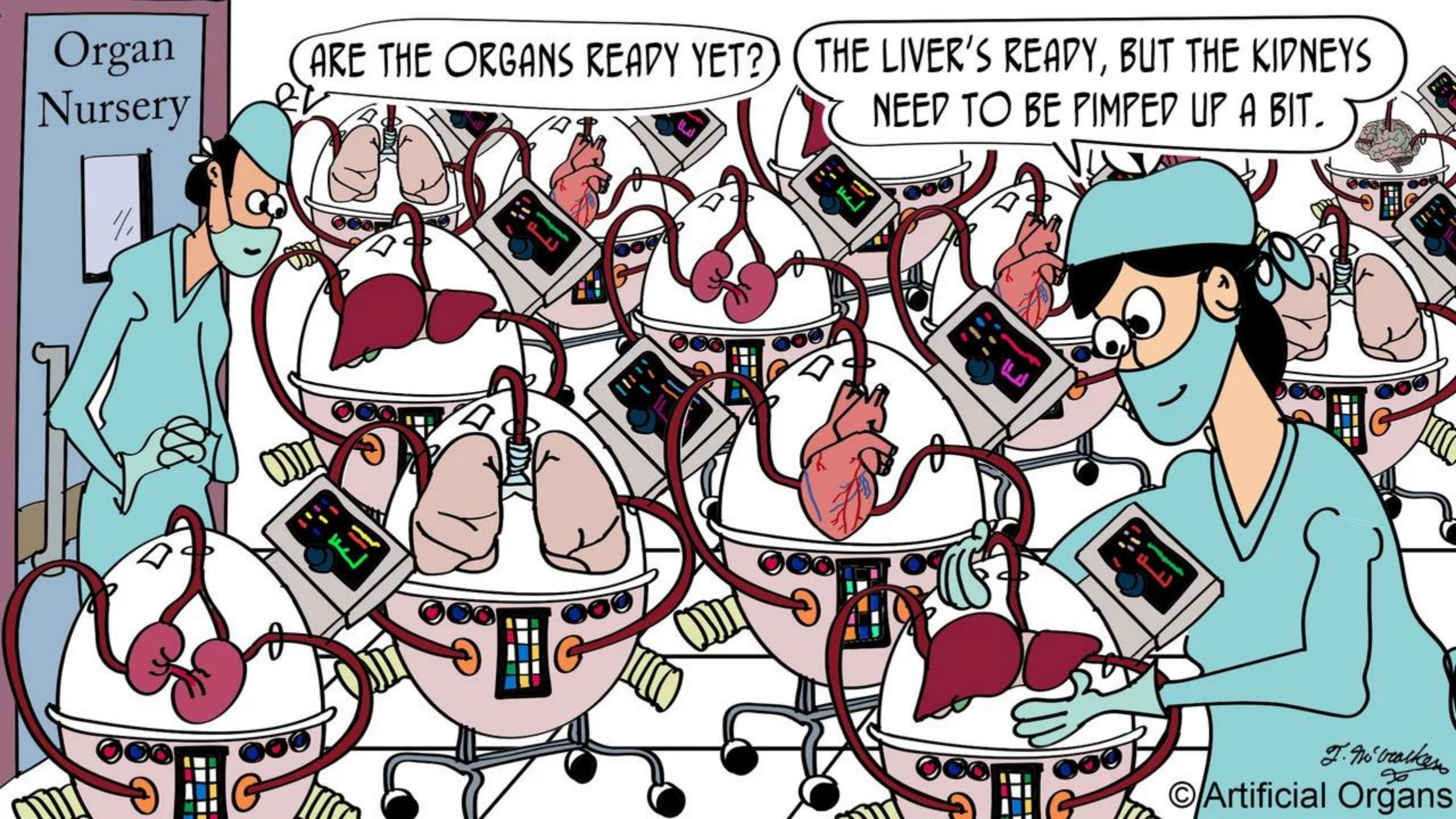
Hypothermic Machine Perfusion of Liver Grafts prior to Transplantation

Xavier Muller, *Guillaume Rossignol, Antoine Breton, Joris Couillerot*

Department of Surgery and Transplantation,
Croix Rousse University Hospital


Organ Nursery
ARE THE ORGANS READY YET?
THE LIVER'S READY, BUT THE KIDNEYS NEED TO BE PIMPED UP A BIT.
T. McCrackens
©Artificial Organs

1

1

2

Transplantation

1

NO OXYGEN

2

Transplantation

Nasralla et al, Nature 2018

1

NO OXYGEN

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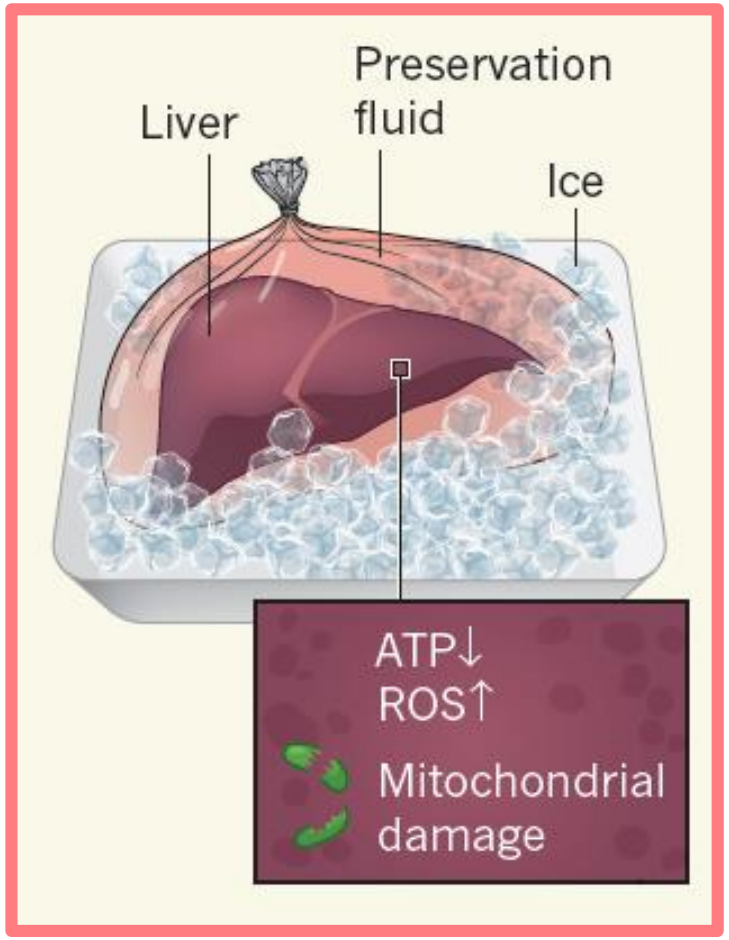
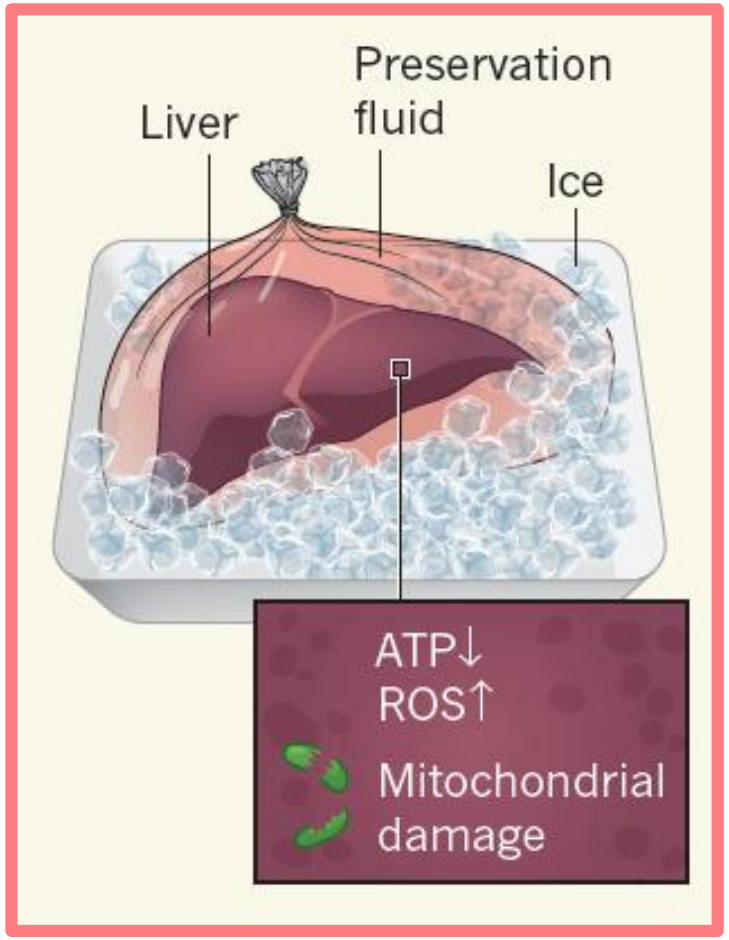
Transplantation



Nasralla et al, Nature 2018

1. Ischemia

NO OXYGEN



Transplantation

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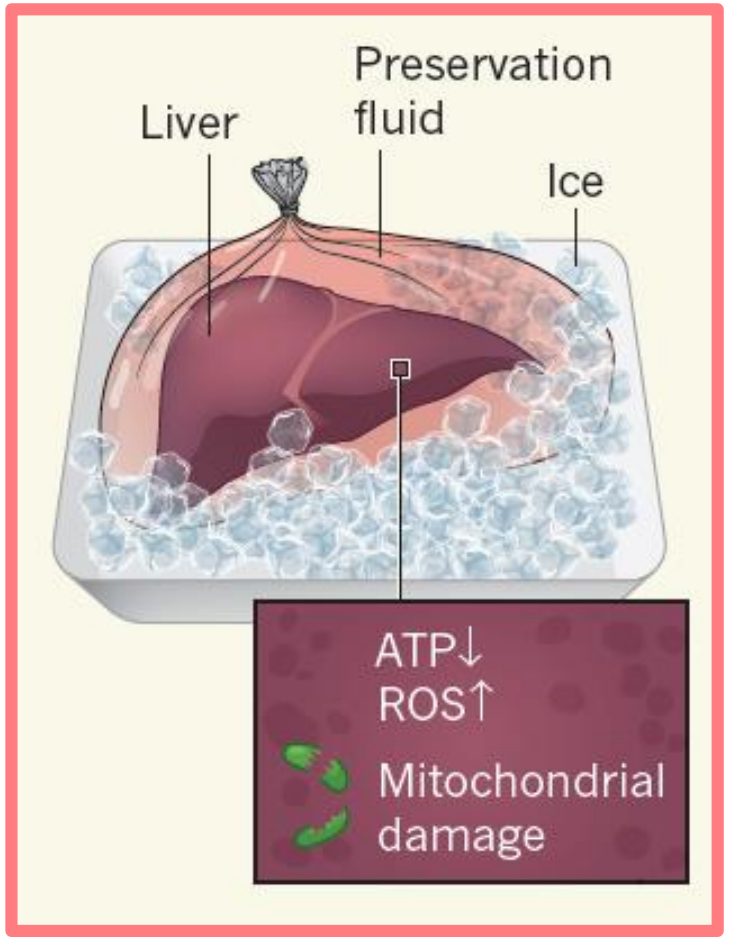

