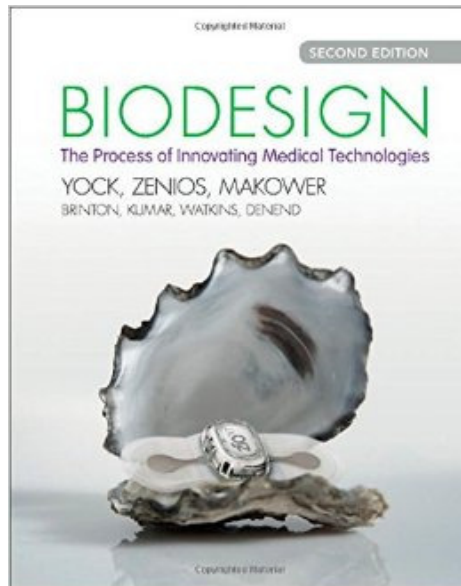


Transferring biomedical research to patients

DR GIUSEPPE RUVIO, NATIONAL UNIVERSITY OF IRELAND
GALWAY



Biodesign



The Process of Innovating Medical Technologies

Stefanos Zenios, Josh Makower, Paul Yock

Overview

“Identifying a compelling clinical need may seem simple and obvious, but it is not. Get it right and you have a chance, get it wrong and all further effort is likely to be wasted.”

Where to look

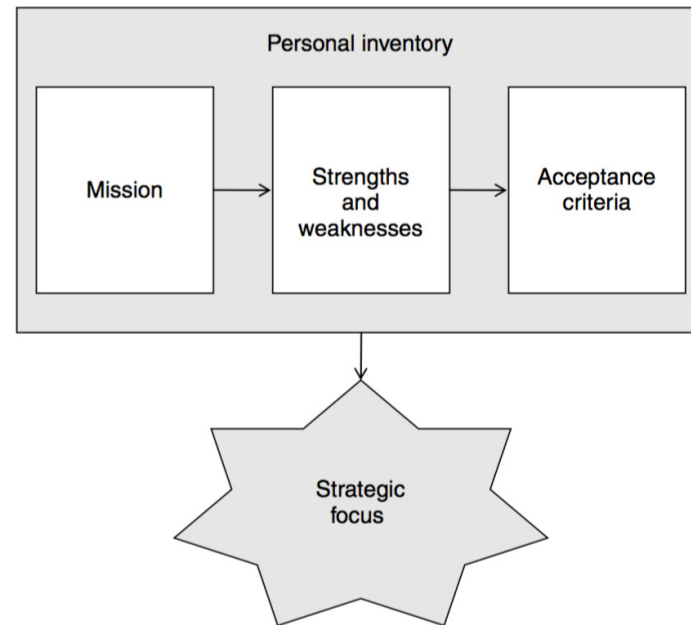
How to look

Which one

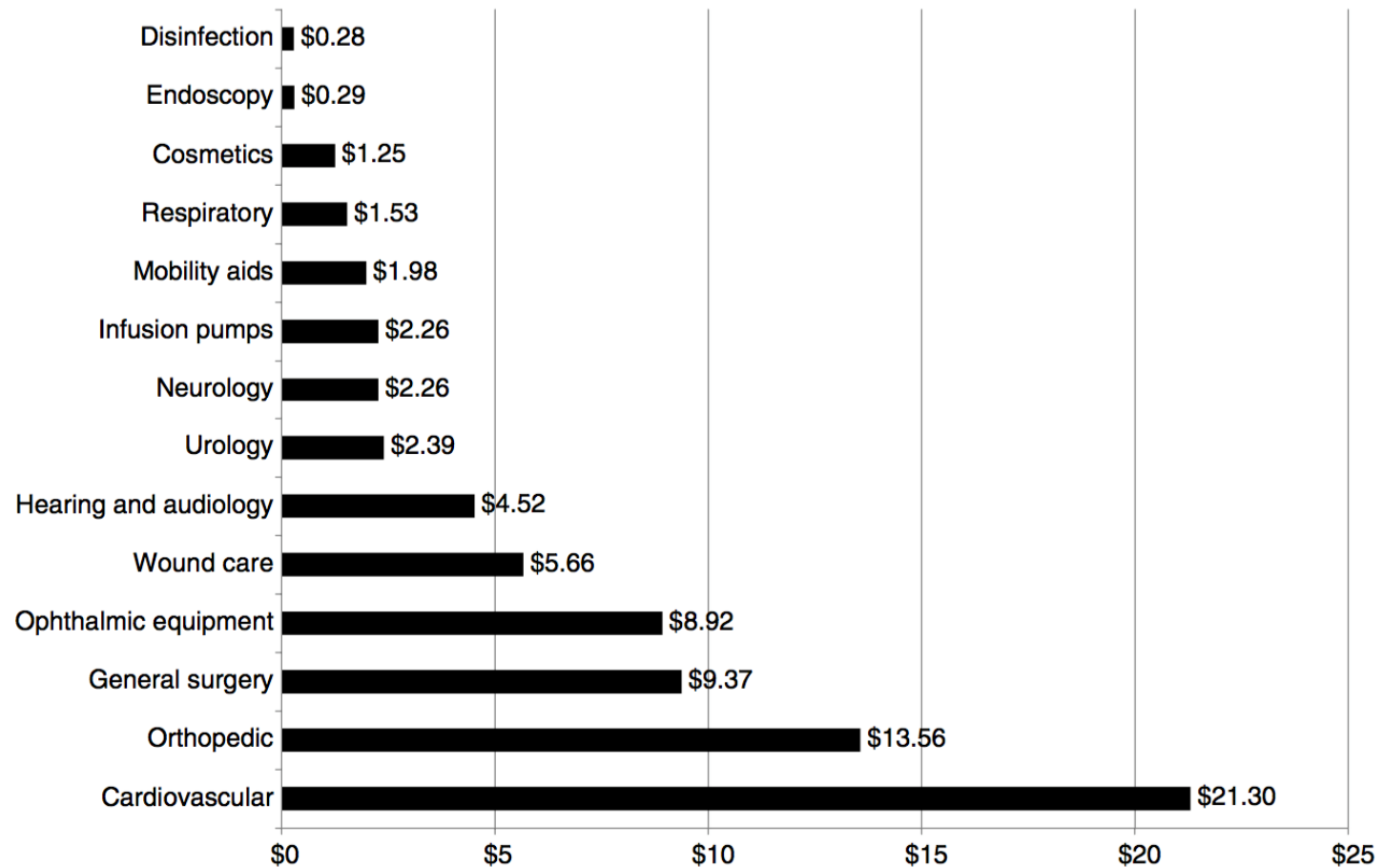


Where to look

Strategic focus



2006 U.S. Revenue (billions)
"U.S. Medical Device Market Outlook," Frost & Sullivan, 2008



Project Acceptance Criteria

- Time to market: maximum 5yrs to FIM
- Minimum acceptable market size: \$200 million
- Clinical / regulatory path
- Technology Strategy: fast follower* / science projects
- IP: must be patentable
- Exit strategy: must be attractive to corporates
- Reimbursement: must have an existing reimbursement code
- Focus must align with team technical abilities
- Must provide a measurable clinical outcome.

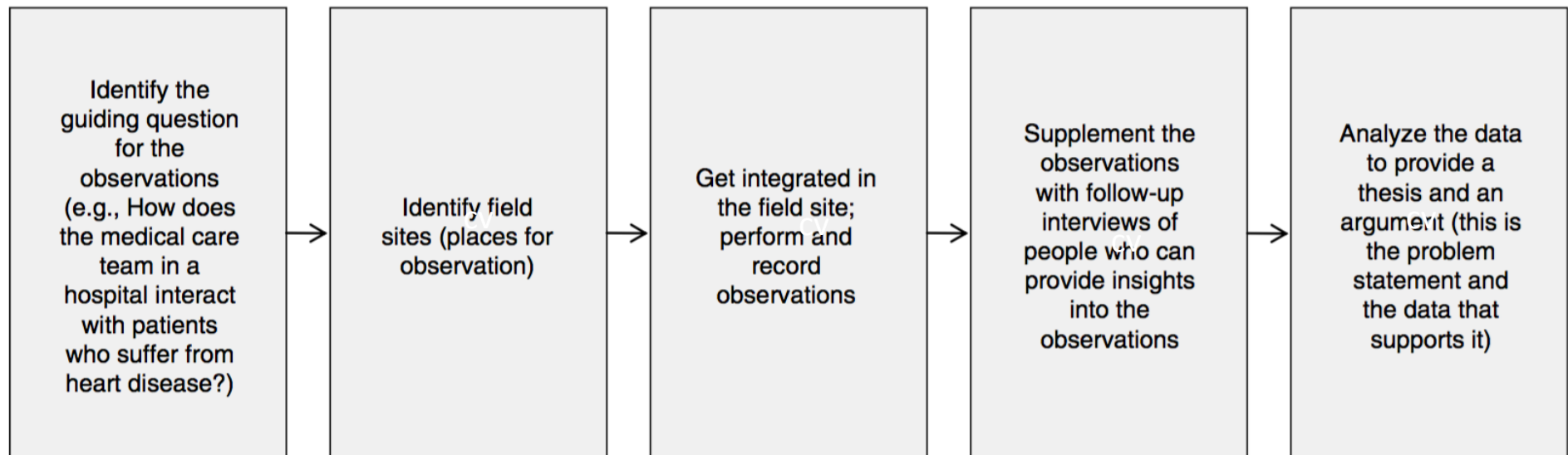
How to look

Observations



Innovators tend to go out and ask doctors what they want rather than observe what they need. When you talk to physicians, as well as others involved in the delivery of care, you've got to learn the difference between what they say, what they want, what they'll pay for, and what they actually do.

The process



Patient Qs

- What did the patient have to undergo in terms of pre-operative tests, appointments, etc., prior to the procedure?
- What time did the patient have to get up to prepare for the procedure?
- Was s/he allowed to eat the night before?
- What sort of preparation was required?
- Did the preparation have any negative or unintended side effects?
- What did the patient experience when s/he arrived at the hospital?
- How long did s/he have to wait?
- Was the patient taken to the operating room in a wheelchair or on a gurney?
- How long did the procedure take?
- What were the steps of the procedure and how long did each one take?
- Did the procedure require a general anesthetic?
- How much pain (or discomfort) did the patient experience during the procedure?
- Post-operatively? After discharge?
- What was involved in the post-operative process?
- What sort of bandage did the patient receive?
- Did the wound require dressing changes or drains?
- How often was the bandage changed/wound drained?
- Was a urinary catheter required?
- Was intravenous (IV) access required?
- Were there any complications that resulted from these procedures?
- How long was it before the patient could discontinue the drain, catheter, or IV?
- Are there any variations in the ways patients are prepared for, treated during, or cared for after a procedure, depending on the environment?
- Did the patient need to stay in the hospital overnight? For how many nights?
- Did the patient need any assistance after hospital discharge?
- What was the time required before the patient could resume normal activities?

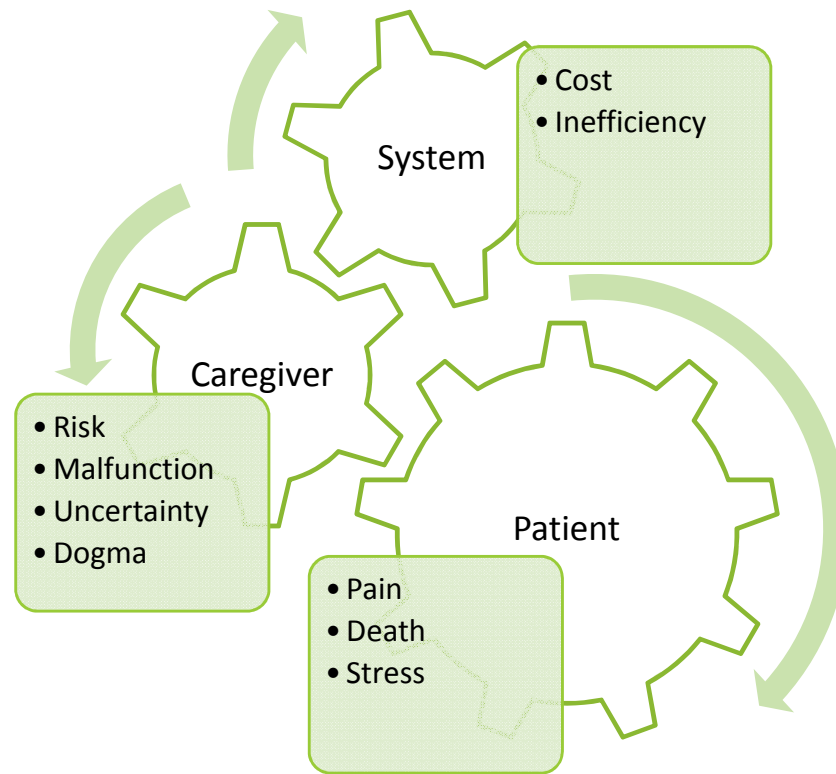
Caregiver Qs

- Who prepares the patient for the procedure?
- How many people are present in the operating room?
- What are their various roles?
- Does the same person perform the procedure from start to finish?
- Are practitioner staffing levels and roles the same across different environments?
- Why is work allocated across practitioners in this way?
- How long has this been the standard of care?
- How was the procedure performed before the current standard?
- What are the accepted primary limitations or difficulties associated with the current procedure?
- Do the devices (or other tools used in the procedure) perform as the providers want/need them to?
- How does the provider use the device?
- Does the provider appear confident using the device? Did the provider have difficulties using the device? Operating? Implanting it? How many hands were required to operate/implant/use the device properly (i.e., did the provider need assistance operating the device)?
- Did the provider make any errors while using the device?
- How much follow-up is required of the surgical provider(s) following the procedure?
- What are the most common complications associated with the procedure?
- Who treats the complications?
- How (and where) are they treated?

