Use of ICG-fluorescence imaging for sentinel lymph node mapping in patients with breast cancer

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PROTOCOL TITLE:

Use of ICG-fluorescence imaging for sentinel lymph node mapping in patients with breast cancer

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

NOTE: Leave this section blank for the initial submission. The revision history should be documented for modifications to approved studies.

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1.0 Study Summary

Study Title	Use of ICG-fluorescence imaging for sentinel lymph node mapping in patients with breast cancer
Brief Summary	The primary objective is to determine the feasibility of using ICG fluorescence through the Asimov Imaging Platform for sentinel lymph node mapping by comparing lymphatic visualization using blue dye and technetium sulfur colloid (standard of care) versus ICG fluorescence imaging. We will enroll 10 patients and assess the image acquisition parameters of using ICG fluorescence through the Asimov Imaging Platform for sentinel lymph node mapping
Number of study sites	One
Study Design	Prospective, single arm feasibility study
Primary Objective	To determine the feasibility of using ICG fluorescence through the Asimov Imaging Platform for sentinel lymph node mapping by comparing lymphatic visualization using blue dye and technetium sulfur colloid (standard of care) versus ICG fluorescence imaging.
Secondary Objective(s)	To assess the image acquisition parameters of using ICG fluorescence through the Asimov Imaging Platform for sentinel lymph node mapping
Research Intervention(s)/ Investigational Agent(s)	ICG-fluorescence Imaging
Drugs/devices used on study (including any IND/IDE #)	Onlume Asimov Imaging Platform
Study Population	Breast cancer patients with clinical T1 or T2, node negative breast cancer undergoing sentinel lymph node mapping
Sample Size	10
Study Duration for individual participants	21 days (day of procedure and post-operative visit)
Study Specific Abbreviations/ Definitions	NA

Note: Include only elements relevant to this study.

2.0 Background

2.1 Sentinel lymph node (SLN) mapping is the current standard of care to stage the axillary lymph nodes for women with clinically node negative axilla.[1-3] Mapping is most commonly performed with radioisotope technetium-99 sulfur colloid and/or vital blue dye. Using this approach, mapping rates exceed 95% with a low false negative rates (5-10%).[3-5]

Although the current approach is effective, there are some gaps. Technetium-99 sulfur colloid is often injected in nuclear medicine prior to the operating room (either same day or day prior).[6] This adds complexity to scheduling of operating room cases as well as cost. In addition, technetium-99 sulfur colloid is an ionizing agent which means that this approach cannot be used in hospital settings without a nuclear medicine department. It also requires extensive safety protocols to be in place. Finally, national shortages in technetium-99 sulfur colloid have been experienced during and since the pandemic which highlight the need for an alternative mapping agent.

In addition, there are some limitations to the use of technetium-99 sulfur colloid for SLN mapping from a patient perspective. The same scheduling issues regarding injection can be inconvenient for patients, especially those that live further from the hospital. Similarly, these injections can be very painful, given they occur at the edge of the areola.[7,8] Patients often ask why these injections can't happen intra-operatively after they have received anesthesia; this is not feasible for many nuclear medicine departments workflow.

2.2 Indocyanine green (ICG) has been described as a dye for SLN mapping since the early 2000's.[9] A recent clinical trial comparing SLN identification rates for 100 patients receiving technetium colloid, blue dye, and ICG demonstrated non-inferiority between ICG and technetium colloid, with successful mapping of 96.1%.[10]

ICG is increasingly used in breast cancer surgery for a variety of indications, including lymphatic mapping for lymphedema treatment and assessment of tissue viability during reconstruction.[11-18] Consequently, many centers have already overcome one of the most significant barriers to the use of ICG mapping, specifically that it requires an intra-operative imaging device. Given the potential to cut costs and improve patient experiences by avoiding the pre-operative injection, there is value in considering the use of ICG for SLN mapping.