2. Reperfusion

Transplantation

Nasralla et al, Nature 2018

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Ischemia-Reperfusion Injury

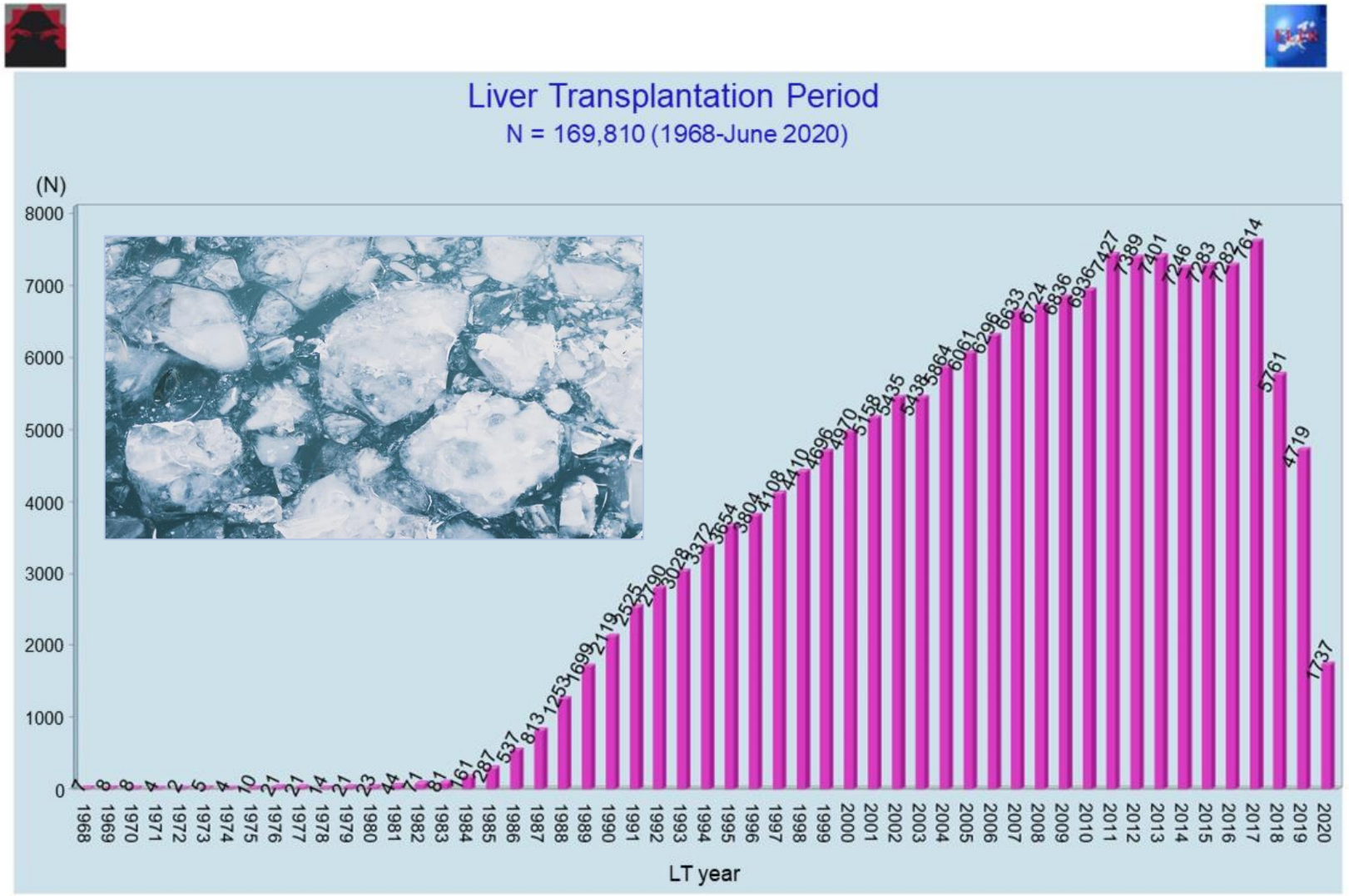
2. Reperfusion

Transplantation

Nasralla et al, Nature 2018

Does Static Cold Storage Work?

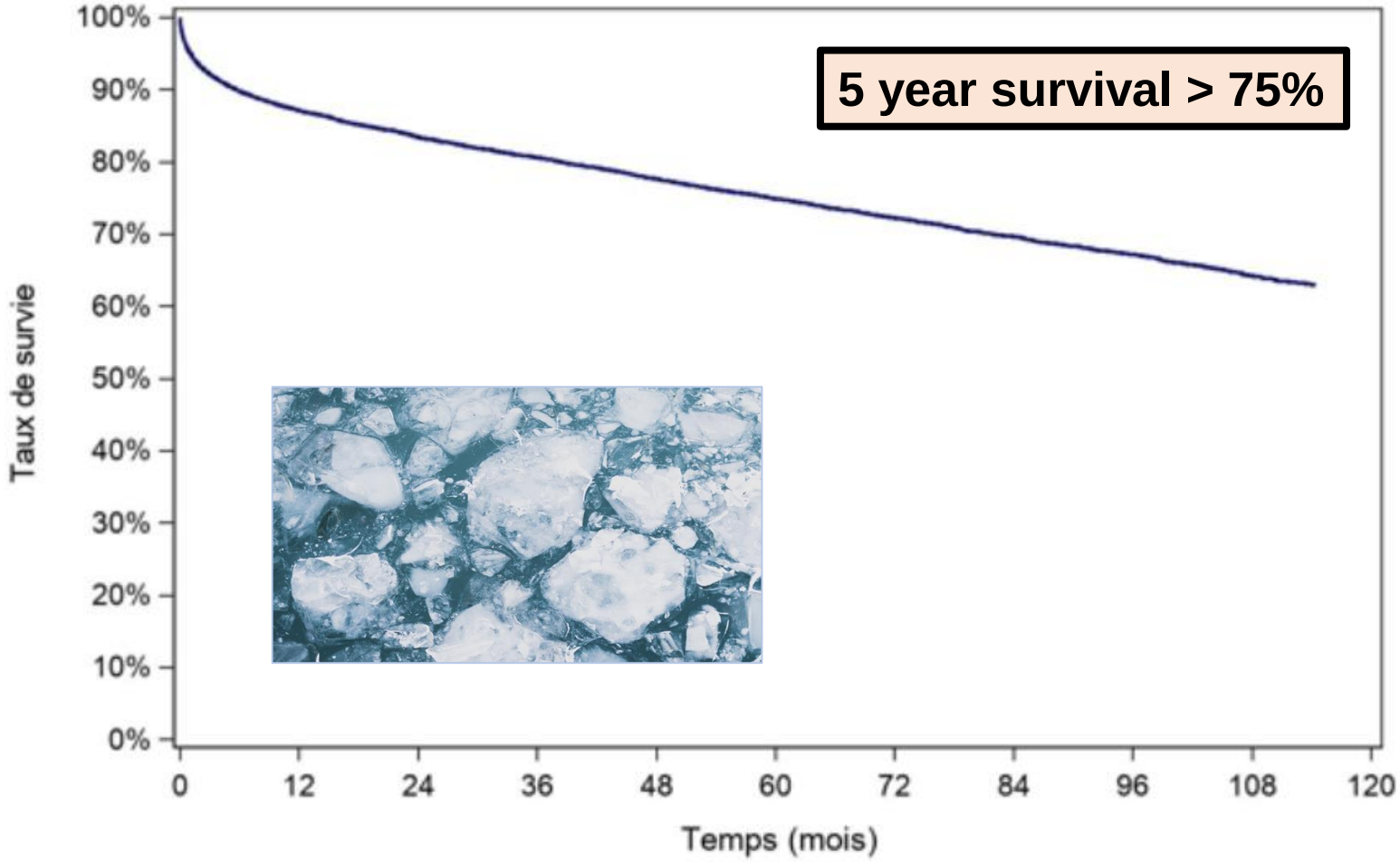
Does Static Cold Storage Work?



ELTR Registry

Does Static Cold Storage Work?

Figure F5. Survie globale du receveur après greffe hépatique (2007-2019)



Données ABM

Do we need Dynamic Graft Preservation?

Research article JHEP|Reports

Should we use liver grafts repeatedly refused by other transplant teams?

2020

Authors
Audrey Winter, Paul Landais, Daniel Azoulay, Mara Disabato, Philippe Compagnon, Corinne Antoine, Christian Jacquelinet, Jean-Pierre Daurès, Cyrille Féray

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- Older donors
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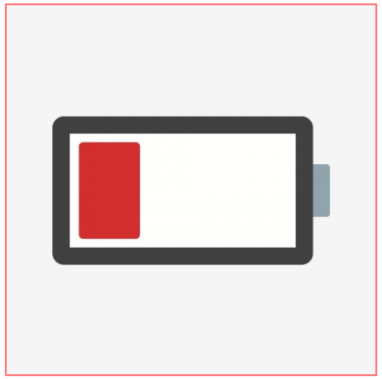

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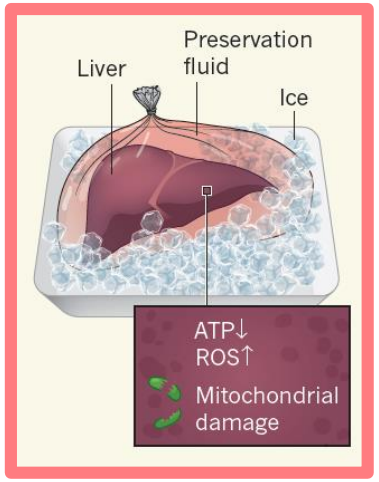
Donation after circulatory death (Maastricht III)

- French cDCD program started in 2015



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Donor Warm Ischemia

Savier et al, Transplantation 2020

Donation after circulatory death (Maastricht III)

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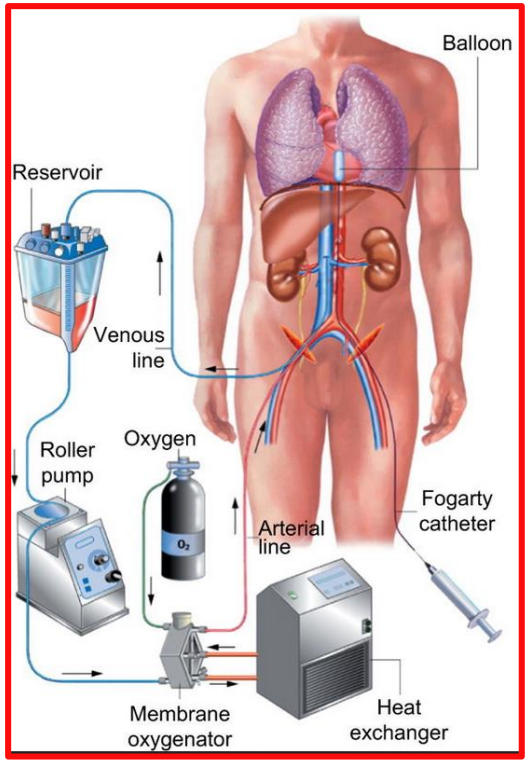

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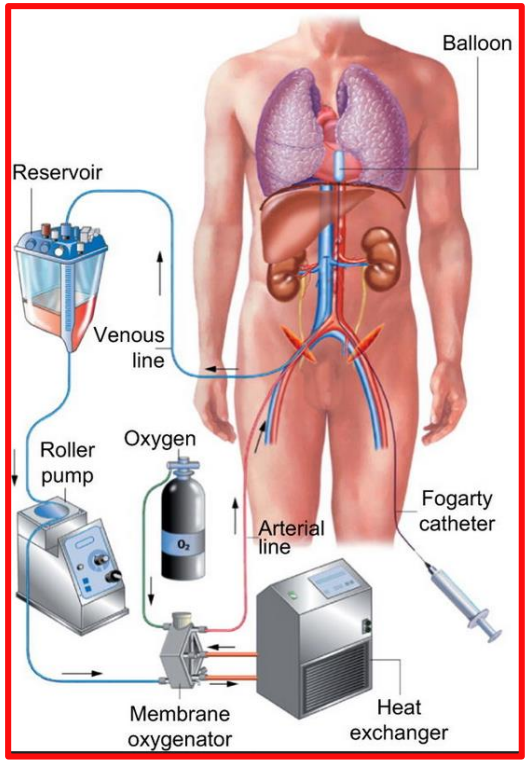