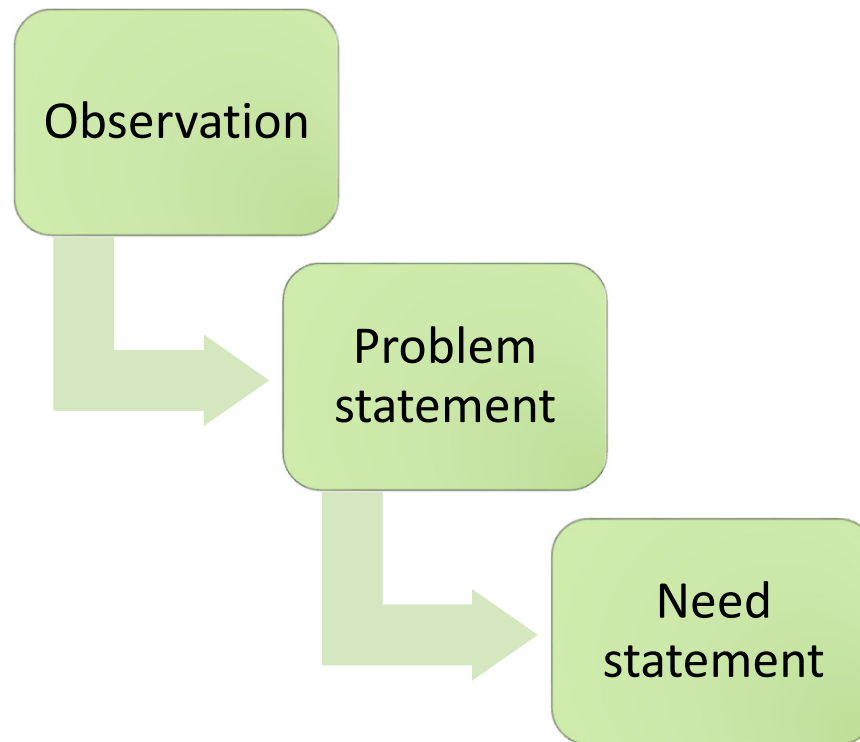
Provider Qs

- How much does the procedure cost?
- At what rate is the procedure reimbursed?
- Is the procedure profitable?
- What factors are most likely to drive up (or down) costs?
- How long does the procedure take to perform?
- What aspect(s) of the procedure take the longest to complete?
- How many resources are tied up as the procedure is being performed?
- What facilities (e.g., rooms) are tied up as a result of the procedure?
- Is the procedure performed in only one setting (e.g., operating room) or can it be performed in other venues (e.g., outpatient procedure or radiology lab)?
- What devices, equipment, or supplies are required to support the procedure?
- How much do the devices, equipment, and supplies cost?
- To what extent do they affect the profitability of a procedure?
- What risks do complications from the procedure present to the system?
- If there are complications to the procedure, who bears the cost?

What to look for

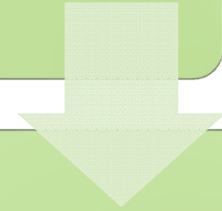


Collating Information



OBSERVATION

Surgeon highlighted that leakage where colon is re- joined can lead to complications



PROBLEM

After an anastomosis is created surgically, the physician can only conduct a qualitative assessment of the join. The only way to test it properly is to wait to monitor it post-operatively for leaks. Leakage is reported to occur in 5% of cases and results in significant morbidity (6-fold increase in hospital stay) and a mortality rate of 6%–14.7%.The effectiveness of the anastomosis will depend on mechanical properties of the colon wall & blood supply in area.



NEED

A way to quantitatively determine the leak resistance of an anastomosis intraoperatively during a colectomy to provide immediate feedback to the clinician and reduce leaks.

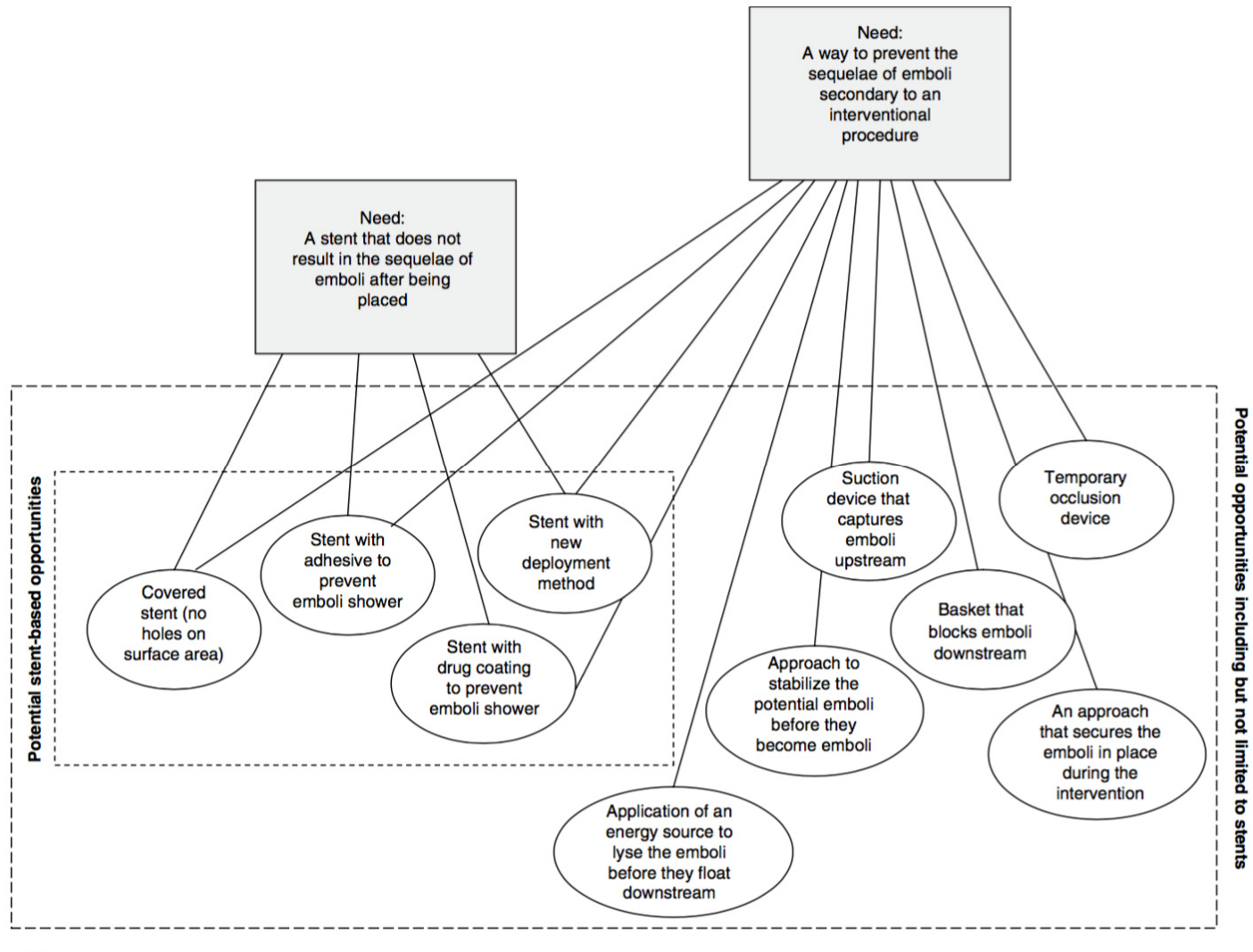


Construction of Need Statements

A method to prevent hip dislocation in high-risk patients.

A method to prevent recurrent hip dislocations in high-risk patients.

A method to prevent recurrent hip dislocations in patients after surgical treatment of a first hip dislocation.

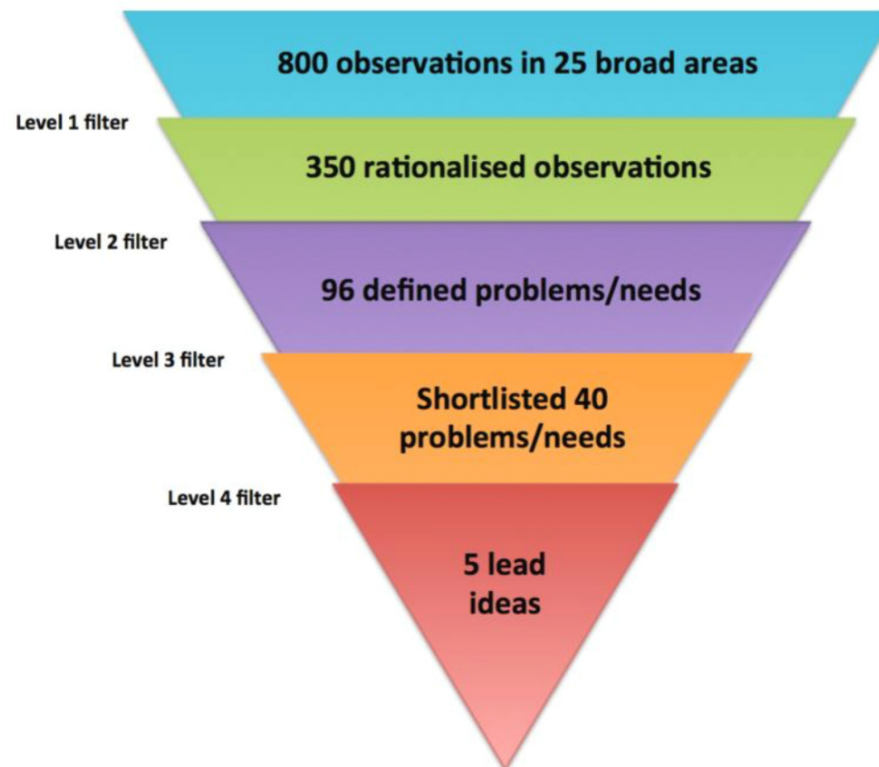


Construction of Need Statements

A way to improve detection rate of flat sessile polyps associated with serrated polyposis syndrome that reduces the miss rates to less than 10%.

Which one

Filtering

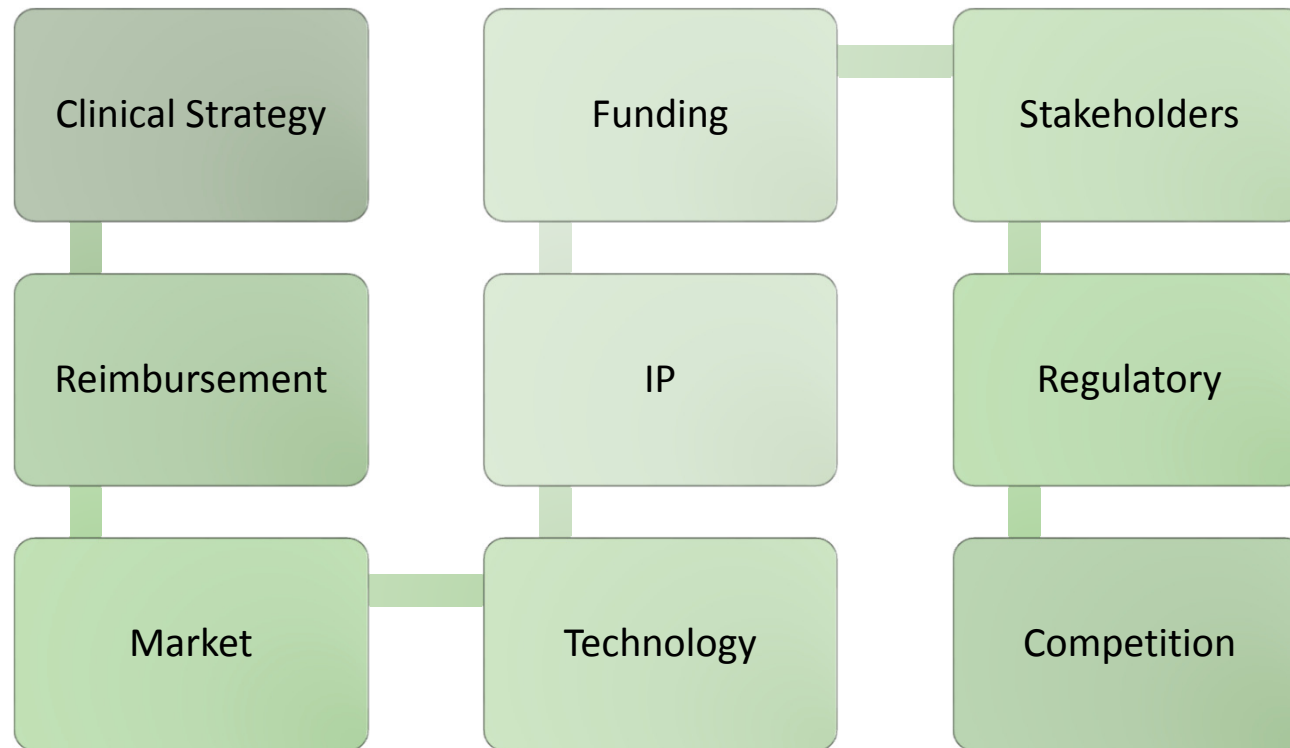


Filtering

Observations

Filtering

Ask the Big Questions:



IDENTIFY

Needs Finding

Observations
Need Statements

Filtering and Specifications

Disease State
Market Analysis
Competition

Need Specification

INVENT

Concepts

Brain Storming

Concept Selection

Intellectual Property
Regulatory Risks
Business Model

Prototyping

IMPLEMENT

Development Strategy

IP Strategy
Regulatory Strategy
Stakeholder Strategy
Marketing Strategy

Competitive Advantage


Development Plan

Manufacturing
Clinical Trials
Operations
Finance

Business Plan

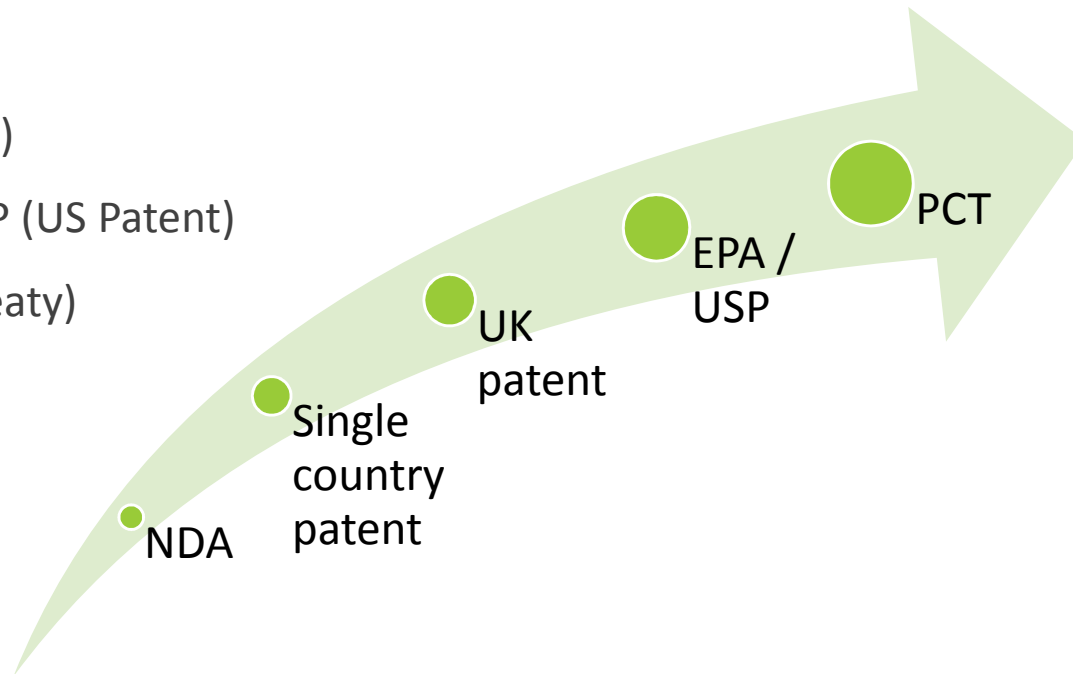
What could go wrong....?