Several potential challenges to using ICG for SLN mapping exist. First, challenges exist related to the devices used to detect ICG fluorescence. Many devices designed for ICG cannot optimally be used with ambient light, making it challenging to use to actively guide surgical dissection into the OR. In this proposal, we will determine the feasibility of using the Asimov Imaging Platform for fluorescence-guided surgery in the operating room. The Asimov can be used without altering external (i.e., room) light functionality or levels. In addition, it is mounted on an arm that can be positioned over the operative field. This facilitates real-time

visualization of lymphatics to support sentinel lymph node mapping during the dissection and would represent a significant advancement.

The second challenge relates to the penetration of the ICG imaging through skin and soft tissue. With the technetium, the option exists to obtain an image in radiology confirming the mapping was successful before coming to the OR; this allows for the potential for a second injection if needed for slow mapping. In the OR, a handheld probe is then used to localize the location of the lymph nodes in order to plan placement of the axillary incision. However, ICG fluorescence does not have the same depth of tissue penetration as technetium. In a recent clinical trial, the lymph nodes were not able to be visualized prior to skin incision using a hand-held fluorescence imaging device called Fluobeam 800. Consequently, the investigators planned their skin incision to be just lateral to the pectoralis muscle (where the majority of breast lymph nodes are located). Importantly, the ICG fluorescence was successful in identifying the sentinel lymph nodes once the skin incision was made. Given variation in device design, it is important to assess the feasibility of the Asimov Imaging Platform in identifying sentinel lymph nodes prior to and after skin incision.

The objective of this study is to assess the feasibility of using fluorescence-guided surgery with ICG dye through the Asimov Imaging Platform for the sentinel lymph node mapping. We will continue to use blue dye and technetium sulfur colloid to guide clinical decision making (standard of care).[6] We will then compare the ICG fluorescence findings using the Asimov imaging Platform (research) with the blue dye and technetium sulfur colloid (standard of care).

3.0 Study Objectives and Endpoints

Specific Aim 1: To determine the feasibility of using ICG fluorescence through the Asimov Imaging Platform for sentinel lymph node mapping by comparing lymphatic visualization using blue dye and technetium sulfur colloid (standard of care) versus ICG fluorescence imaging.

Specific Aim 2: To define optimal image acquisition parameters of using ICG fluorescence through the Asimov Imaging Platform for sentinel lymph node mapping to inform the clinical workflow.

2a. To define dynamic range of ICG fluorescence signal in lymph nodes and background tissue.

2b. To assess image contrast as a function of ICG dose and time post-injection.

4.0 Number of Participants

We plan to enroll 10 patients in this feasibility pilot study.

5.0 Inclusion and Exclusion Criteria

5.1. Screening and recruitment: Patients being cared for by Dr. Neuman within the UW Breast Center will be eligible for consideration. Dr. Neuman will identify eligible patients from her clinical practice.

5.2 Inclusion criteria:

- ≥ 18 years of age
- Diagnosis of clinical T1 or T2 breast cancer clinically node negative breast cancer requiring surgical lymph node evaluation
- Surgery at University of Wisconsin Hospital and Clinic

5.3 Exclusion criteria:

- Pregnant: It is not known whether indocyanine green can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Women of child-bearing age will undergo a urine pregnancy test on the day of surgery, which is standard of care prior to anesthesia.
- Breastfeeding: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when indocyanine green is administered to a nursing woman. We will exclude women who are breastfeeding.
- Unable to provide informed consent
- Allergy to indocyanine green
- History of ipsilateral breast or axillary surgery

6.0 Special Populations

We will not enroll special populations in this feasibility pilot study.

7.0 Recruitment Methods

7.1 Dr. Neuman will identify eligible patients from her clinical practice.

7.2 Dr. Neuman will introduce the study to them at the time of their clinic visit. A member of the study team will then discuss the study in detail with interested patients. As much time as needed will be given for potential subjects to decide whether or not to participate in this study. Subjects will be informed that they are not obligated to participate in the study.

8.0 Consent/Assent Process

The consent process will occur either at the Breast Center or in the pre-operative area on the day of surgery, based on whether a member of the study team is available to approach the patient on the day of their clinic visit. Patients will then be consented in a closed private room. Subjects will receive a copy of the consent form and will be given contact information for member of the study team and PI for any additional questions.