Original Clinical Science—Liver

ILTS

Favorable Outcomes of Liver Transplantation from Controlled Circulatory Death Donors Using Normothermic Regional Perfusion Compared to Brain Death Donors

Savier et al, Transplantation 2020

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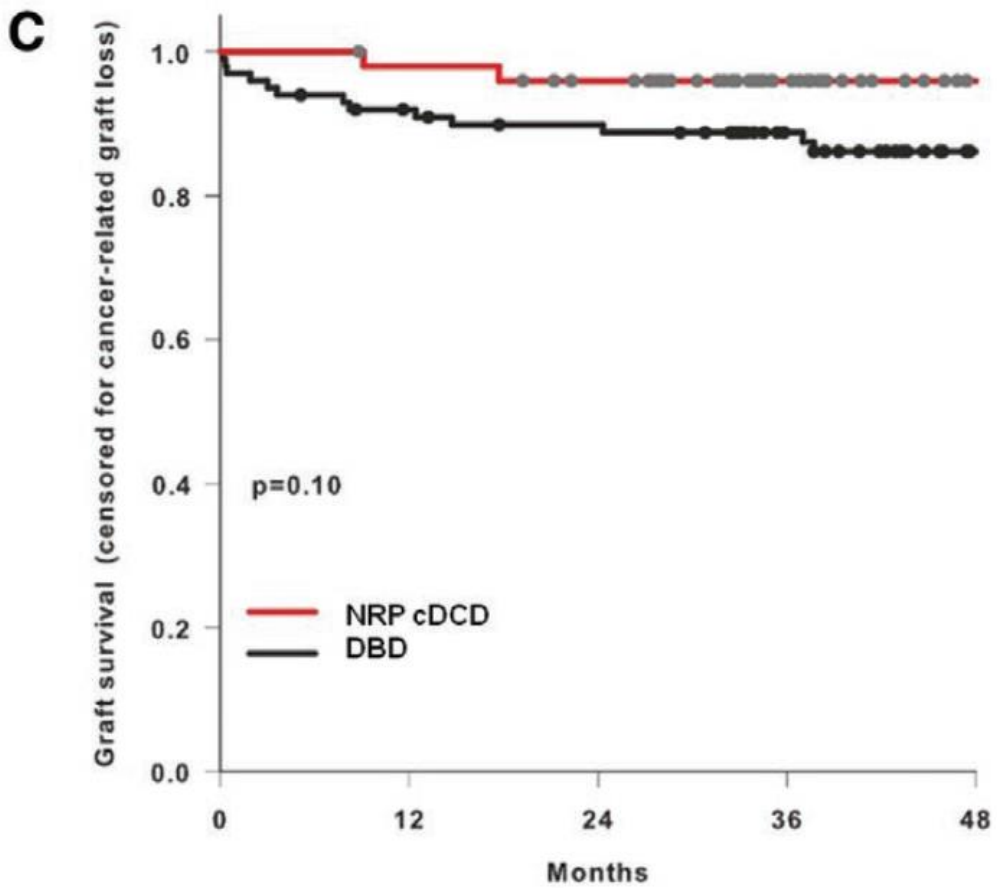

Savier et al, Transplantation 2020

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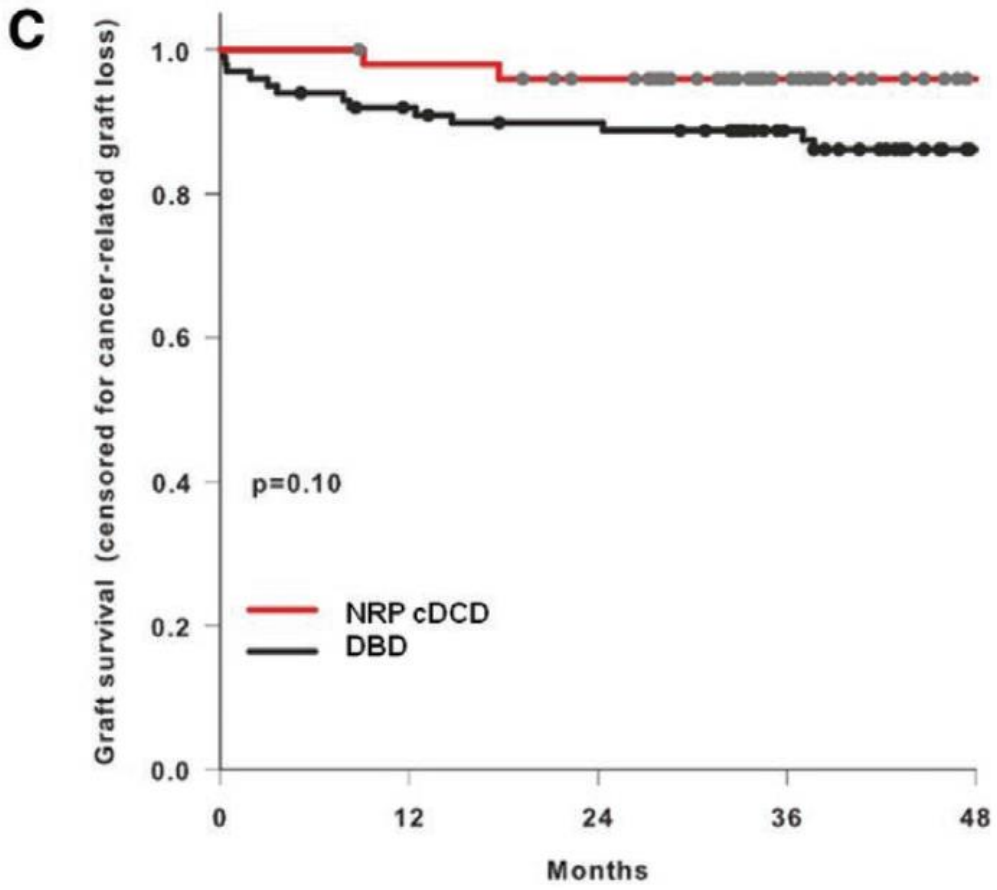

Comparable outcomes to standard DBD

Savier et al, Transplantation 2020

MAIS!

Deviation from the protocol occurred in 21 cases: Age > 66 y (n=1); NRP < 1 hour (n=1); functional warm ischemic time > 30 min. (n=9); cold ischemic time > 8 hours (n=5); MELD > 25 (n=3); abnormal AST/ALT kinetic during NRP (n=1) wrong recipient selection (ABO incompatible) (n=1).

Antoine et al, Liver Transplantation 2020

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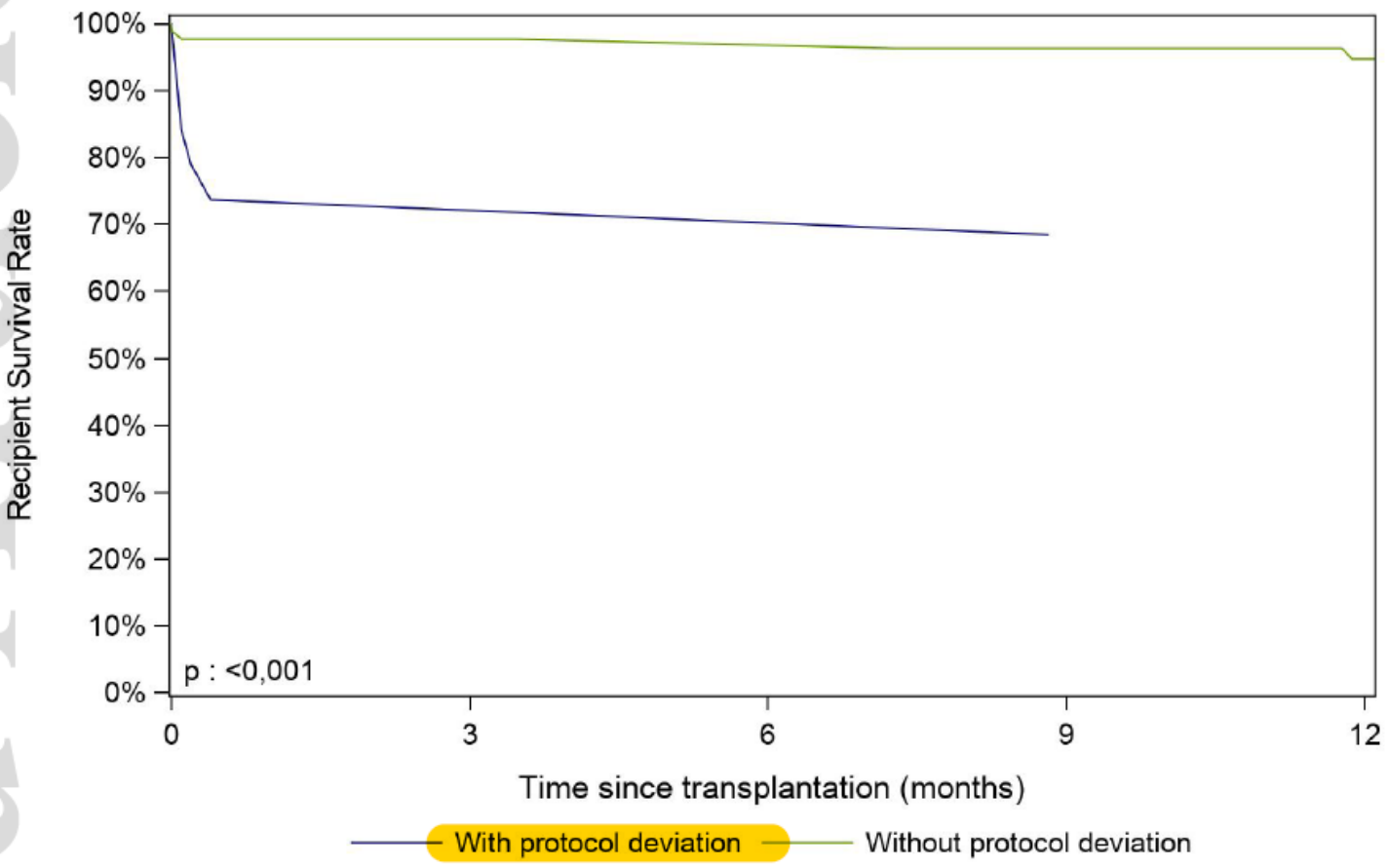
Figure 2. One-year graft survival according to deviation from the national protocol