Medical device start-up companies fail for one or more of the following reasons:

- addressing the wrong clinical need
 - unsuitable solution, or
 - inadequate execution.
- 

Protecting IP

- Non-disclosure Agreement (NDA) in all discussions with potential partners / suppliers / contractors
- Single-country patent
- UK patent (English language)
- EPA (European Patent) / USP (US Patent)
- PCT (Patent Cooperation Treaty)

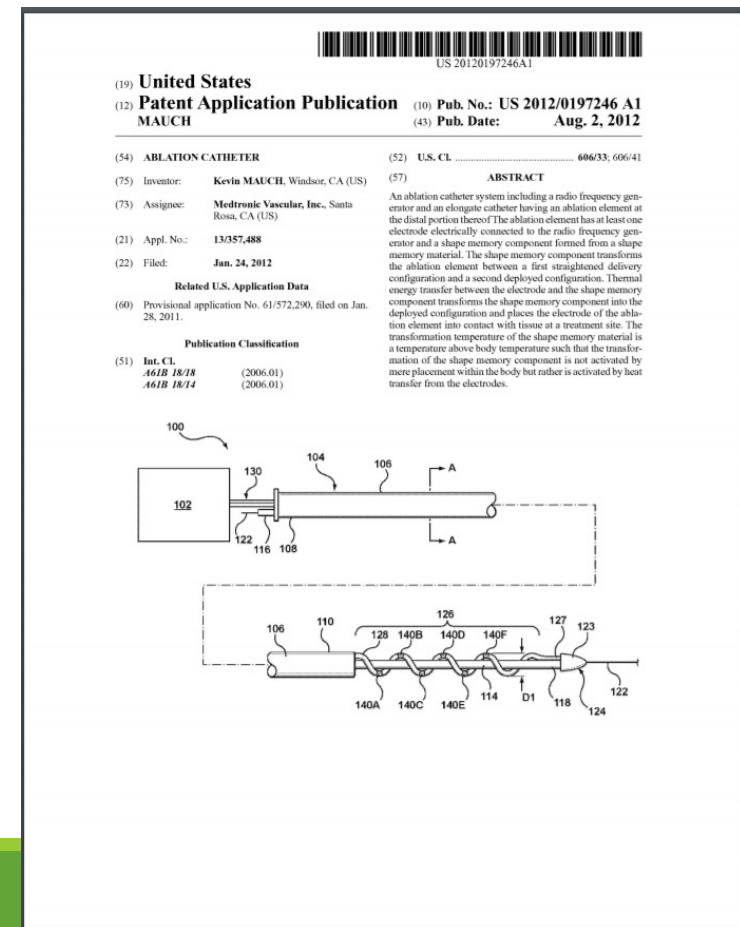


Characteristics of patents

- **Novelty:** An invention is not new and therefore not patentable if it was known to the public before the filing date of the patent application, or before its date of priority if the applicant claims priority of an earlier patent application.
- **Inventive step and Non-obviousness:** the invention is an adequate distance beyond or above the state of the art.
- **Inventorship / industrial applicability**
- **Patentable subject matter:** subject matter which is susceptible of patent protection. The laws or patent practices of many countries provide that certain subject-matter is excluded from patentability, even if the invention is novel and non-obvious (es. Algorithms).
- **Person skilled in the art**
- **Prior art:** all information that has been made available to the public in any form before a given date that might be relevant to a patent's claims of originality. If an invention has been described in the prior art or would have been obvious over what has been described in the prior art, a patent on that invention is not valid.
- **Utility:** an invention is "useful" if it provides some identifiable benefit and is capable of use.

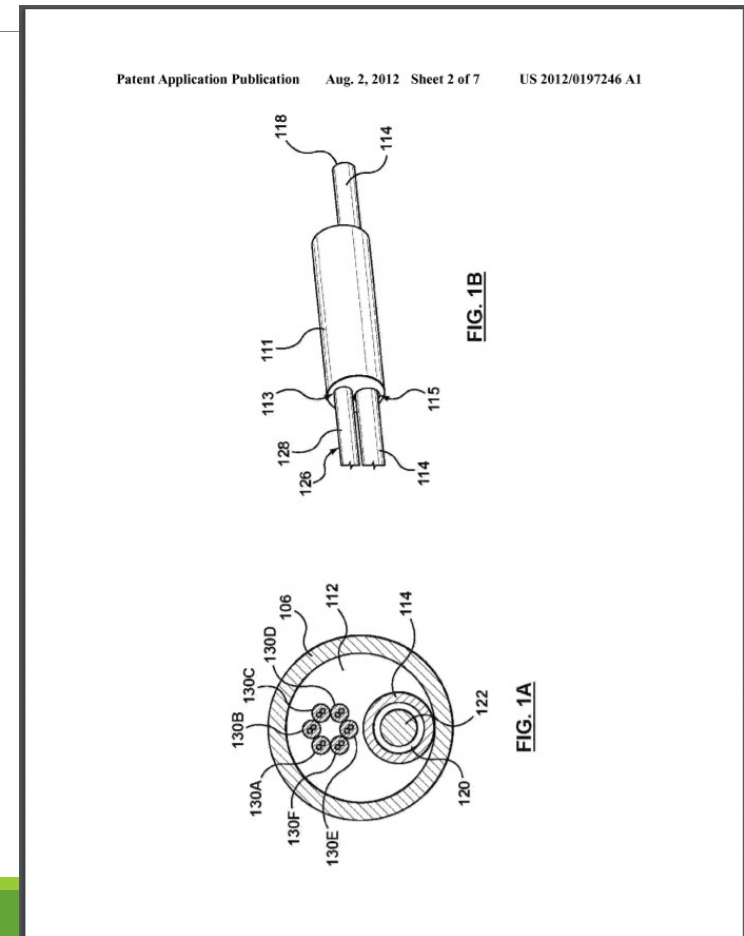
Writing a patent application

- **Language:** A patent is a legal document. It originates from a technical document (applicant) and is translated into a legal document (patent attorney).
- **It has to talk to everybody!**
- **Self-consistent**
- **Good skills are required to achieve a solid document from both parts, i.e. the applicant and the patent attorney.**




Writing a patent application

- **Figures:** clear, black and white, no shading. They must closely correspond to the text. Use as many as you need to clarify the concepts. But don't disclose more than you are intended to.



Key elements

- **Priority date**
 - **Balanced background**
 - **Clear understanding of the uncompromisable coverage to achieve**
 - **Start from broad and narrow down if requested**
 - **Main claim**
 - **Sub-claims**
- 
- A solid green horizontal bar spanning the width of the slide, located at the bottom.

Main claim / sub-claims

What is claimed is:

1. An ablation catheter system comprising:
an energy source; and
a catheter having an ablation element disposed at a distal portion thereof, the ablation element including,

at least one electrode electrically connected to the energy source and
a shape memory component formed from a shape memory material, wherein thermal energy transfer between the at least one electrode and the shape memory component transforms the shape memory component and thereby the ablation element from a straightened delivery configuration to a deployed configuration for placing the at least one electrode of the ablation element into contact with tissue at a treatment site.

Main claim

2. The ablation catheter of claim 1, wherein the catheter includes an outer shaft and an inner shaft and the ablation element extends between a distal end of the outer shaft and a distal end of the inner shaft.

3. The ablation catheter of claim 2, wherein a distal end of the ablation element is slidably coupled to the distal end of the inner shaft via a dual lumen sleeve.

4. The ablation catheter of claim 1, wherein the ablation element further includes an insulating component disposed between the at least one electrode and the shape memory component to electrically isolate the at least one electrode from the shape memory component, the insulating component being formed of a material that allows the thermal energy transfer between the at least one electrode and the shape memory component.

Sub claims

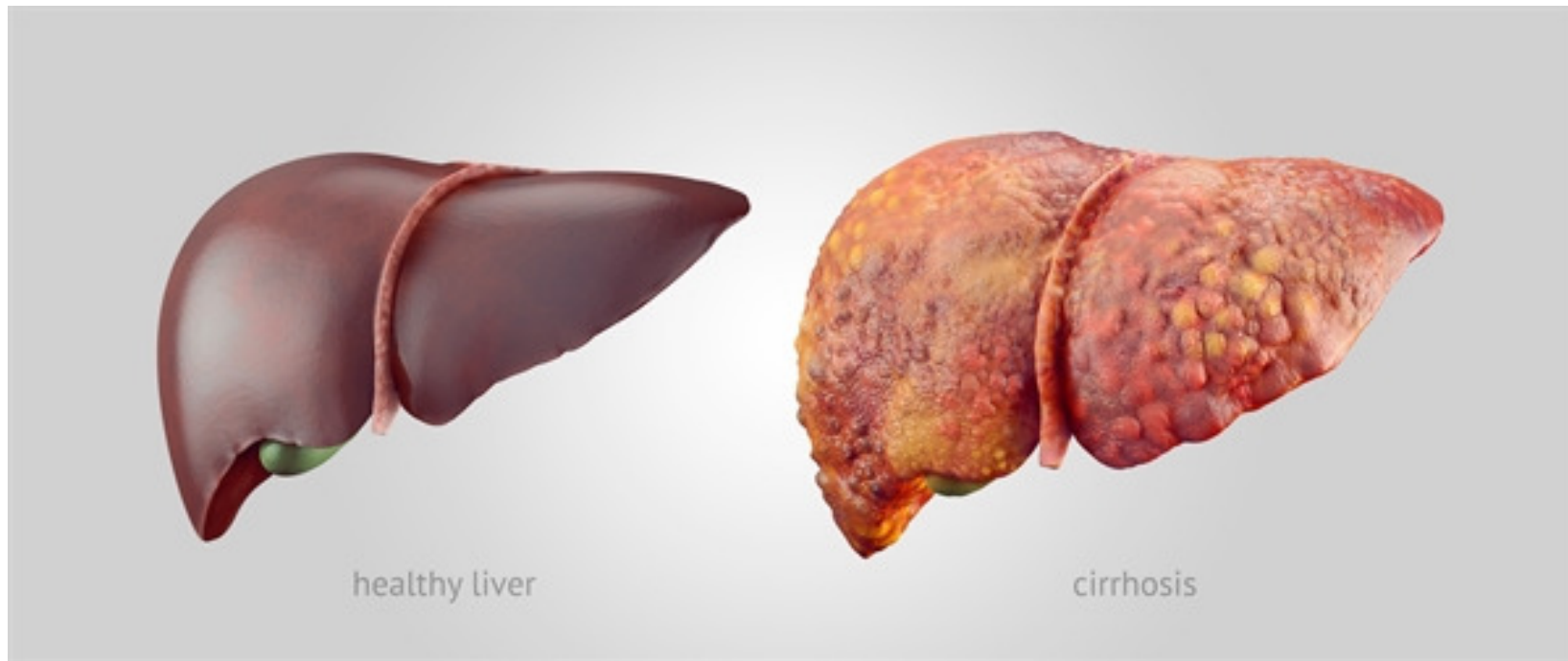
A case study:

“A better way to endoscopically treat gastroesophageal varices
in a single intervention that reduces the risk of rebleeding”