9.0 Setting

Patients will be recruited from the UW Breast Center. Surgery will occur within the operating rooms at UW Health.

10.0 Study Intervention

Standard of Care Procedures:
SLN mapping using technetium-99m +/- isosulfan blue dye: For patients enrolled in the study, sentinel lymph node mapping and biopsy will be performed using technetium-99m sulfur colloid and isosulfan blue dye (unless there is a contraindication to blue dye); this is an acceptable standard of care.[6] Injection of the technetium-99m sulfur colloid will be performed by the nuclear medicine team as per standard of care. The isosulfan blue dye injection will be performed by the participating surgeon in the operating room; as per standard of care, injection will be subareolar. Incisions will be planned based on the technetium-99m activity or at the lateral aspect of the pectoralis muscle, per usual care.

Research Procedures:
SLN mapping with ICG fluorescence using the Asimov Platform: The research procedures will include using ICG-fluorescent imaging for the SLN mapping. OnLume will provide a sterile drape designed specifically for the OnLume Asimov Platform. 25 mg of ICG and 10 mg Sterile Water will be dispensed for injection by UW Health pharmacy. Before the image acquisition of each patient, ICG will be reconstituted under sterile conditions with Sterile Water (2.5 mg/1 ml). The vial will be gently shaken to dissolve. Reconstituted ICG must be used within 6 hours after reconstitution. The total dose of dye will be kept below 2 mg/kg of patient body weight. The dose of ICG to be injected is based on the existing literature.[9,10] 2 ml (5 mg) of ICG solution will be injected intradermally in 1-4 injection sites in the lateral areolar region.[10] After injection, gentle manual massage will be performed for 5 minutes. ICG imaging will be obtained prior to incision. After incision is made (following standard of care procedures), the axilla will be visualized using the Asimov Platform to assess for ICG-fluorescence in sentinel lymph nodes.

Impact on clinical care of the ICG mapping: The objective of this study is to evaluate the feasibility of using ICG fluorescent imaging through the Asimov Imaging Platform for SLN mapping. Compared to other platforms, the Asimov Imaging Platform allows real time imaging without altering ambient light. Clinical decisions regarding which lymph nodes are considered sentinel lymph nodes (and should be removed) will be made based technetium-99 activity and/or vital blue dye, as per standard of care. However, we will image with the Asimov Platform throughout to determine whether ICG-fluorescent imaging would have led to identification of different lymph nodes.

11.0 Study Timelines

The duration of an individual participant's participation is limited to the OR day and the post-operative visit. We anticipate enrolling the 10 participants in <12 months.

12.0 Procedures Involved

Patients will be consented either in clinic or on the day of surgery. A medical record review will collect pre-operative and post-operative data. We will inject the ICG and

collect imaging data as described above. We will collect procedural data related to the ICG injection and fluorescent imaging. We will assess adverse events related to the injection at the post-operative visit.

Overview of Study Calendar

Visit Number	Screening/recruitment	Pre-op Medical Record Review	Day of Surgery	Post-op Visit	Post-op Medical Record Review
Informed Consent/Assent	X				
Review Eligibility	X				
Demographics/prior medical history/clinical tumor characteristics		X			
Pregnancy Test			X		
Operative data collection			X		
Fluorescent Imaging Data			X		
Pathologic tumor characteristics					X
Adverse Event Assessment			X	X	

Medical Record Review: We will collect data through UW Health electronic medical record review. We will record limited demographics about the patient including: age, race/ethnicity, BMI, type of breast surgery, receipt of neoadjuvant systemic therapy, prior receipt of radiation, clinical and pathologic cancer stage (tumor size and lymph node status), and receptor status (estrogen receptor, progesterone receptor, her2neu). We will also collect surgical and pathologic details related to breast/axillary surgery.