94,8%

68,4%

Antoine et al, Liver Transplantation 2020

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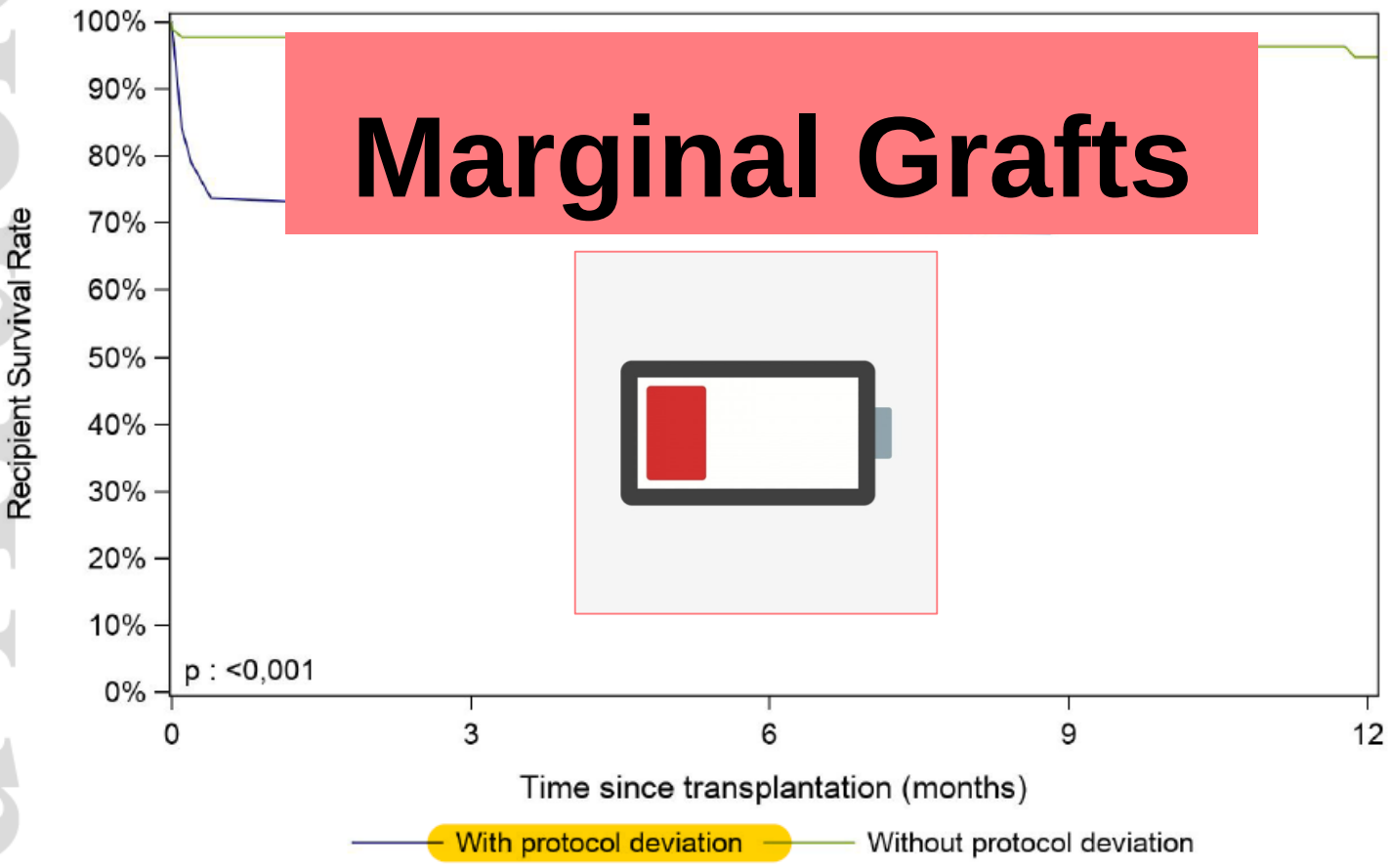

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Antoine et al, Liver Transplantation 2020

Do we need Dynamic Preservation?

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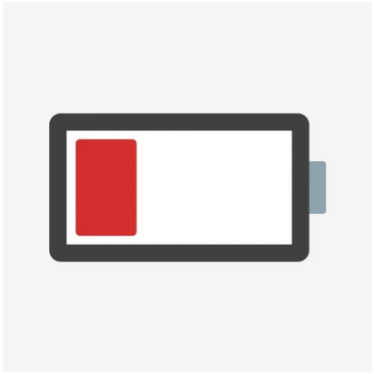
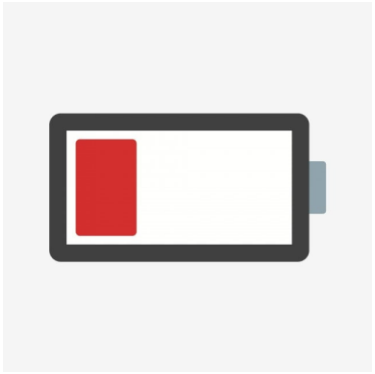
Marginal Liver Grafts



Do we need Dynamic Preservation?

DYNAMIC PRESERVATION

Marginal Liver Grafts



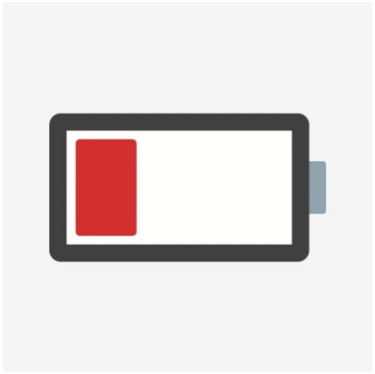
Safe ?

Protect ?

Assess Viability ?

Do we need Dynamic Preservation?

Marginal Liver Grafts



DYNAMIC PRESERVATION

Safe ?

Protect ?

Assess Viability ?

CLINICAL OUTCOMES

Optimize Outcomes

Increase Utilization Rates

Improve Donor-recipient matching

MARS 2024

Denver 1967

Denver 1967

HOMOTRANSPLANTATION OF THE LIVER IN HUMANS

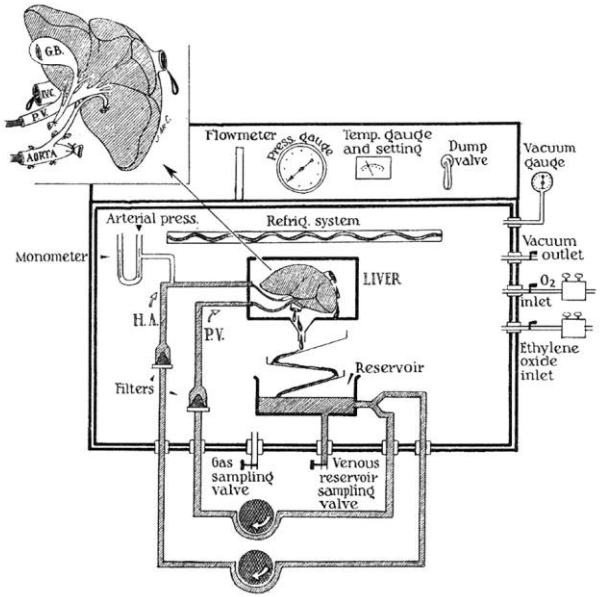
T. E. STARZL, M.D., F.A.C.S., T. L. MARCHIORO, M.D., K. N. VON KAULLA, M.D., G. HERMANN, M.D., R. S. BRITTAIN, M.D., and **W. R. WADDELL, M.D., F.A.C.S.**
Denver, Colorado

Although the technique of hypothermic perfusion has made liver transplantation feasible, the method has definite limitations in extending the postmortem viability of hepatic tissue.

Denver 1967

SUCCESSFUL ORTHOTOPIC TRANSPLANTATION OF LIVER HOMOGRAFTS AFTER EIGHT TO TWENTY-FIVE HOURS PRESERVATION

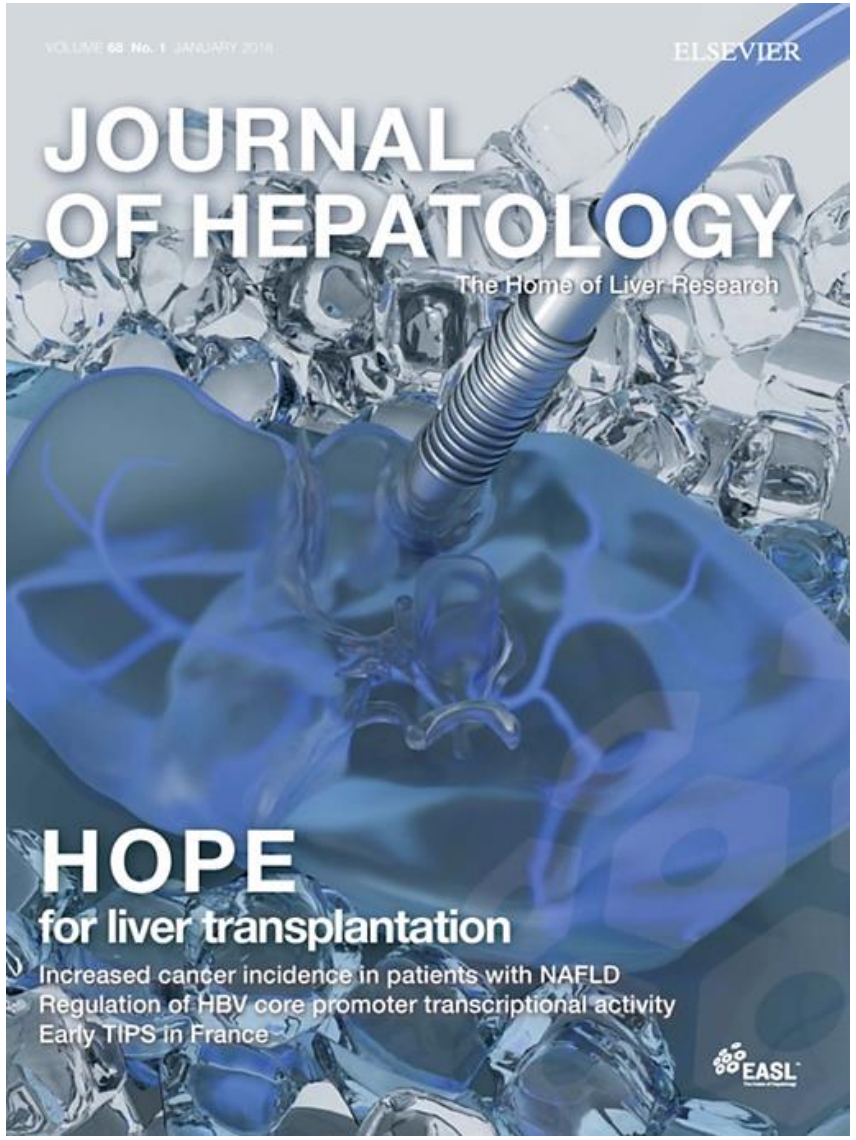
Lawrence Brettschneider, M.D., P. M. Daloze, M.D., C. Huguet, M.D., C. G. Groth, M.D., N. Kashiwagi, M.D., David E. Hutchison, M.D., and **Thomas E. Starzl, M.D., F.A.C.S.**
University of Colorado Medical School and Veterans Administration Hospital, Denver



CONCLUSIONS

The combined use of hypothermia, hyperbaric oxygenation, and perfusion with diluted blood at the rate of 6 ml./gm. tissue/hr. permitted successful storage of hepatic homografts for 8 hr. and with less consistency for more than a day (Group III). When used as orthotopic transplants these livers supported life both immediately and chronically. The deterioration of results with reduction (Group II) or elimination (Group VI) of perfusion, omission of blood from the perfusate (Group V), or elimination of high pressure oxygen (Group IV) suggests that each of these preservation components may have played a significant beneficial role.