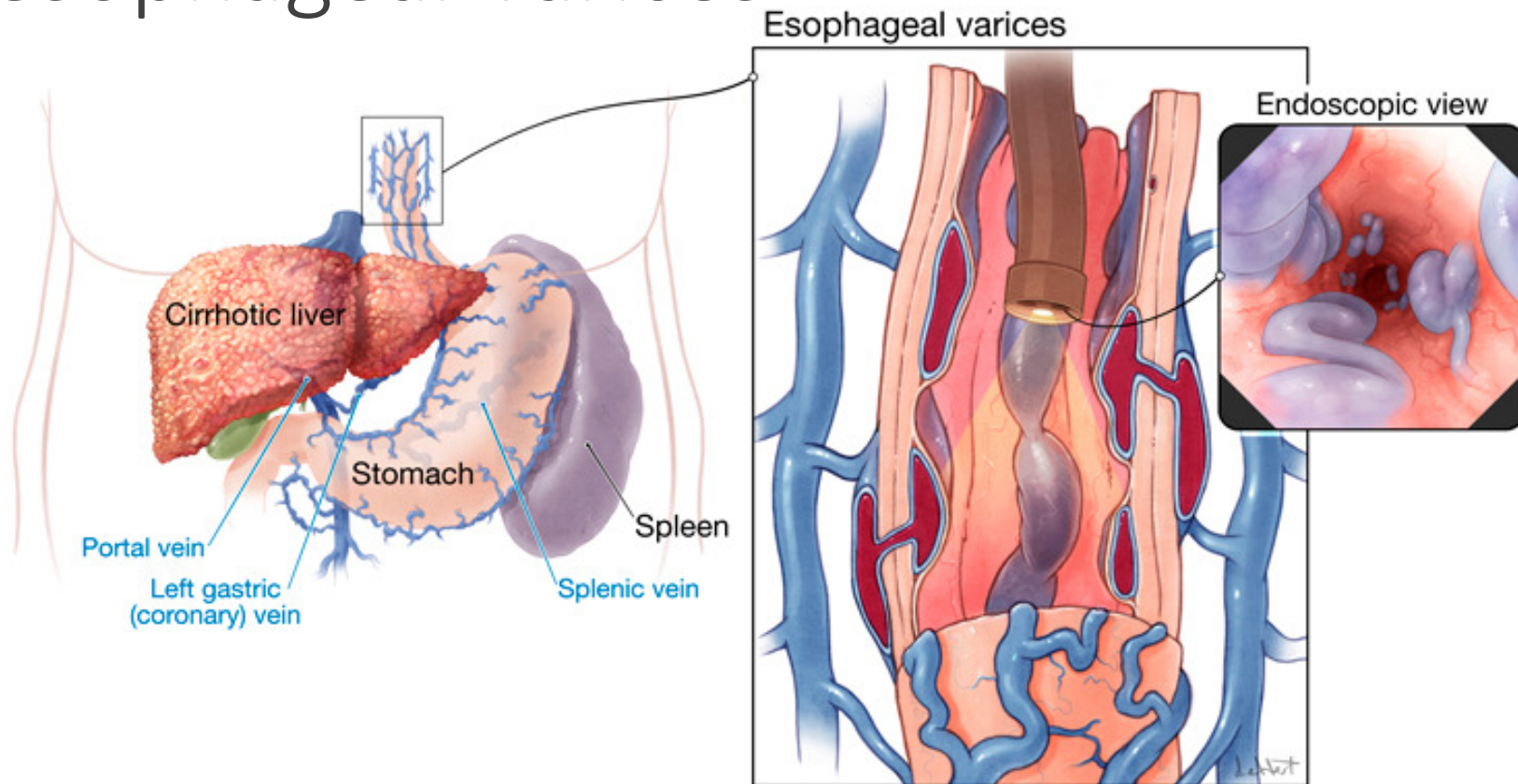
Background



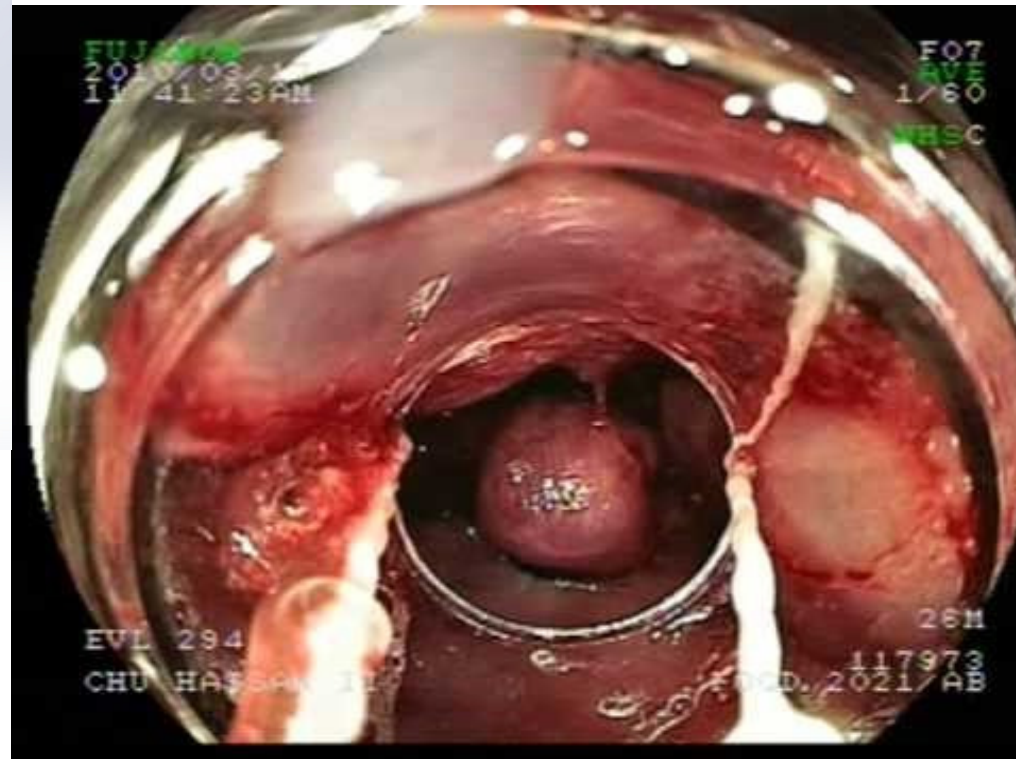
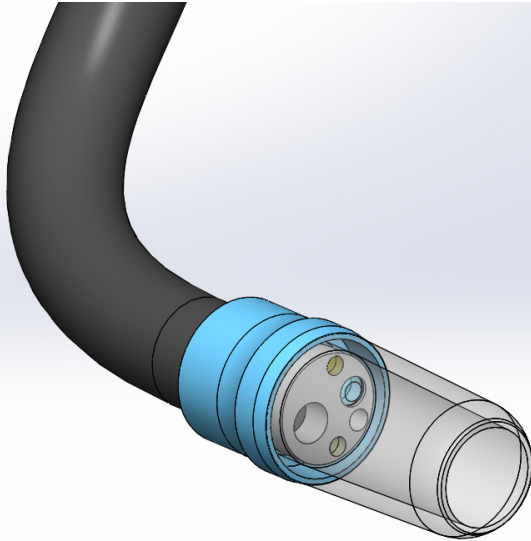
Liver Cirrhosis



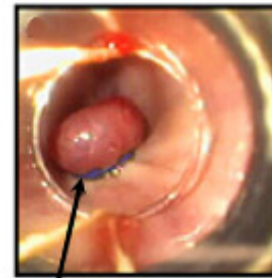
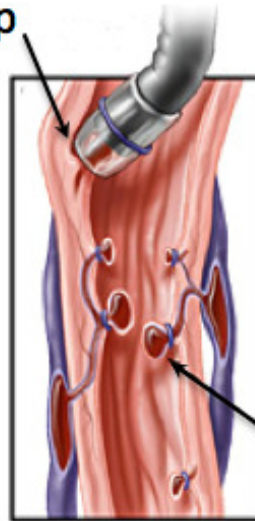
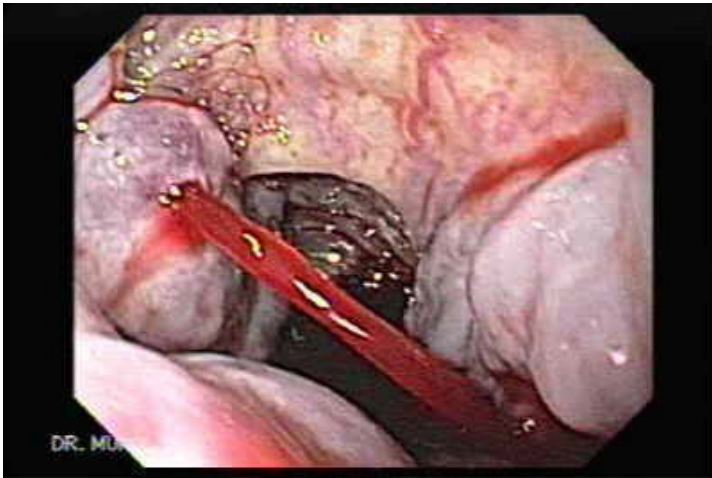
Oesophageal Varices



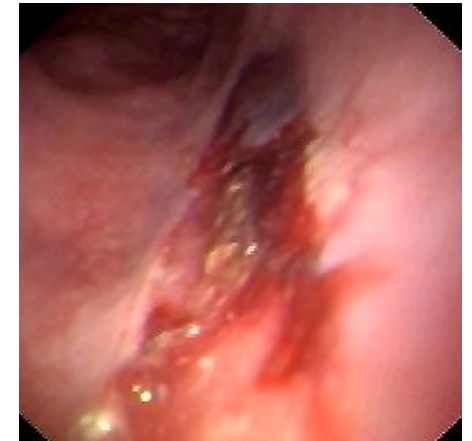
Band Ligation



Scope used to
capture target
varix in cap

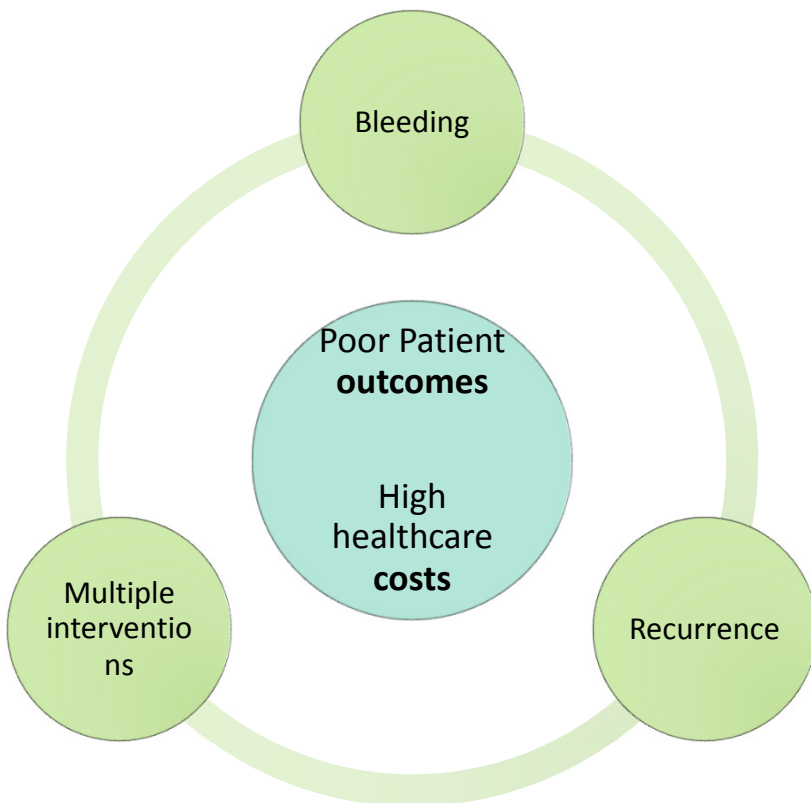


Band delivered to
occlude varix



20-30% Mortality rate

The Problem:



Cost:

2-4 interventions
Bleeds in varices awaiting treatment

Safety:

12% of patients rebleed after banding
Rebleeds result in 4x increase in cost and length of stay

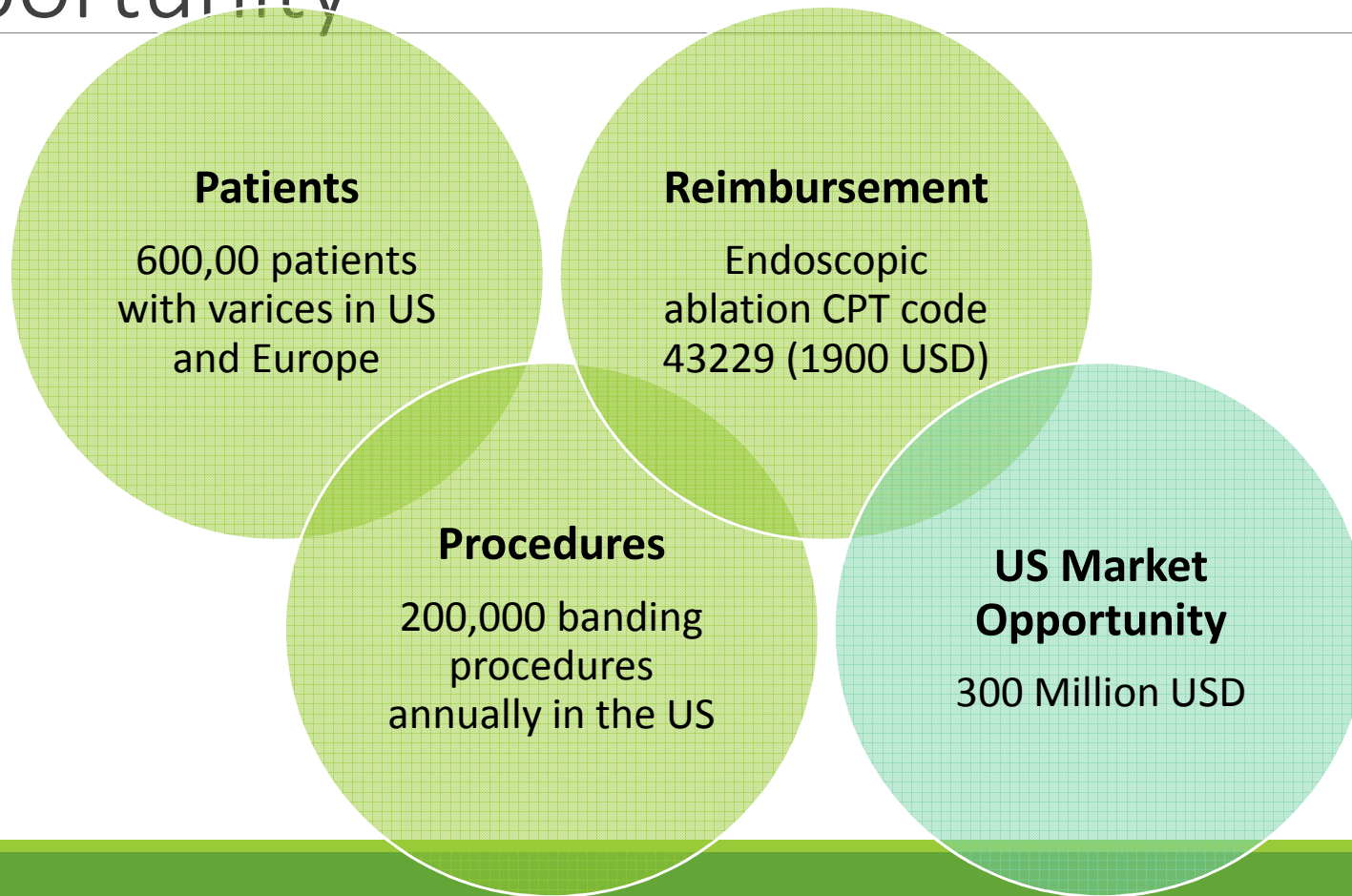
Efficacy:

Average treatment takes 50 days
Recur in 75% of patients 2 years after banding

The clinical need

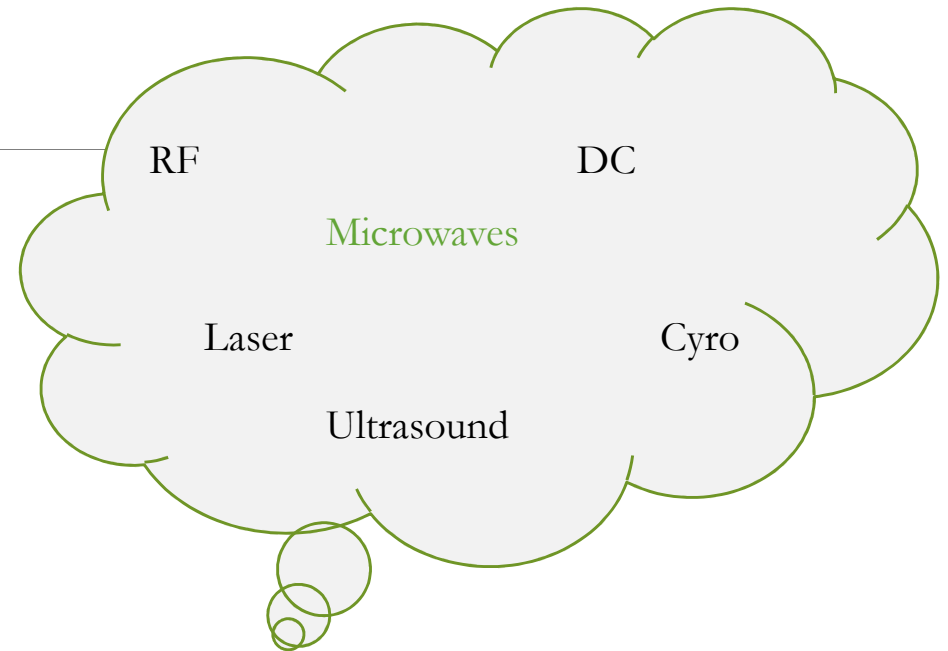
“A better way to endoscopically treat gastroesophageal varices in a single intervention that reduces the risk of rebleeding”

The Opportunity



Why MWs?

- Direct heating
- Speed
- Penetrates through tissue
- Effective at heat sinks
- Sparing of surface tissue
- Not affected by tissue heterogeneity
- Endoscopic delivery



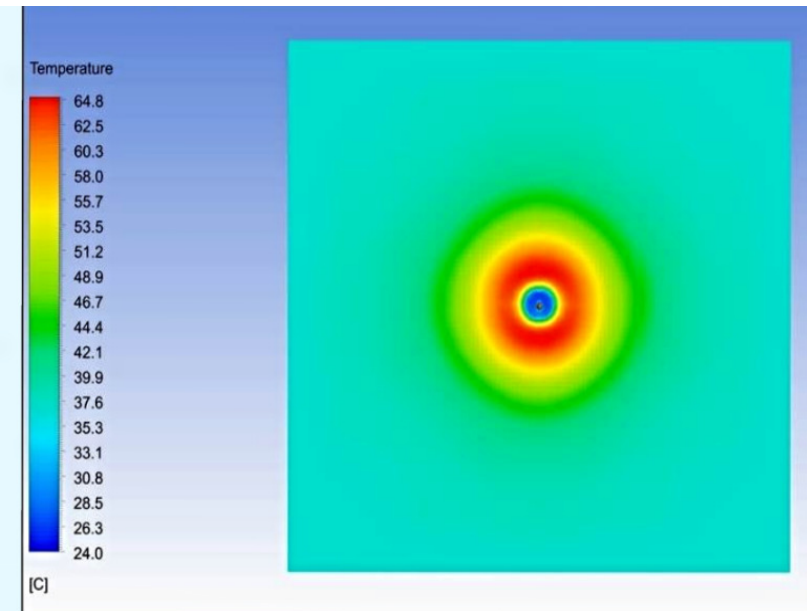
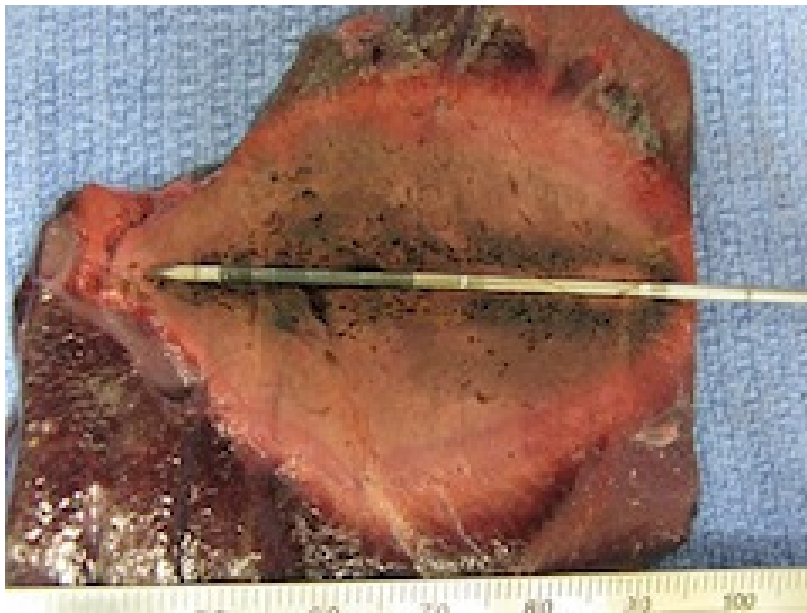
Competitive treatments

- Drug therapies, e.g. non-selective beta blockers, are sub-optimal (efficacy 40%) and have numerous side effects
- Endoscopic Sclerotherapy
 - Largely abandoned in favour of Endoscopic Band Ligation
- Endoscopic Band Ligation
 - Multiple suppliers – Boston Scientific, Cook Medical, Conmed, numerous me-too suppliers
 - Little differentiation
 - 2-4 interventions per patient, average treatment takes 50 days
 - Bleeds in varices awaiting treatment
 - 12% of varices rebleed due to ulceration caused by banding
 - 75% of varices recur within 2 years post banding
- Endoscopic Ultrasound mediated therapies
 - Glue and coils
 - Suitable for gastric varices and not oesophageal varices
 - Opportunity for MW ablation via EUS

Technical challenges

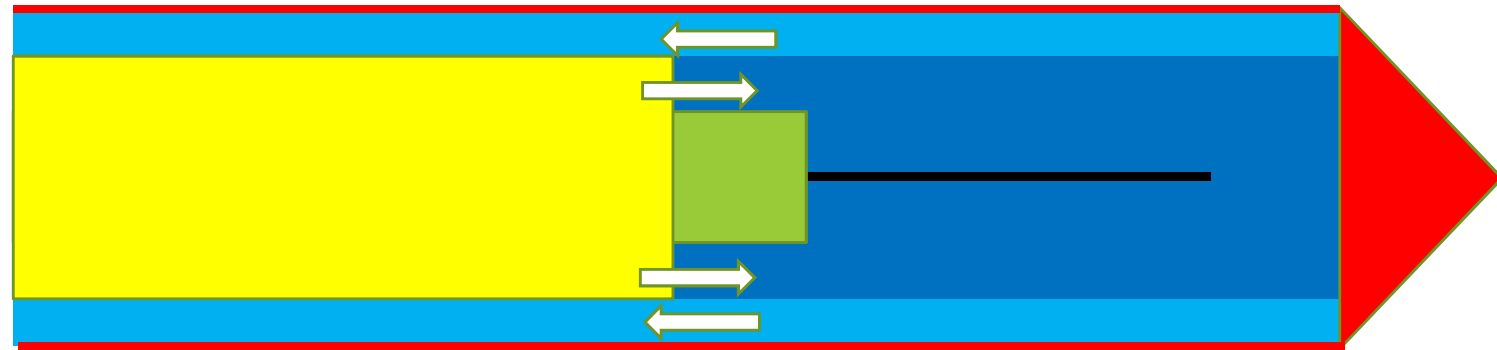
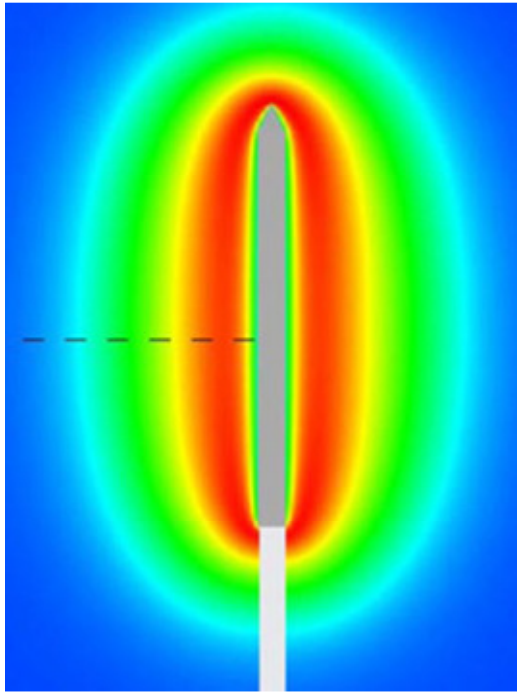
- Fast treatment duration
- Effective treatment on targeted tissues
- Safe on untargeted tissues
- Highly controllable
- Negative feedback system

Antenna design: the microwave liver ablation case



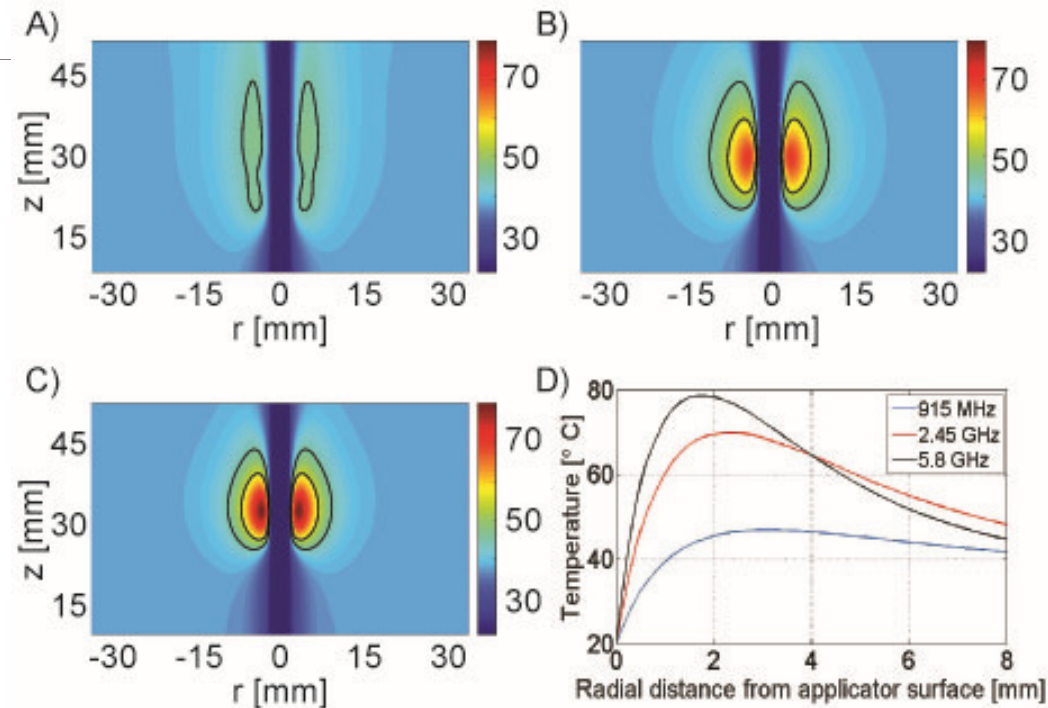
Omnidirectional ablation zone
“Chimney” effect in proximity of large vessels
“Comet-shaped” ablation zone