Operative data collection:
We will collect the following procedural data:

- We will document whether ICG-fluorescence is visualized prior to incision (yes/no).
- At each time point when the axilla is examined for technetium-99 activity, we will document whether technetium-99 activity, ICG-fluorescence and blue dye is visualized We will also document whether lymphatic vasculature is visualized with the ICG-fluorescence or blue dye.
- Each lymph node removed will be assessed for blue dye, technetium-99 activity, and ICG fluorescence and the findings recorded.
- Time ICG is mixed, injection, time of start and end of massage, start of axillary surgery, time of removal of lymph nodes, time of fluorescent imaging

- Number of lymph nodes removed. For removed lymph nodes, we will record whether removed lymph nodes had radiotracer, blue dye, or fluorescence.
- After removal of sentinel lymph nodes, we will document whether there is residual background technetium-99 activity and ICG-fluorescence in the axilla.

Imaging data:
Subjects will receive fluorescence imaging using the Asimov Imaging Platform. Beginning at the time of ICG injection, image and video capture of contemporaneous white light reflectance and fluorescence imaging will be collected. Following the operation, post-processing will be conducted to elucidate injection technique superiority. We will use quantitative fluorescence to define optimal image acquisition parameters. In order to evaluate injection technique performance, the critical image acquisition parameters that provide surgeons detectable contrast (CNR) and fluorescence intensities in the lymphatic vessels and SLN will be measured with respect to post-injection time at each time point the axilla is examined.

Adverse Event Assessment: We will assess for complications related to the injection of the ICG intraoperative and at the post-operative visit.

Regulatory status of drugs and devices:

The Onlume Asimov Imaging Platform is a non-significant risk device. A letter supporting this is attached.

ICG is FDA approved as an optimal imaging agent for visualization of lymph nodes and lymphatic vessels. The Investigational Drug Brochure is attached to this application. ICG contrast meets requirements for IND exemption because:

(i) ICG is lawfully marketed in the United States
(ii) The investigation focuses on the Asimov Imaging Platform is not intended to be reported to FDA in support of a new indication for use nor intended to support any other significant change in the labeling for ICG;
(iii) This investigation focusing on the Asimov Imaging Platform is not intended to support a significant change in the advertising for ICG;
(iv) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use ICG. ICG has been used extensively in clinical practice with an exceedingly good safety profile.
(v) The investigation is conducted in compliance with the marketing limitations described in 21 CFR § 312.7.

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13.0 Comparison of usual care and study procedures

If patients chose to not participate in this study, they will receive usual standard of care treatment for their cancer. This would include SLN mapping as per standard of care using technetium-99 +/- vital blue dye.

14.0 Withdrawal of Participants

Patients will be withdrawn from the study at their request. In addition, if their clinical situation evolves so that the SLN mapping is longer applicable to them or they no longer meet eligibility criteria, they will be withdrawn.

15.0 Data Management and Confidentiality

15.1 Describe the steps the researchers will take to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission. If HIPAA rules apply to the study, review information on the Office of Compliance HIPAA page and consult HIPAA Privacy and Security Coordinators to ensure that data management methods are compliant. Select all that apply:

- ■ Data will be coded, and the "key" linking identities to codes will be kept separately from the data.
- ☐ Data will be coded, and the "key" linking identities to codes will be kept on paper only. The study data will be stored electronically and labeled only with codes.
- ■ Only those listed as key personnel will have access to the "key."
- ☐ Access to the "key" will be limited to the following person (e.g., Database Administrator): _____
- ■ This study is funded by the National Institutes of Health and is covered by a Certificate of Confidentiality.
- ☐ This study is NOT funded by the National Institutes of Health but because it will collect sensitive information, the research team will apply for a Certificate of Confidentiality to protect data from being requested without the subject's consent as part of a legal proceeding.
- ☐ Other: _____

15.3 Describe how and where data and/or specimens will be stored and maintained. Select all that apply:

- ■ Online Collaborative Research Environment (OnCore) Biospecimen Management
- ■ Research Electronic Data Capture (REDCap) *Specify which instance you will be using (e.g., ICTR's, Department of Medicine's)*: _____

- ☐ Other software option that will be stored on departmental server. *Specify the department*: _____
- ■ Locked filing cabinet or drawer inside a locked room. Specify the building: _Clinical Science Center (K6)_____
- ☐ Other (describe): _____
- ☐ Data will not be stored or accessed on portable devices.
- ☐ Portable devices will be used to access secure web-based data collection sites such as ICTR's REDCap. No data will be stored locally on the device.
- ■ Data stored on portable devices will be coded with the key stored separately. No identifiers will be stored on portable devices.
- ■ Data stored on portable devices and therefore only encrypted devices will be used.