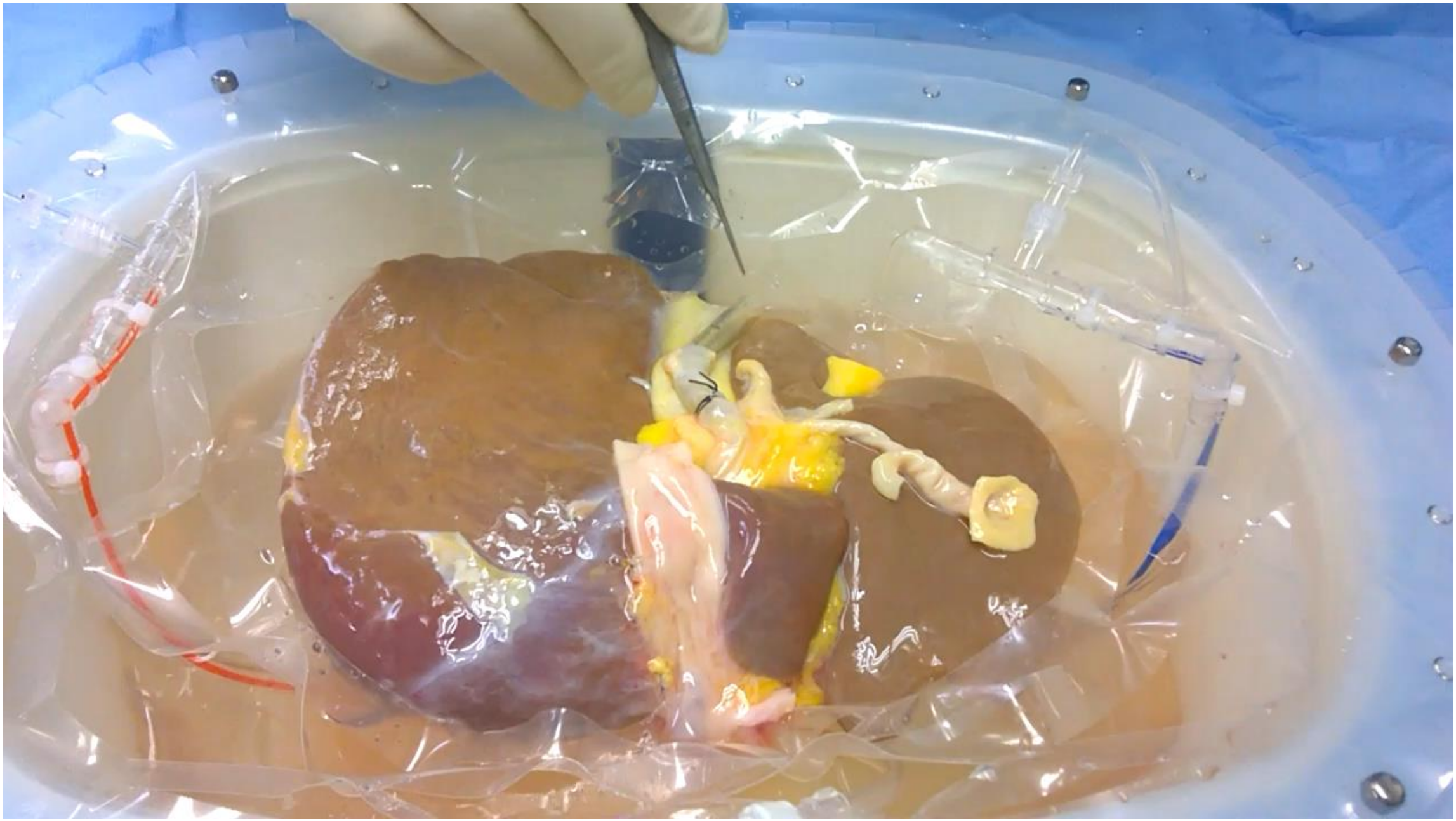
And in 2021?



Hypothermic **Oxygenated** Perfusion (HOPE)

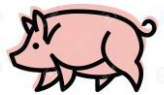
- COLD: 8-12 °C
- Hyper OXYGENATED
- End-ischemic
- **Short 2-4h (during hepatectomy)**

Muller, Schlegel, Clavien, Dutkowski et al, JHE 2018



What is the evidence?

From Bench to Bedside



2009

ORIGINAL ARTICLES

One Hour Hypothermic Oxygenated Perfusion (HOPE) Protects Nonviable Liver Allografts Donated After Cardiac Death

Olivier de Rougemont, MD, Stefan Breitenstein, MD,* Boris Leskosek,* Achim Weber, MD,† Rolf Graf, PhD,* Pierre-Alain Clavien, MD, PhD,* and Philipp Dutkowski, MD**

De Rougement et al, Annals 2009
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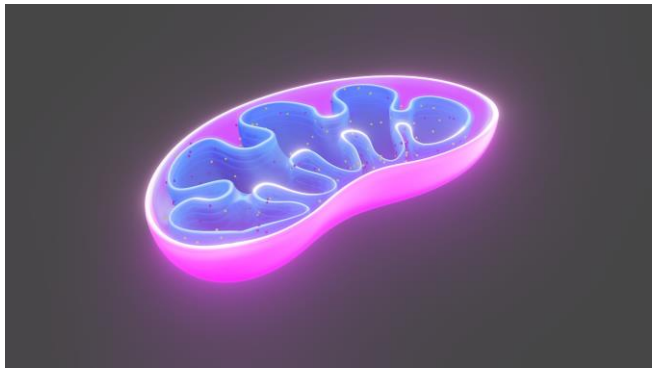
Uploading Cellular Batteries: Caring for Mitochondria Is Key



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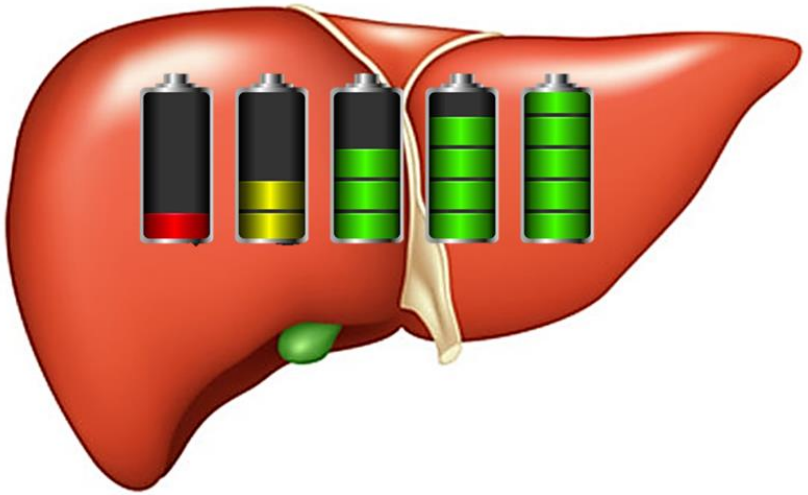

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1st RCT

The NEW ENGLAND JOURNAL of MEDICINE

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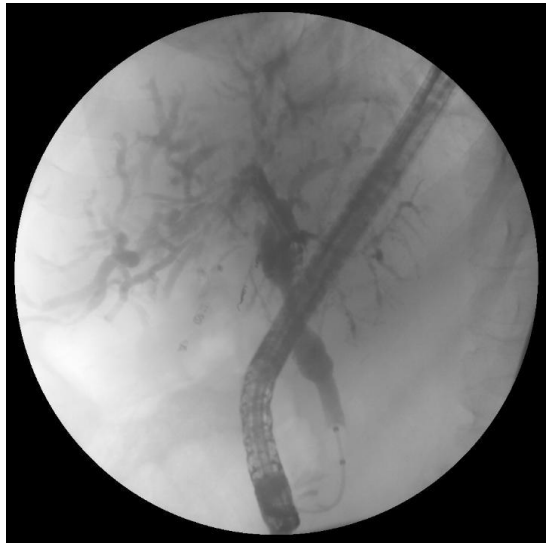

- Multicenter trial in the Netherlands
- 2016-2019
- cDCD with super rapid procurement (NO NRP!!!)
- **End ischemic HOPE (2h) vs Static Cold Storage**

Van Rijn et al, NEJM 2021

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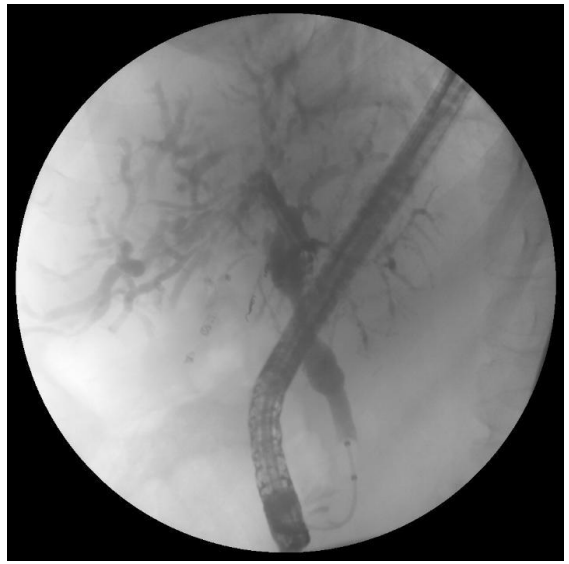

- Multicenter trial in the Netherlands
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- **End ischemic HOPE (2h) vs Static Cold Storage**
- Primary endpoint :

→ **Symptomatic Non-anastomotic bile strictures at 6 months**

Van Rijn et al, NEJM 2021

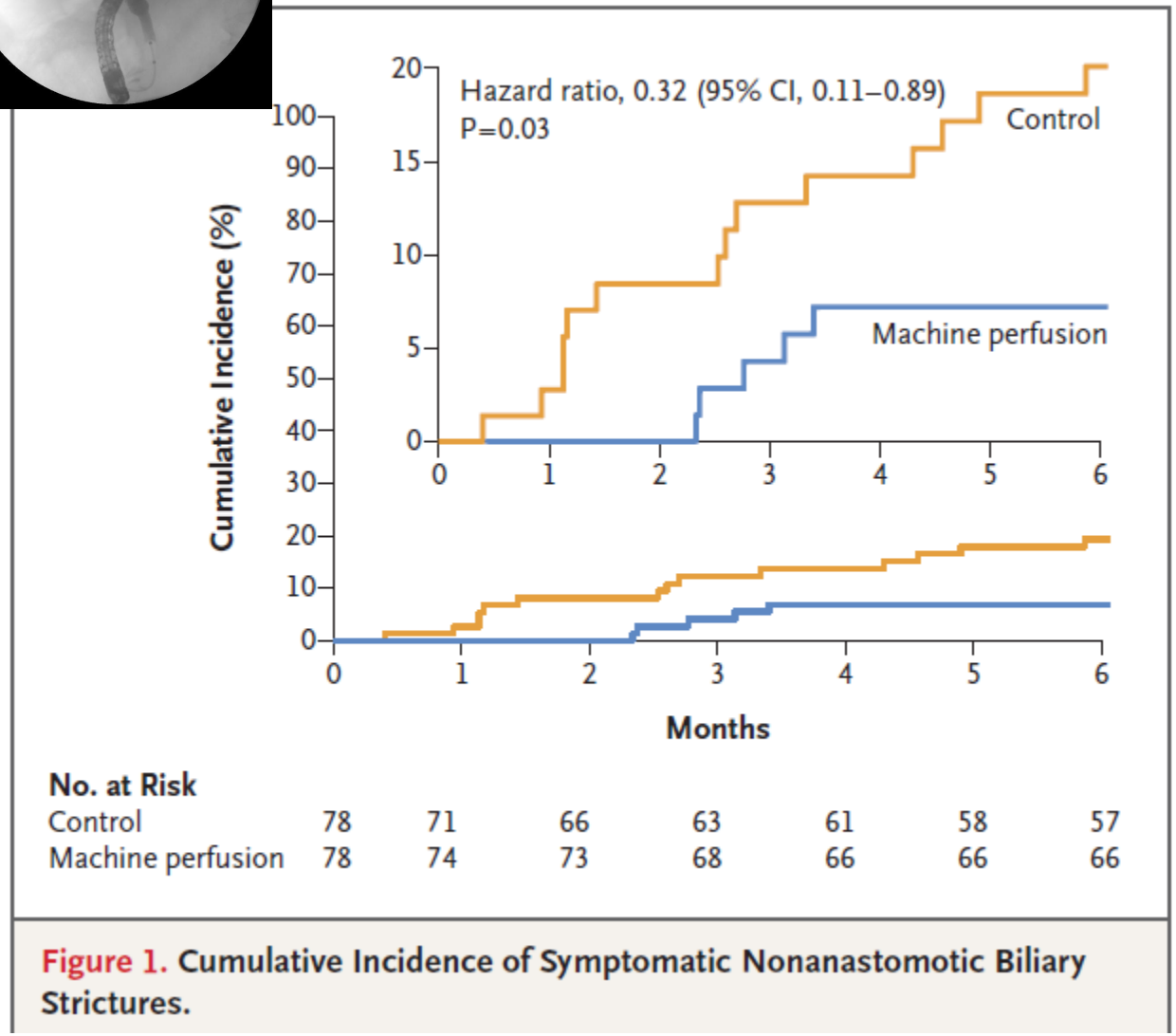


Figure 1. Cumulative Incidence of Symptomatic Nonanastomotic Biliary Strictures.