Omnidirectional antenna design: the cooled monopole



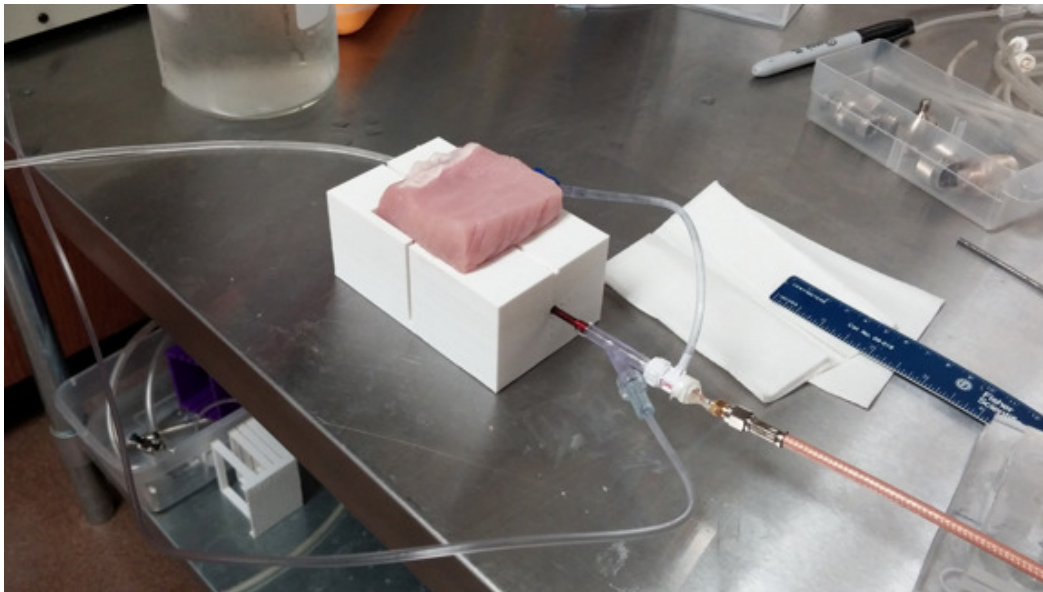
- “Spherical” heat zone
- Preventing back heat propagation on the feeding cable (tear-drop effect) by using a choke or triaxial cable
- Miniaturisation (minimum diameter)
- Mechanical robustness
- Restricted to medical grade materials and assembly

Omnidirectional antenna design: the operating frequency



Comparison of temperature profiles in tissue after 40 s for A) 915 MHz, B) 2.45 GHz and C) 5.8 GHz. Solid black lines highlight the areas of temperature higher than 45°C (outer black line) and 55°C (inner black line). Subplot D) shows linear temperature profiles for each frequency in radial cuts where maximal temperature is achieved

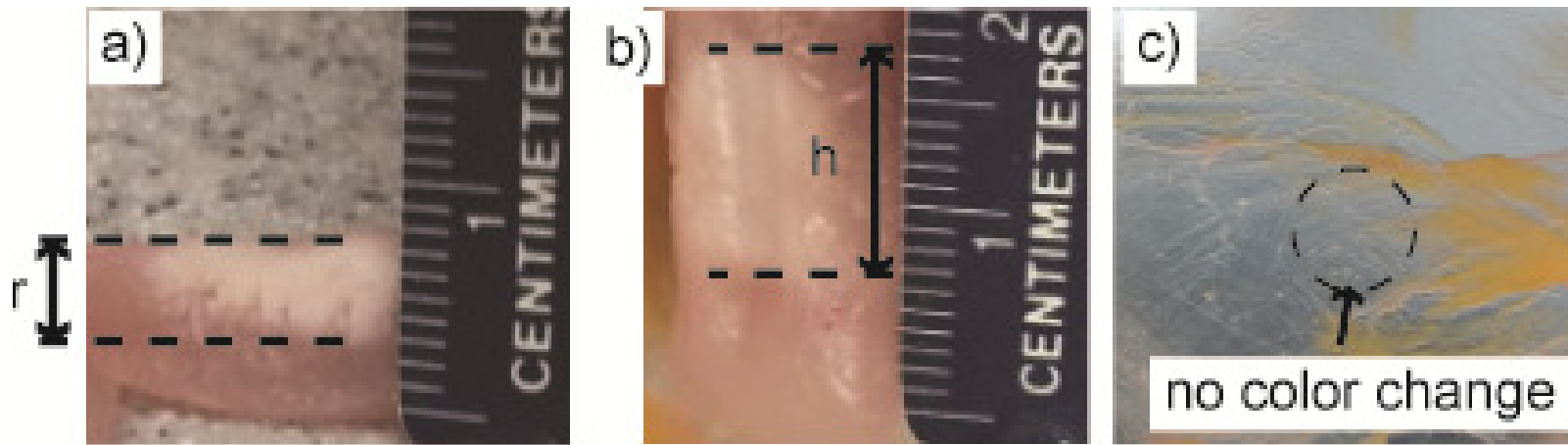
MW Applicator Development



Bench testing at KS with MW antenna

- Can we ablate tissue using MWs?
 - Time / power required
 - Optimum frequency
 - Suitable antenna for use with endoscope cap
- Can we ablate while preserving the mucosa?
- Can this system be used to treat varices?
 - Coagulate blood
 - Collapse vessel

Sparing the mucosa

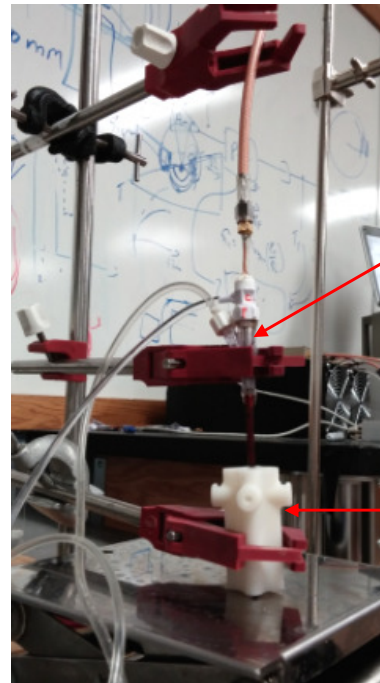


a) Radial ablation extent " r ", b) Axial ablation extent " h ", c) Mucosa layer after experiment