15.4 Management of Identifiers:

- ☐ Identifiers will be destroyed after all data has been collected.
- ☐ Identifiers will be destroyed at study closure.
- ■ Identifiers will be destroyed at study closure or at the time of publication.

15.5 Describe any planned sharing of data and/or specimens outside the study team / institution. Include sharing required by funding agencies and publications.

Imaging data will be coded with a unique sample ID # (e.g., 123) and will be stored on the secure surgery server and on the OnLume's off-campus data server. Data will be transferred using an encrypted USB drive. No PHI will be stored on the OnLume data server. The subject code is linked to a separate spreadsheet, which lists the subject number and the patient identifiable information including medical record number. The code will be stored separately from the research data on the secure Department of Surgery server. All electronic data is password and firewall security protected. When a patient is imaged through the Asimov Imaging Platform, only the subject ID will be entered into the system. In this way, the imaging will always be "coded" from the time of image acquisition. From the OnLume system, the imaging data will be transferred using an encyrpted USB hard drive. Once data is confirmed to be successfully transferred to OnLume and the secure Dept. of Surgery server, it will be permanently deleted from the imaging platform.

Datasets containing patient identifiers will not be copied or shared with others outside of the UW study team for analysis. Only datasets without identifiers can be shared for analysis; the Onlume team will only receive coded data. Upon completion of this research, the link to identifiable information will be destroyed, permanently de-identifying the data.

16.0 Provisions to Protect the Privacy Interests of Participants

16.1 Describe the steps that will be taken to protect participants' privacy interests. "Privacy interest" refers to a person's desire to place limits on with whom they interact or to whom they provide personal information. If any of the following apply, check the box for convenience:

- ☒ Procedures will be performed in a private area where others cannot see the procedures being performed or overhear the conversation between subjects and researchers.
- ☒ All members of the study team are up to date on their institutional HIPAA training.
- ☒ The study is not collecting information that could pose legal or reputational risks to participants.

The consent process will occur at the Breast Center and pre-operative areas of UW Health. Subjects will be consented in a closed private room by a member of the study team. As much time as needed will be given for potential subjects to decide whether or not to participate in this study.

Patients being cared for by Dr. Neuman within the UW Breast Center will be eligible for consideration. Dr. Neuman will identify eligible patients from her clinical practice and introduce the study to them. A study team member will then discuss the study in detail and obtain informed consent. Once consent is obtained, a member of the research team with valid, approved access to HealthLink will conduct the chart abstraction from the health care record.

17.0 Sharing of Results

This is a feasibility study where patients' care will proceed using standard of care means. Dr. Neuman will share with an individual patient the ICG-fluorescent imaging findings post-operatively at patients' request. Results will not be reported in the health record.

18.0 Data and Specimen Banking

We are not planning to retain data collected for future unrelated research projects.

19.0 Study Analysis

Baseline demographic and outcome variables will be summarized using descriptive statistics. We will report whether ICG-fluorescent lymph nodes were visualized percutaneously (prior to incision). We will describe concordance rates between technetium-99 and ICG-fluorescence for each sentinel lymph node removed (mean 2.8 nodes with a standard deviation of 2.2).[4] We will also assess concordance at the patient level; using the technetium-99 as the gold standard,

we will describe the number of lymph nodes that would have been missed (i.e. technetium-99 + but ICG- in removed SLN) or would have been excised unnecessarily (i.e. residual ICG-fluorescence in axilla but no residual technetium-99) if ICG-fluorescent imaging had guided the SLN. We will summarize any adverse events.

Planned reporting of concordance rates between technetium-99 and ICG per excised sentinel lymph node			
	Technetium-99 +	Technetium-99 -	Total
ICG +			
ICG -			
Total			

20.2 Sample Size Justification:

No power calculation is calculated for this feasibility study. We anticipate that the sample size of 10 will be enough to assess initial feasibility of this approach and whether further study is warranted.