75% lower RISK of NAS After HOPE

Van Rijn et al, NEJM 2021

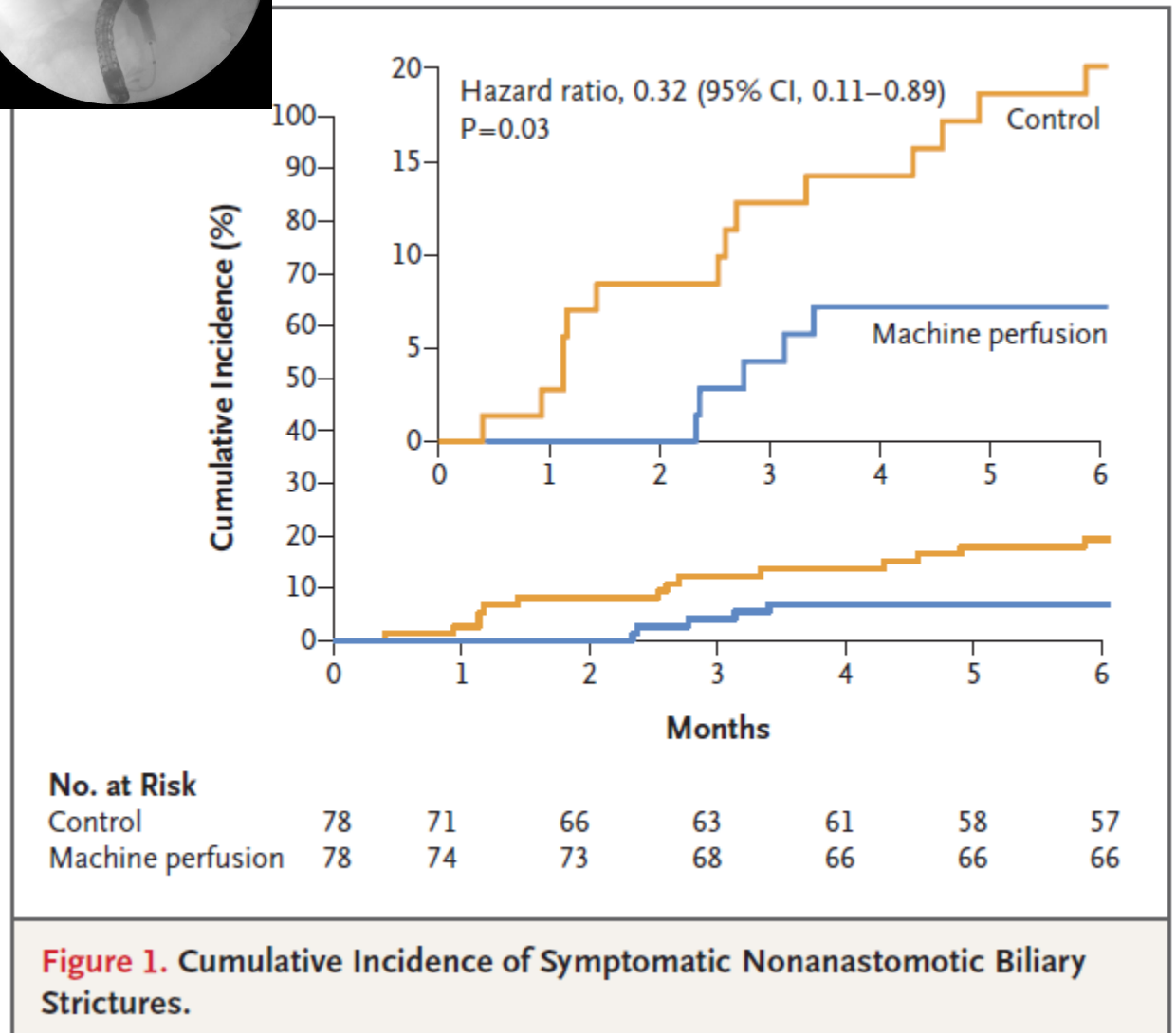


Figure 1. Cumulative Incidence of Symptomatic Nonanastomotic Biliary Strictures.

75% lower RISK of NAS After HOPE

4x reduction in cumulative number of treatments for biliary complciations

Van Rijn et al, NEJM 2021

Limitations

1. Asymptomatic NAS 28% in the HOPE arm at 6 month

(Detected on routine MRI)

→ **Longer follow-up needed to confirm results**

2. Procurement Strategy not applicable in France

→ **NRP procurement**

Van Rijn et al, NEJM 2021

And in France?

HOPExt trial

NIH U.S. National Library of Medicine

ClinicalTrials.gov

- Multicenter RCT
- 8 centers in France
- HOPE vs Static Cold Storage
- Extended DBD grafts

And in France?

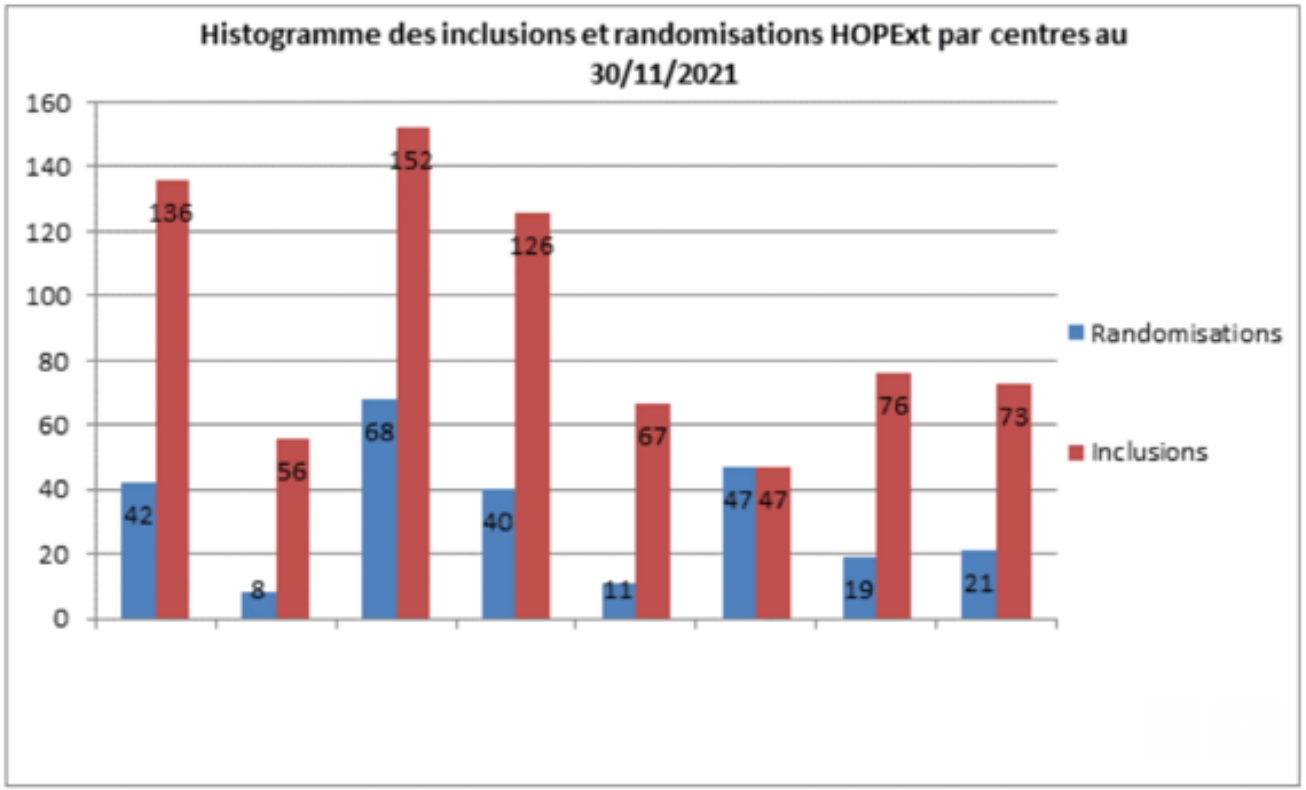
HOPExt trial

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Results next year

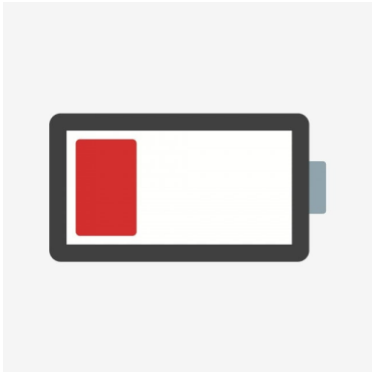
256 patients randomisés au total sur 266 attendus.



Do we need Dynamic Preservation?

HOPE

Marginal Liver Grafts



Safe

Protect

Do we need Dynamic Preservation?

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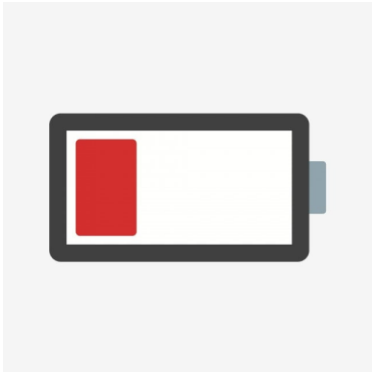