Benchtop Testing



Test specimen

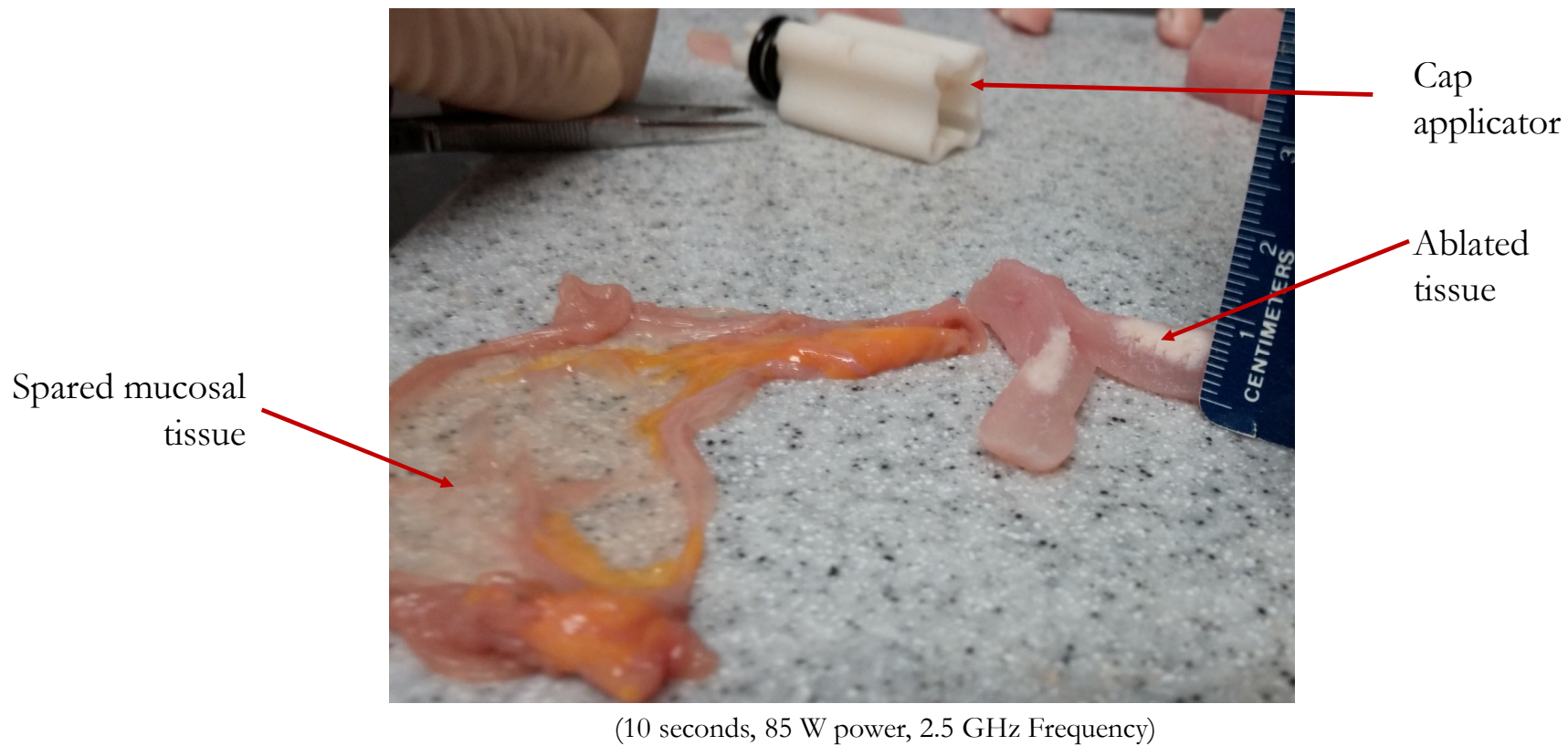


Antenna

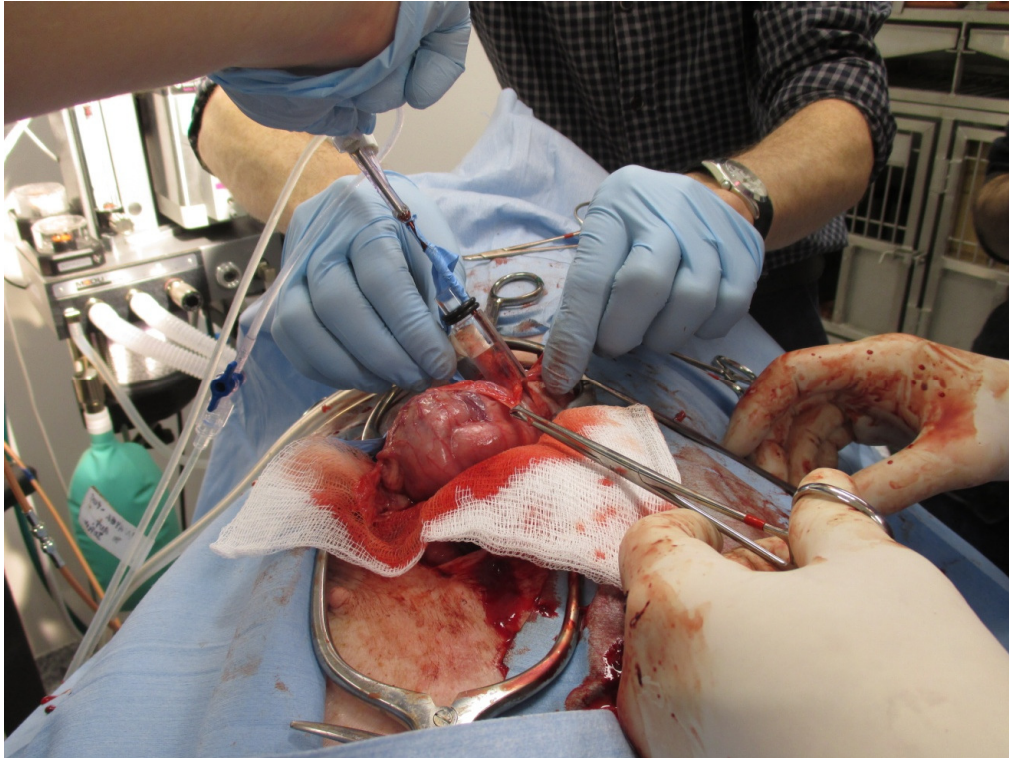
Test cap

Bench testing arrangement

Results of Tissue Ablation

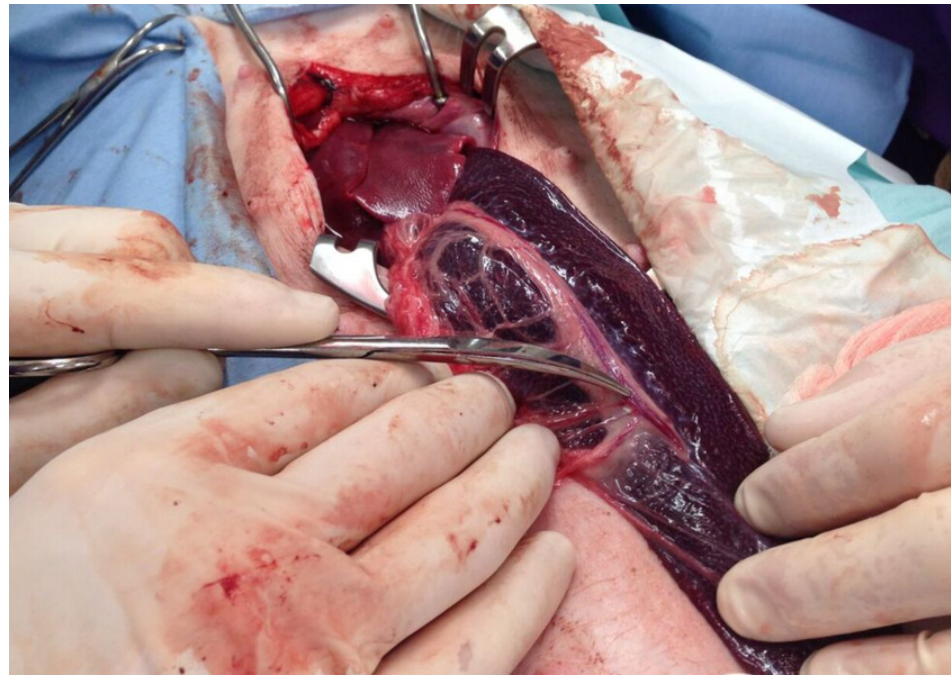


In-vivo testing: porcine splenic vein



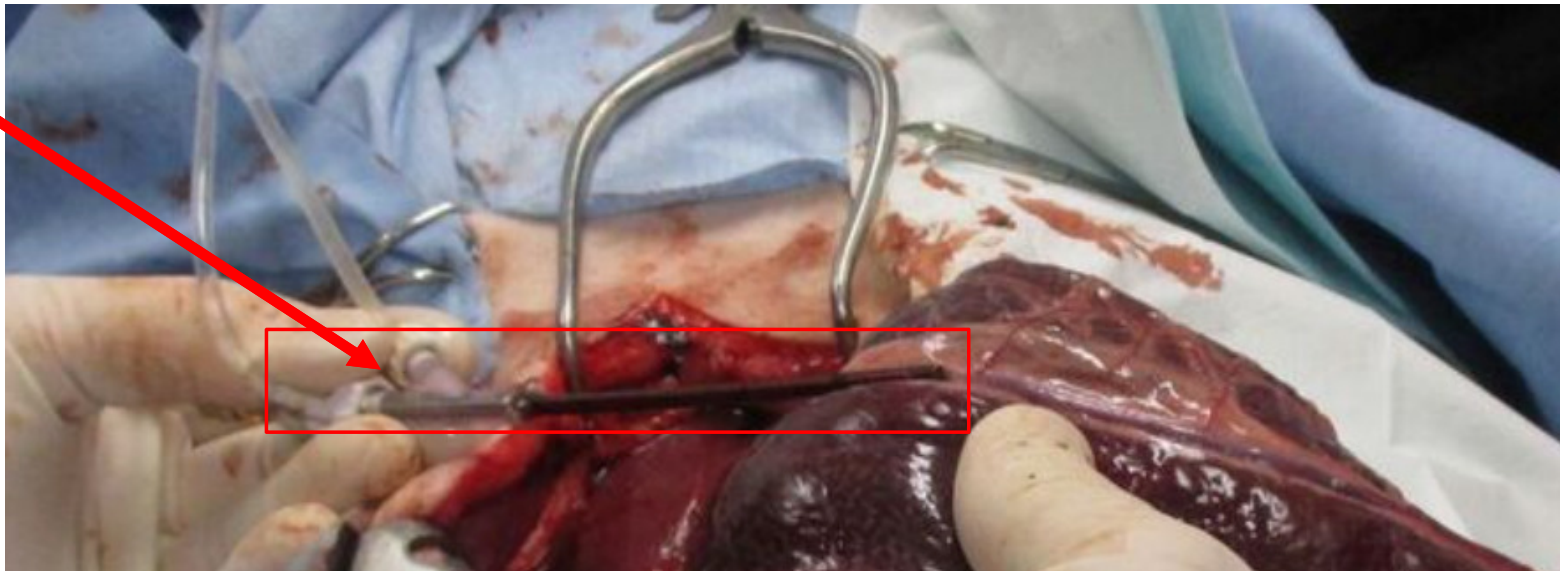
- Plan in advance
- Find the right institution and the right team
- Define an appropriate model
- Define a balanced experimental protocol. The rationale of the experiment must be very clear to the ethical committee

Porcine splenic vein



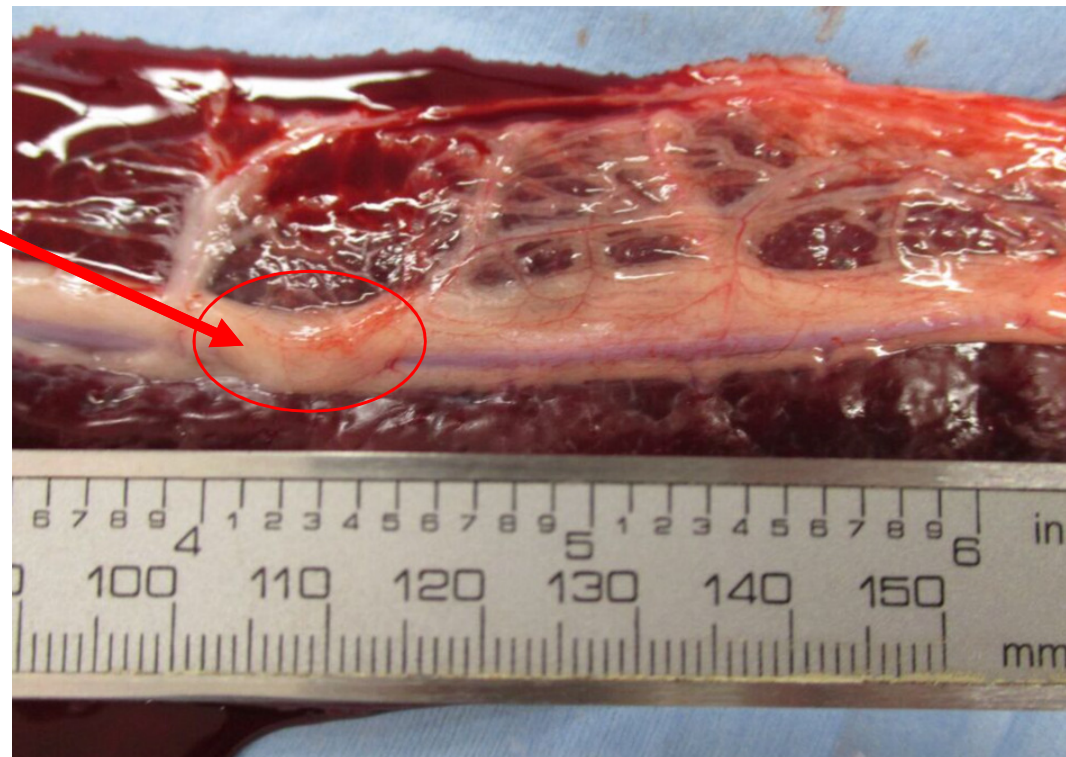
Ablation process

MW probe

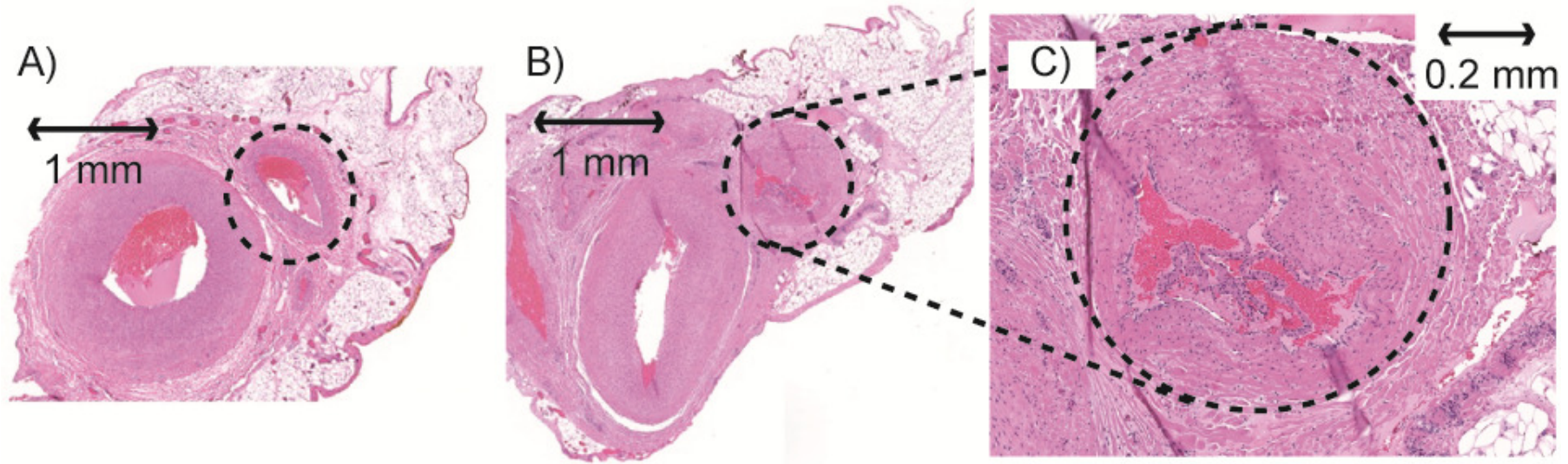


Results

Ablation

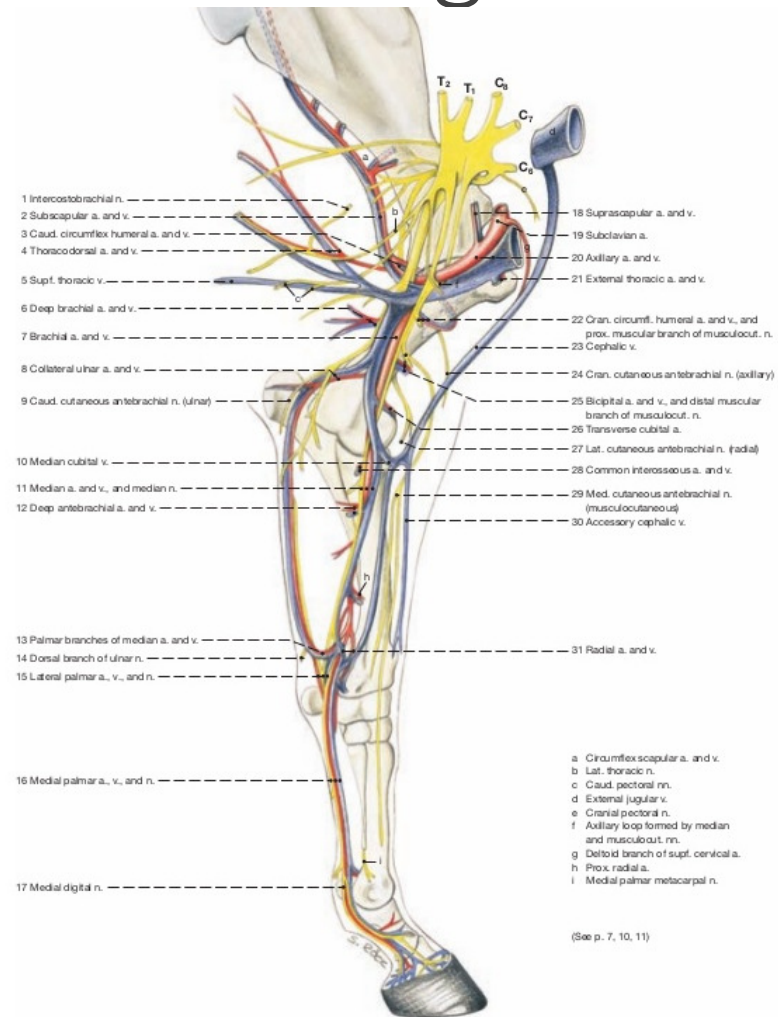


In-vivo testing: splenic vein in pig



Histopathology images of porcine vein, which was A) left intact and B), C) thermally sealed

