phys* **38**, 5873-5878, doi:10.1118/1.3641877
(2011).
- 32 Kagadis, G. C. *et al.* Emerging technologies for image guidance and device navigation in
interventional radiology. *Med Phys* **39**, 5768-5781, doi:10.1118/1.4747343 (2012).
- 33 Stummer, W. *et al.* Favorable outcome in the elderly cohort treated by concomitant
temozolomide radiochemotherapy in a multicentric phase II safety study of 5-ALA. *J*
Neurooncol, doi:10.1007/s11060-010-0400-9 (2010).
- 34 Hillemanns, P. *et al.* Pharmacokinetics and selectivity of porphyrin synthesis after topical
application of hexaminolevulinate in patients with cervical intraepithelial neoplasia. *Am J*
Obstet Gynecol **198**, 300 e301-307, doi:10.1016/j.ajog.2007.07.045 S0002-
9378(07)00924-6 [pii] (2008).
- 35 Wang, X. L. *et al.* Study of protoporphyrin IX (PpIX) pharmacokinetics after topical
application of 5-aminolevulinic acid in urethral condylomata acuminata. *Photochem*
Photobiol **83**, 1069-1073, doi:PHP178 [pii] 10.1111/j.1751-1097.2007.00178.x (2007).
- 36 Hautmann, H. *et al.* In-vivo kinetics of inhaled 5-aminolevulinic acid-induced
protoporphyrin IX fluorescence in bronchial tissue. *Respir Res* **8**, 33, doi:1465-9921-8-33
[pii] 10.1186/1465-9921-8-33 (2007).
- 37 Valdes, P. A. *et al.* Quantitative, spectrally-resolved intraoperative fluorescence imaging.
Sci Rep **2**, 798, doi:10.1038/srep00798 (2012).
- 38 Bekelis, K. *et al.* Quantitative and qualitative 5-aminolevulinic acid-induced
protoporphyrin IX fluorescence in skull base meningiomas. *Neurosurg Focus* **30**, E8,
doi:10.3171/2011.2.FOCUS1112 (2011).
- 39 Kaufman, M. B. Pharmaceutical Approval Update. *P T* **42**, 673-683 (2017).
- 40 Cozzens, J. W. *et al.* A Phase 1 Dose-Escalation Study of Oral 5-Aminolevulinic Acid in
Adult Patients Undergoing Resection of a Newly Diagnosed or Recurrent High-Grade
Glioma. *Neurosurgery* **81**, 46-55, doi:10.1093/neuros/nyw182 (2017).

- 41 Valdes, P. A. *et al.* Quantitative fluorescence using 5-aminolevulinic acid-induced
protoporphyrin IX biomarker as a surgical adjunct in low-grade glioma surgery. *J*
Neurosurg **123**, 771-780, doi:10.3171/2014.12.JNS14391 (2015).
- 42 Widhalm, G. Intra-operative visualization of brain tumors with 5-aminolevulinic acid-
induced fluorescence. *Clin Neuropathol* **33**, 260-278, doi:11601 [pii] (2014).
- 43 Valdes, P. A. *et al.* 5-Aminolevulinic acid-induced protoporphyrin IX fluorescence in
meningioma: qualitative and quantitative measurements in vivo. *Neurosurgery* **10 Suppl**
1, 74-82; discussion 82-73, doi:10.1227/NEU.0000000000000117 (2014).

Figure & Table Captions

Table I. The six categories of concern are listed in columns, with examples of sub-categories listed in rows. Each of these are topics to be discussed in a Work Group on FGS approved by the AAPM.

Figure 1. The hardware components of a generic system are illustrated (a) to show the complexity of choices in lenses, filters, coupling, spectrum, readout and processing. The probe molecules and pharmaceutical medicine of their delivery are illustrated (b) to illustrate the range of molecules used and the complexity of the pharmacokinetics which can be observed.

Figure 2. The range of issues for testing are illustrated in (a) including albedo, tissue optical property performance, depth sensitivity, as well as the traditional issues of spatial and contrast resolution with field homogeneity. The relevant stages of development are listed in (b) along with the needed professional society guidance, systems standards bodies, and government regulatory bodies.

Table 1: The six categories of concern are listed in columns, with examples of sub-categories listed in rows. Each of these are topics to be discussed in a Work Group on FGS approved by the AAPM.

Device design	Optical Agents	Tissue Optics	Image Process & Display	Performance Testing	Guidelines & Regulations
Illumination	Pharm/toxicity	Absorption/scatter effects	Post processing	Trial role	Self-developed goals
Optical filtering	Class of agent	Tissue layer effects	Display used	Performance characteristics	Consensus study goals
Imaging system	Light interactions	Background signals	Image fusion & registration	Phantom testing & needs	Professional society guidance
Electronics	Specificity to disease	Model-based interpretation	Signal interpretation	Standards	Standards approvals
System integration	Timing & biological effects			Training	Certifications, Approval, clearance