HOPE

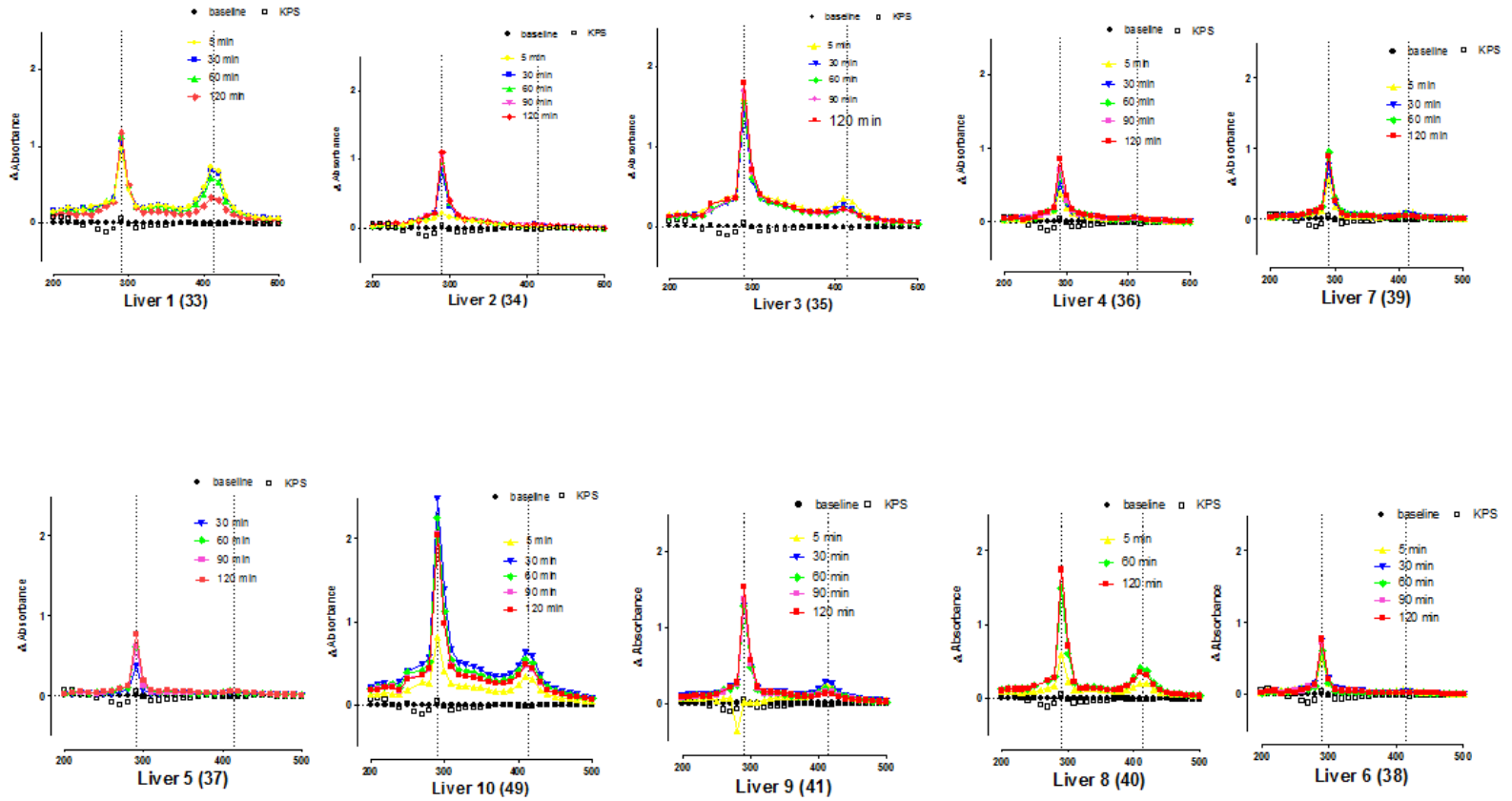
Safe

Protect

Assess Viability

Metabolic Fingerprint of Liver Grafts

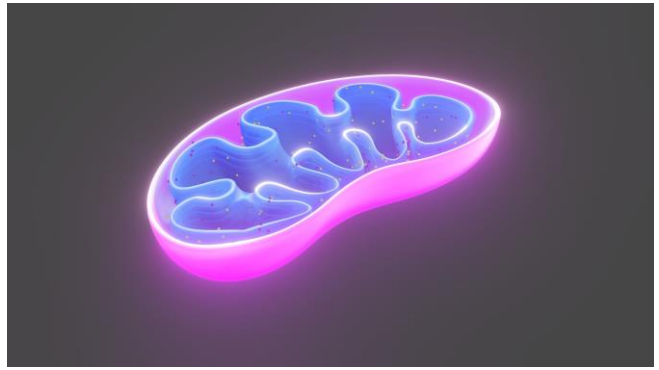
> 1000 Proteins



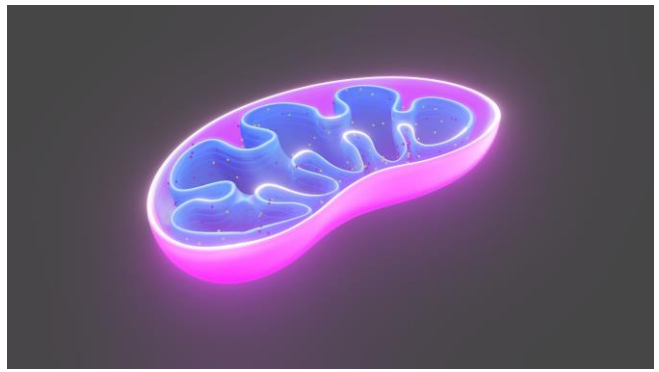
Schlegel, Muller et al, EbioMedicine 2021

Novel Real-time Prediction of Liver Graft Function During Hypothermic Oxygenated Machine Perfusion Before Liver Transplantation

Xavier Muller, MD, Andrea Schlegel, MD,* Philipp Kron, MD,* Dilmurodjon Eshmuminov, MD,* Michael Würdinger, MD,* David Meierhofer, PhD,† Pierre-Alain Clavien, MD, PhD,* and Philipp Dutkowski, MD*✉*



Muller et al, AoS 2019



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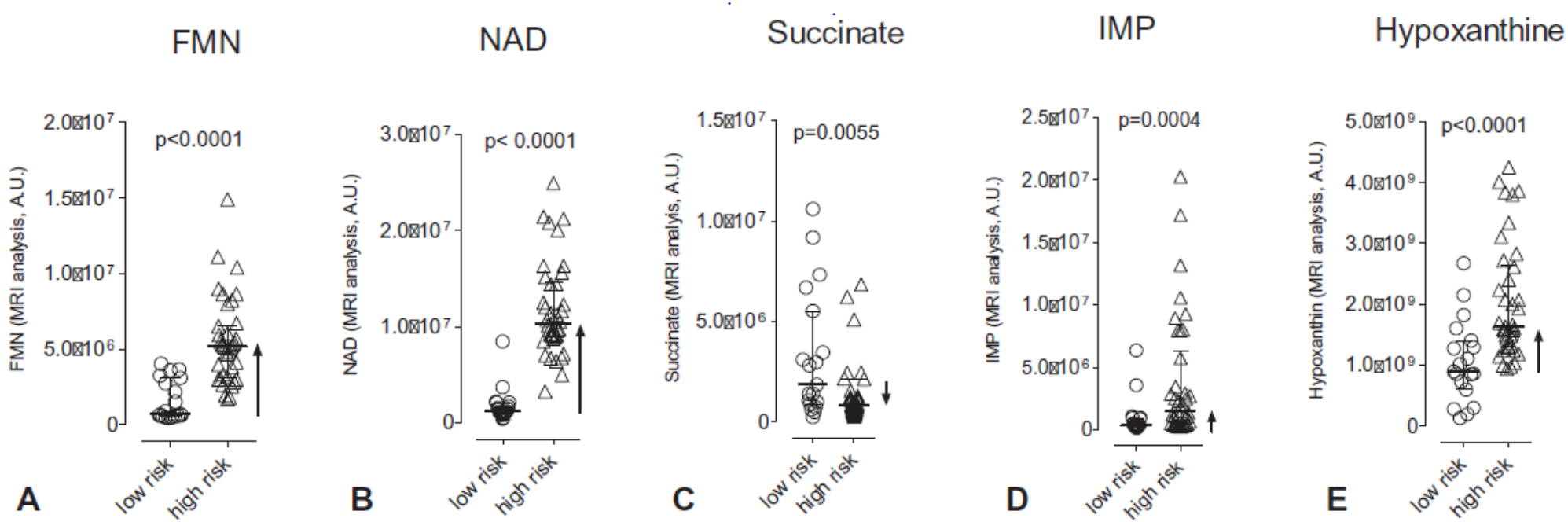
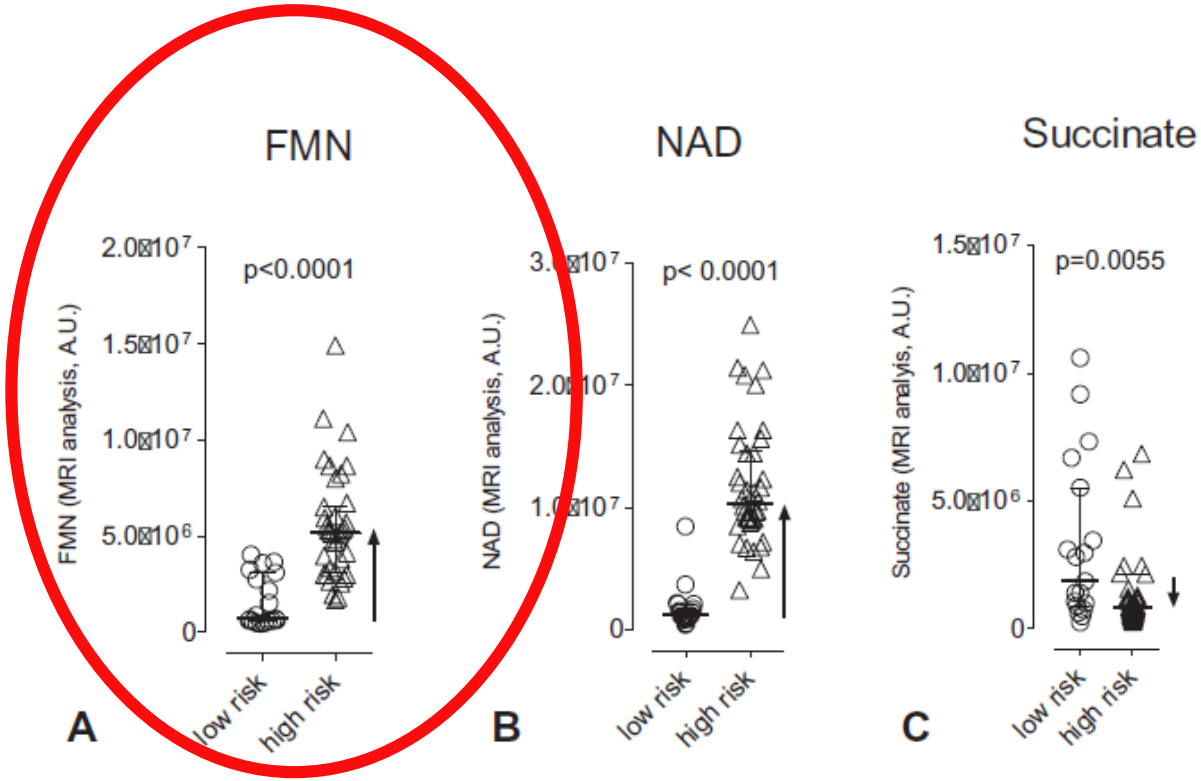
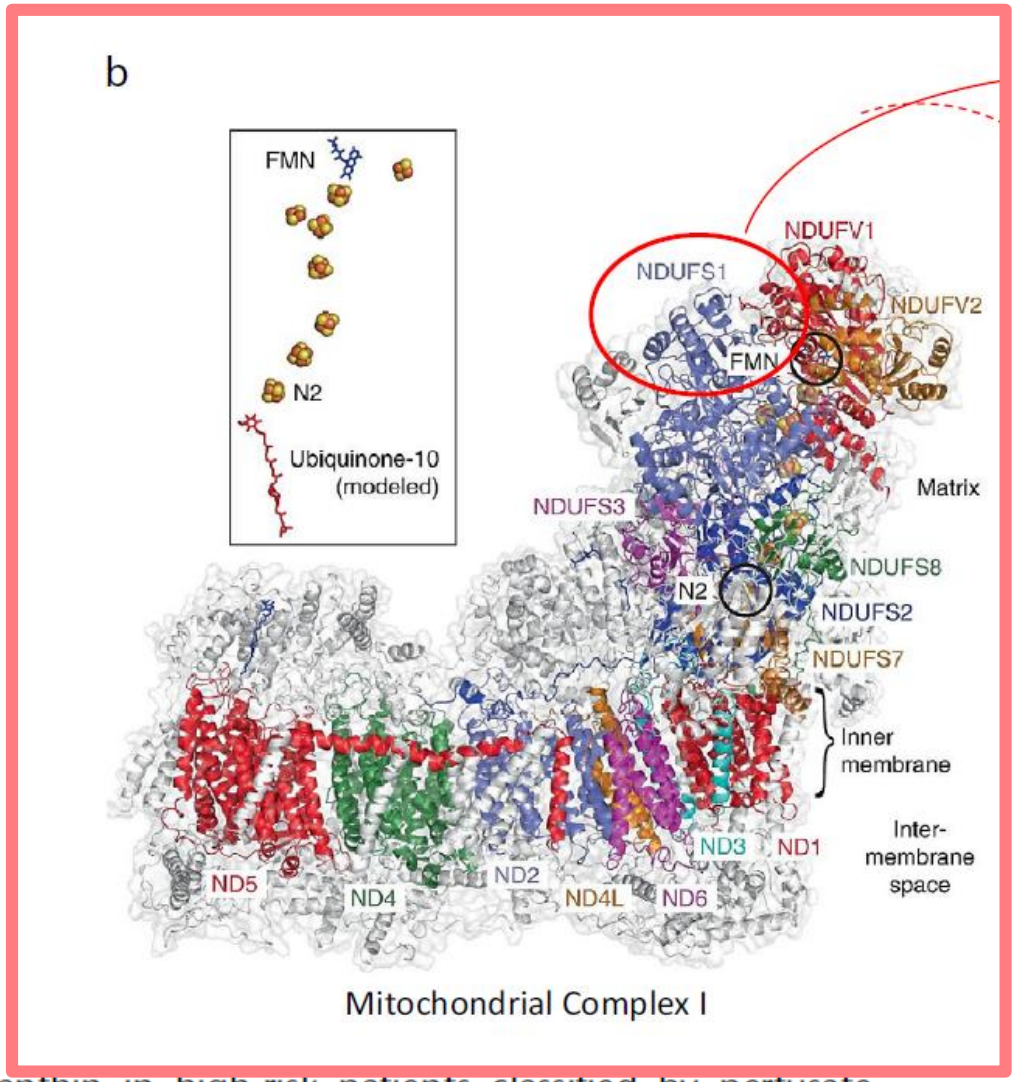


FIGURE 4. Analysis of perfusate FMN, NAD, succinate, IMP, and hypoxanthin in high-risk patients classified by perfusate FMN>10000 AU.