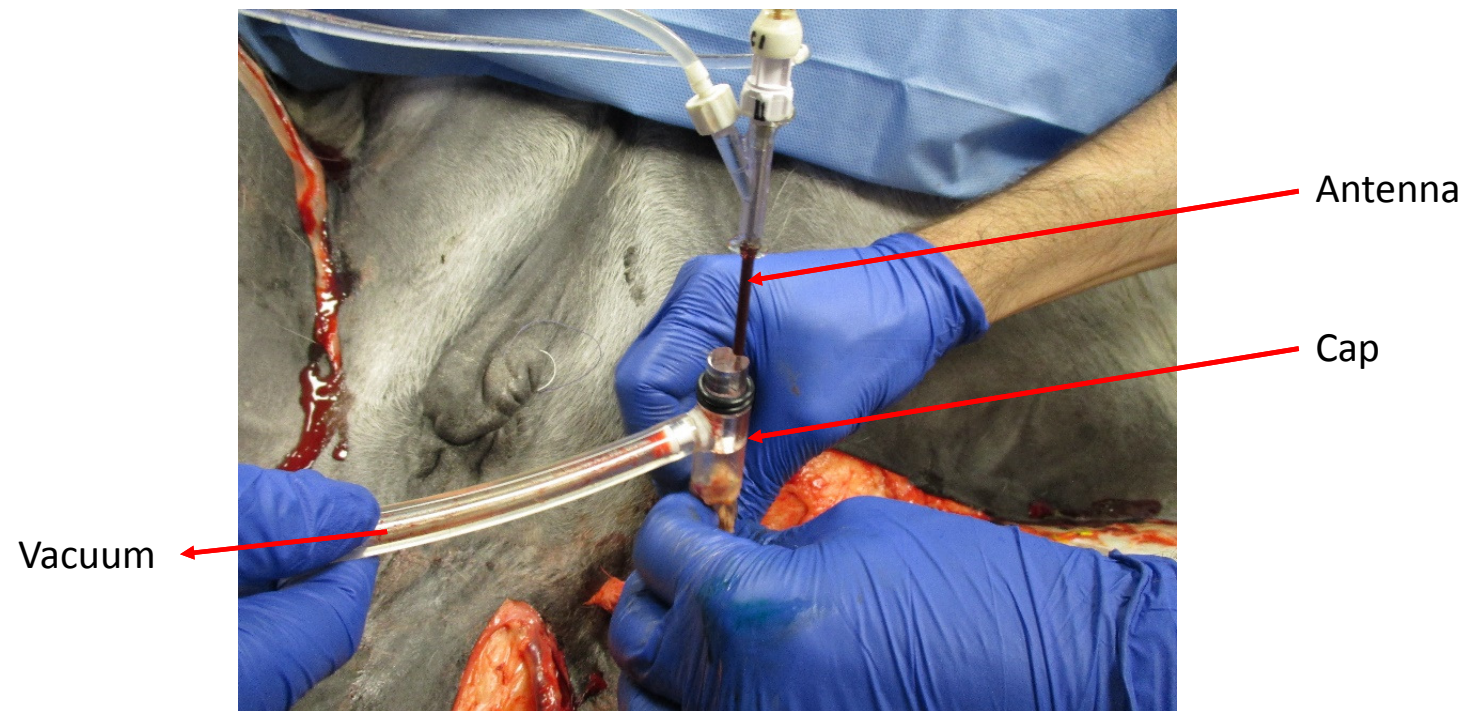
Ex vivo equine model: inguinal veins



Ex vivo equine model: inguinal veins



Ablation using cap



Results



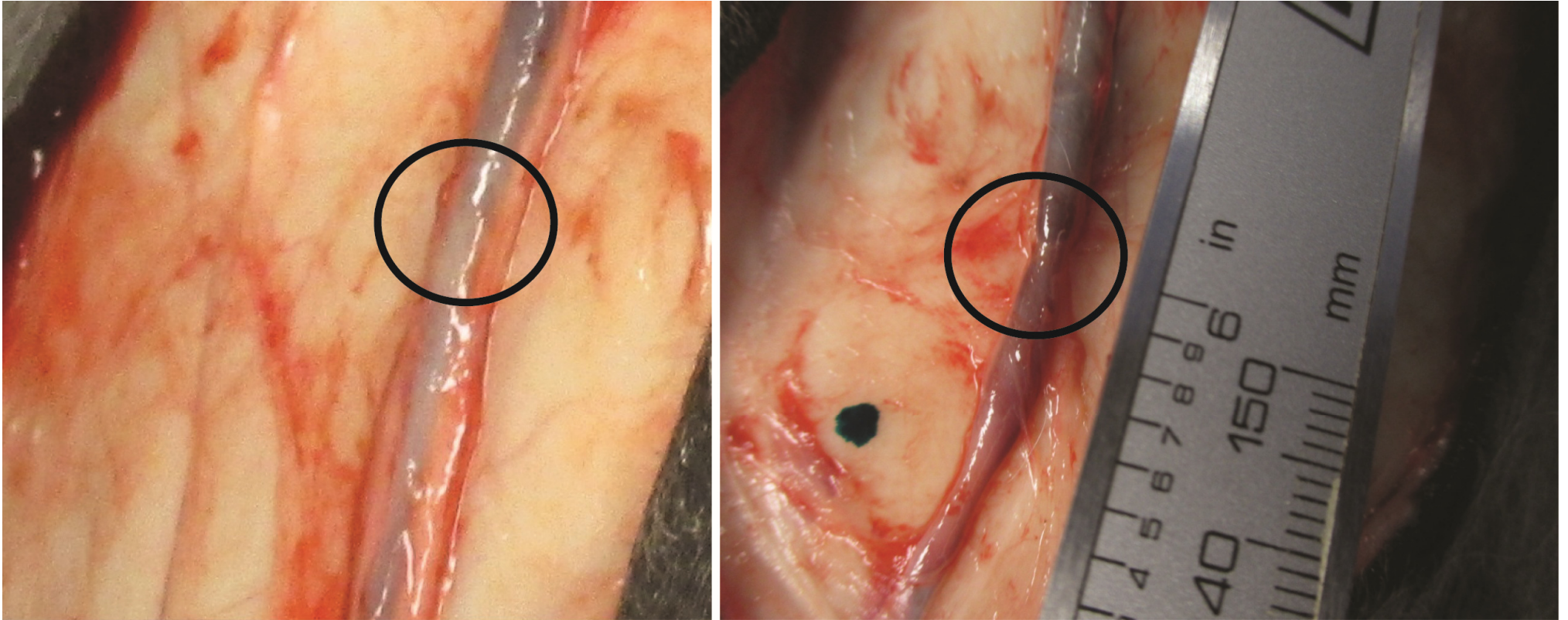
Ablation zone

30 seconds

85 w

2.45 GHz

Ex vivo equine model: inguinal veins



Ex vivo experiment on horse before and after 10 s ablation (location marked by a circle)

Target market validation

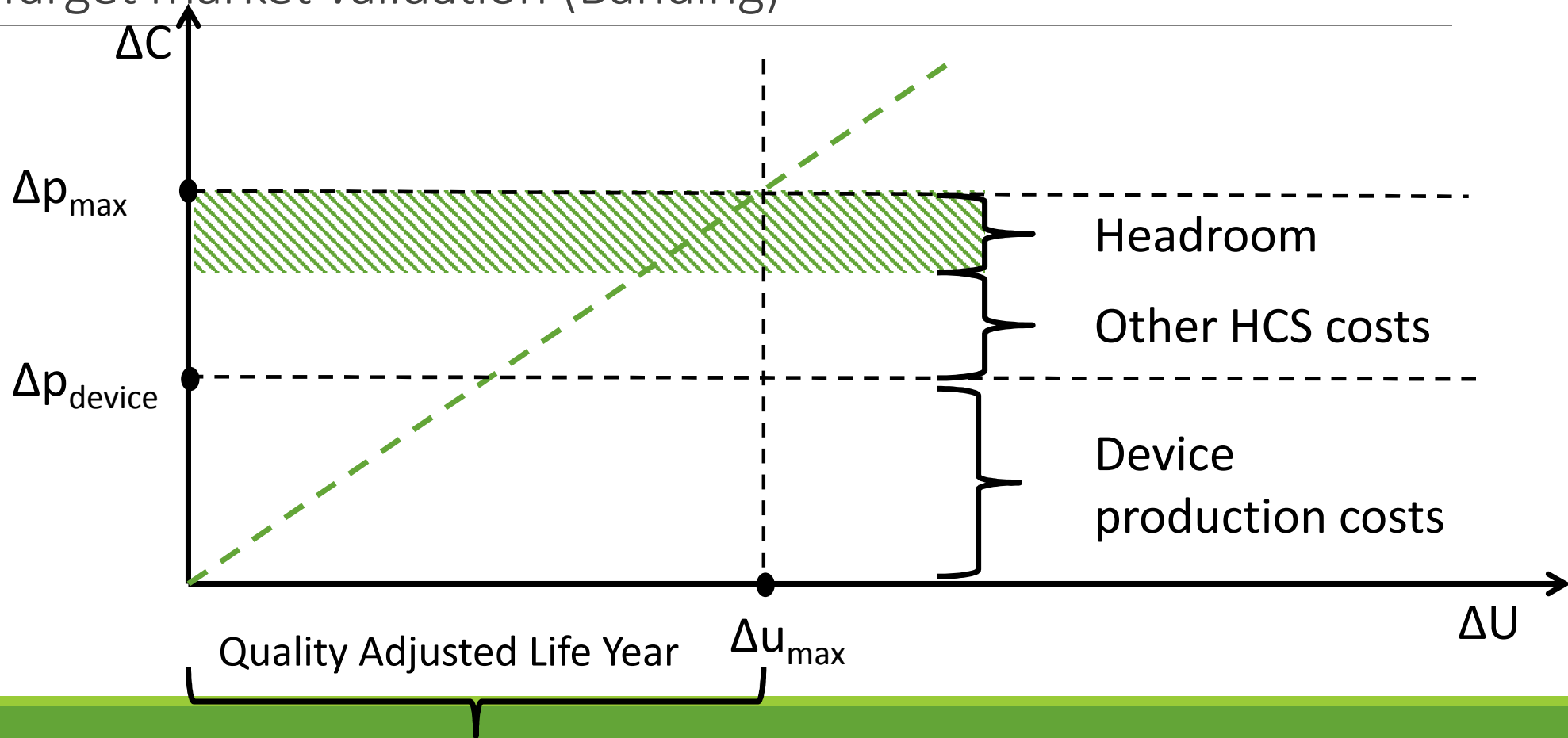
- 600,000 patients with varices in US and Europe (clinical literature review)
- 200,000 banding procedures annually in the US (Millennium Research Report 2014)
- Well established and growing market
- Growing trends in new procedures such as ESD and EUS requiring new ablation/haemostasis devices
- Thermal Ablation of the upper GI tract is experiencing CAGR of 10%-30%
- Total Market 200k x \$1000 ASP = \$200M

Target market validation

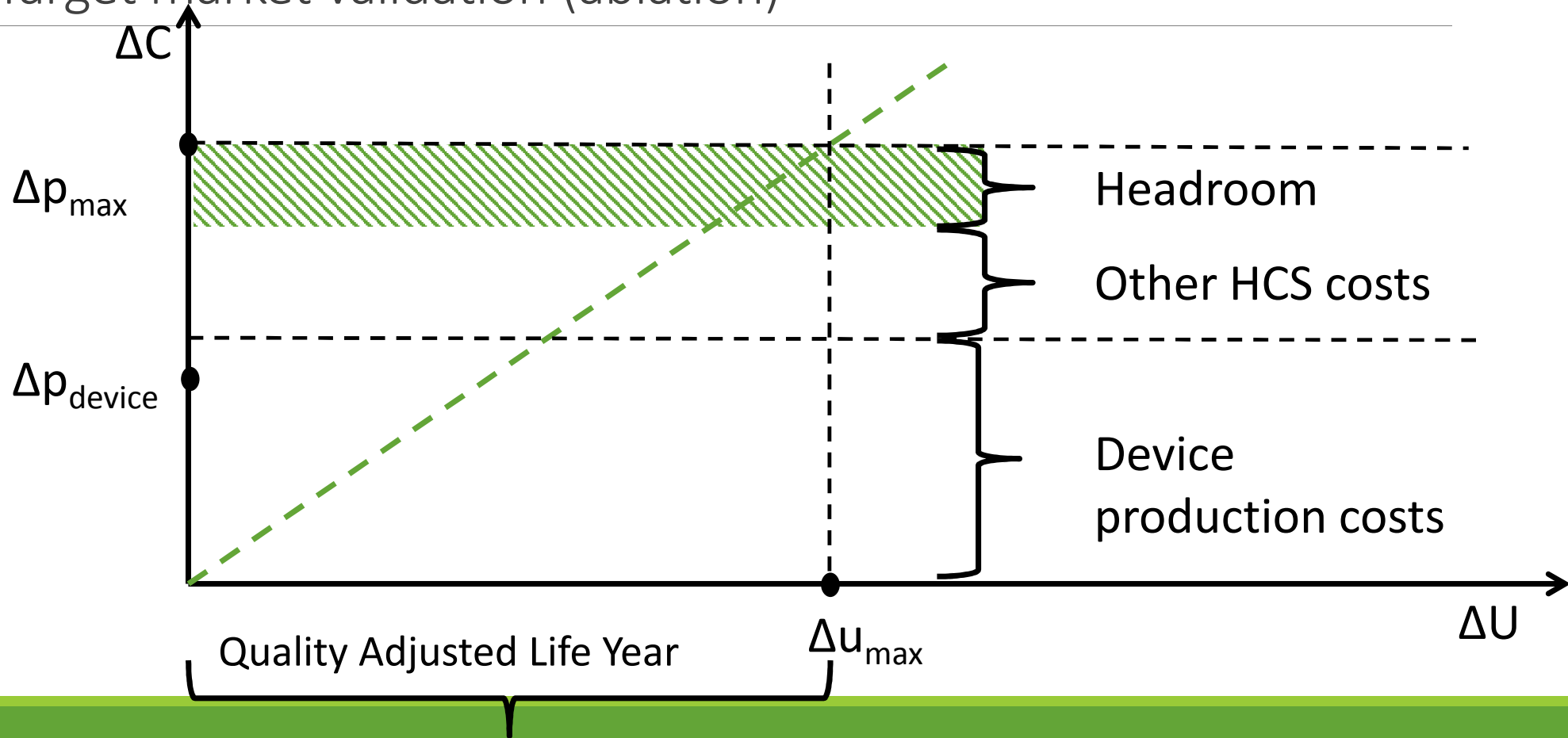
- Reimbursement assessment complete
 - Ablation reimbursement available
 - CPT 43229 = \$1980
 - 2x approx. banding reimbursement

CPT Code	Description	Physician ¹	ASC	Hospital – Medicare Natl OPPS	
				APC / Status ²	Payment
Esophageal Varices					
43229	Esophagoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)	\$213.04 (F) \$733.99 (NF)	\$1,107.43	5303 / T	\$1,980.43
43243	Esophagogastroduodenoscopy, flexible, transoral; with injection sclerosis of esophageal/gastric varices	\$254.93	\$416.80	5301 / T	\$745.36
43244	Esophagogastroduodenoscopy, flexible, transoral; with band ligation of esophageal/gastric varices	\$263.88	\$608.39	5302 / T	\$1,088.00

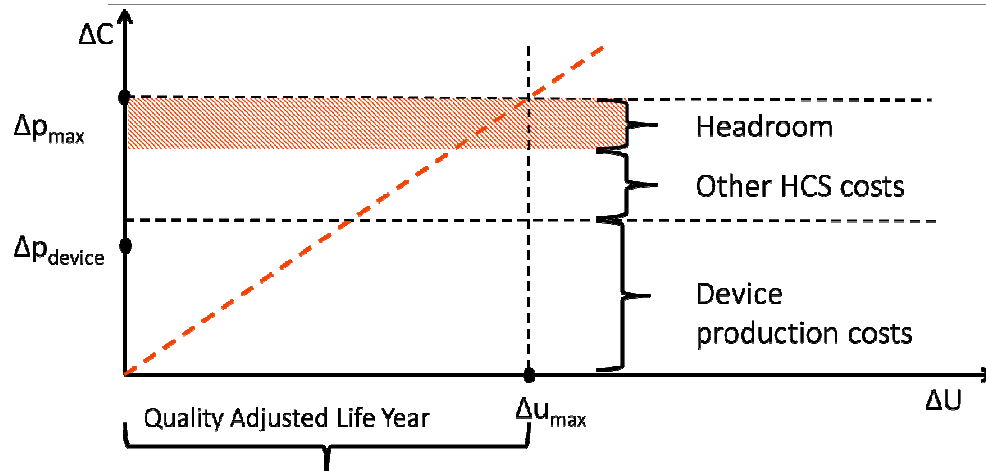
Target market validation (Banding)



Target market validation (ablation)



Target market validation (ablation)



- Is this headroom sufficient?
- Satisfactory ROI?
- Worth of investing?
- **Are other possible clinical applications with higher incremental cost-effectiveness ratio?**



Device adaptation for EUS treatments (pancreas and lung cancer)