20.0 Potential Benefits to Participants

There is no direct benefit to patient participation in this study.

21.0 Risks to Participants

There are low risks expected related to study participation.

Potential risks from ICG are minimal as it is a well-known, FDA-approved dye that has a very good safety profile (adverse event rate: 1 in 42,000) when administered intravenously.[11,19,20] Adverse events can range from a redness of the skin or hives, up to cough or difficulty swallowing. In the operating room, these would be treated with medication such as antihistamines, H2 blockers, and/or epinephrine. Although ICG is approved for intravenous administration, it has been safely injected into interstitial, subcutaneous (SC) or intradermal locations in hundreds of patients, including breast tissue. In a recent trial of 100 patients undergoing SLN with ICG-fluorescence, no ICG-related complications or adverse events were reported. In our own experience at UW using ICG for a lymphatic mapping study, no ICG-related complications have been experienced for the 6 patients enrolled to date. Similarly, no adverse reactions have been reported in other studies evaluating ICG for lymphatic mapping, with study sizes as large as 689 patients.[14-17,21]

Potential risks from the use of the OnLume Asimov Imaging platform are low since the imaging device will be used in a similar manner as its FDA 510(k) clearance. The duration of the surgery is not expected to be significantly longer in

duration (<20 minutes) with the additional use of the OnLume System imaging than with just the standard of care. Per discussions with anesthesia staff, the additional time for anesthesia poses no foreseeable additional risk to the patient. The risk associated with the injection of the dye will be minimized by close observation of the patient after injection. Injection will occur in the OR when extensive monitoring is already occurring.

As with any study, there is a remote risk of breach of confidentiality. This risk has been minimized through data protection efforts. Only approved study personnel will have access to the direct identifiers.

22.0 Provisions to Monitor the Data to Ensure the Safety of Participants

The PI and study team will be involved in ongoing monitoring for data and safety concerns.

Our proposed phase II, non-blinded clinical trial represents a low risk of adverse events, and the described DSMP is commensurate with this level of risk. The PI and study team will meet weekly to discuss recruitment, accrual and retention of participants. They will also review any safety concerns during these meetings. The study team will discuss data quality monthly. The study team has developed a comprehensive checklist of study activities that resides within a regulatory binder. This will be reviewed before and after each patient is enrolled.

We feel that the risks to participating in this study are minimal and our research team will be continually reviewing data and subject safety at weekly study team meetings to discuss study progress including recruitment/enrollment, data integrity, and adverse events (AEs). This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for routine toxicity and adverse event (AE) reporting. Incisional pain, breast seromas, and breast/arm swelling are expected events after breast and axillary surgery. We will consider injection site reactions, such as redness of the skin or hives, to be unexpected adverse events. We also consider allergic reactions to the dye (such as cough or difficulty swallowing) to be unexpected adverse events. We will submit any unanticipated adverse effects to sponsor and to the IRB as soon as possible, but no event later than 10 working days after the investigator first learns of the effect. Unexpected and immediately life-threatening or severely debilitating events, whether related to the ICG or the Asimov Imaging Platform, will be reported with 1 business day.

The focus of this study is to test the feasibility of ICG mapping through the Asimov Imaging Platform. Potential advantages to the Asimov Imaging Platform compared to other means of immunofluorescence detection is that it allows real time imaging without altering ambient light.

Only coded data related to the imaging acquisition will be stored on the OnLume off campus data server. Data will be transferred on an encrypted USB drive to OnLume. After confirmation that the data has transferred and is not been corrupted, the source data will be deleted from the imaging platform. Imaging data will also be stored on the surgery servers using the same method of encrypted USB. No PHI will be stored outside of the UW Department of Surgery secure server (see section that follows).

23.0 Economic Burden to Participants

There are no direct costs to patients to participating in this study.

24.0 Resources Available

Will the research be conducted outside School of Medicine and Public Health or UW Hospitals and Clinics (e.g. the researcher does not have an SMPH research feasibility attestation for this study)?	☐ YES (complete 25.1) ■ NO (remove text below, but retain this section)

25.0 Multi-Site Research

NA

26.0 References

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