Muller et al, AoS 2019

FLAVIN MONONUCLEOTIDE





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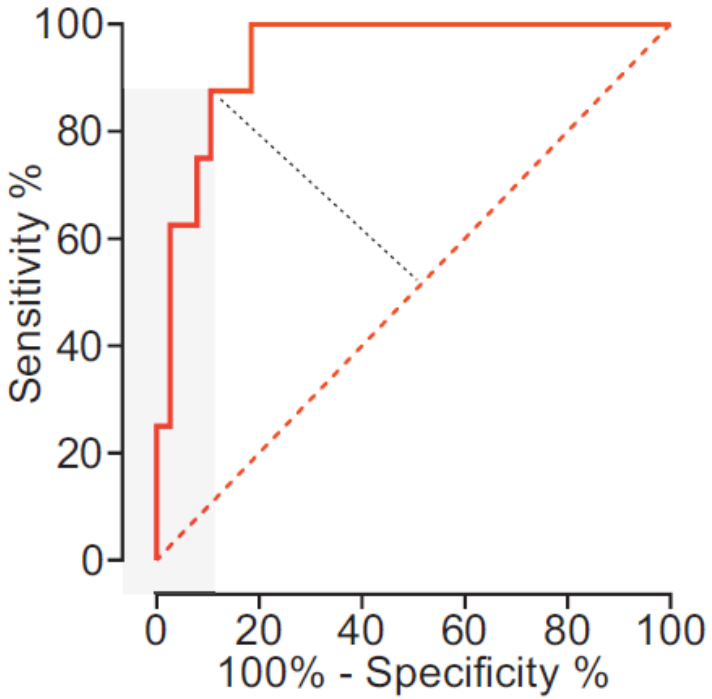
Muller et al, AoS 2019

Flavin Mononucleotide (FMN)

c ROC curve analysis at 30 minutes of HOPE and prediction of graft loss

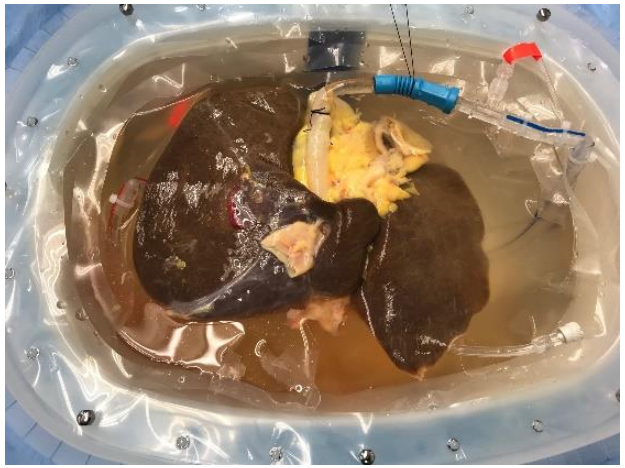
Area	0.9441
Std. Error	0.03331
95% confidence interval	0.8788 to 1.000
P value	<0.0001



Predict Early Graft Loss by real-time FMN measurment at 30 min of perfusion

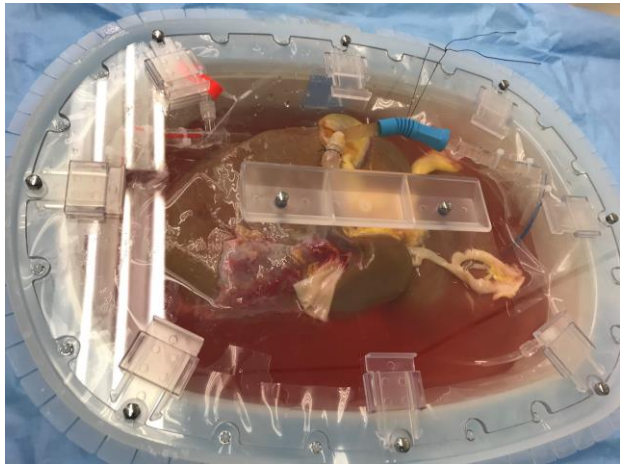
Muller et al, AoS 2019
Schlegel, Muller et al, EbioMedicine 2021

Viability assesment during HOPE



Organ offer B:

DBD, 55y
No cardiac arrest
Short donor ICU stay, no transaminase increase
no relevant steatosis
donor hepatectomy time 30 min

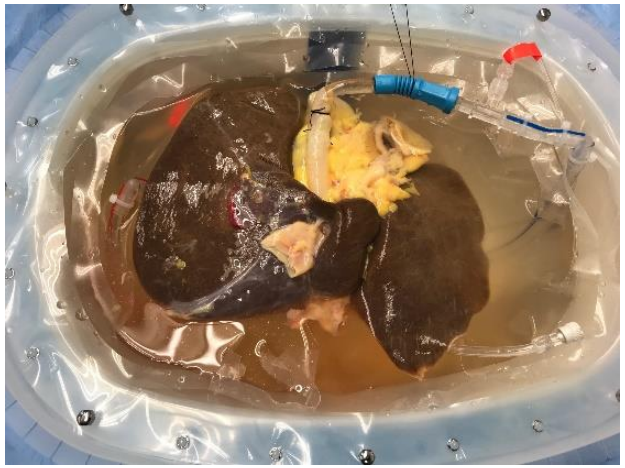


Organ offer A:

DBD, 83y
Cardiac arrest
>10 days ICU stay, ase
20 % macristeatosis, 5 % microsteatosis
donor hepatectomy time 40 min

Muller et al, 2019

Viability assesment during HOPE



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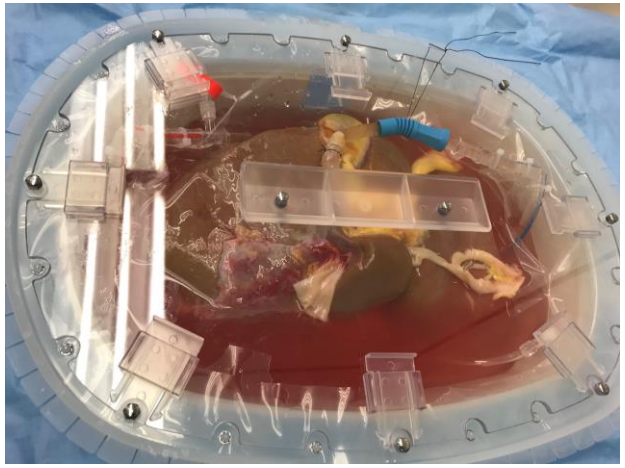

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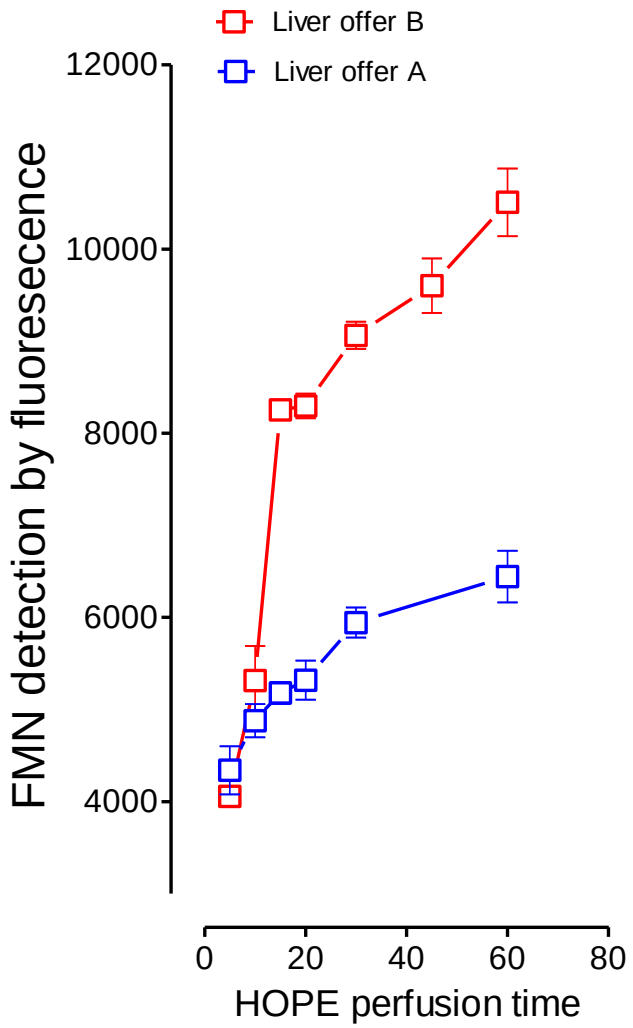
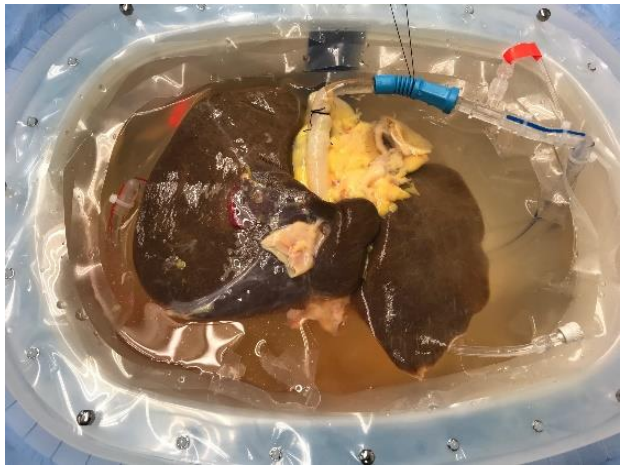
Muller et al, 2019

Viability assesment during HOPE

Real Time FMN Detection





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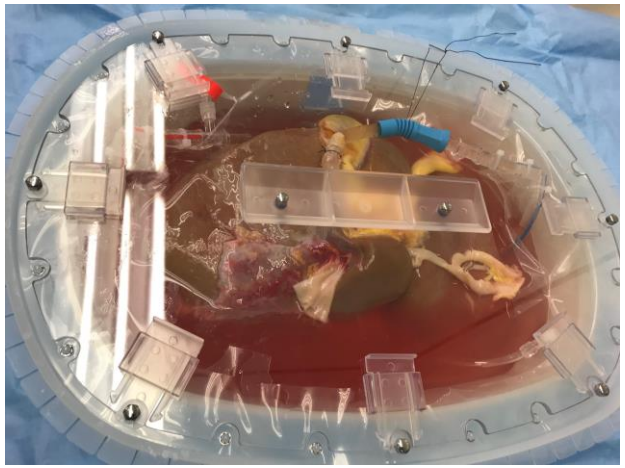

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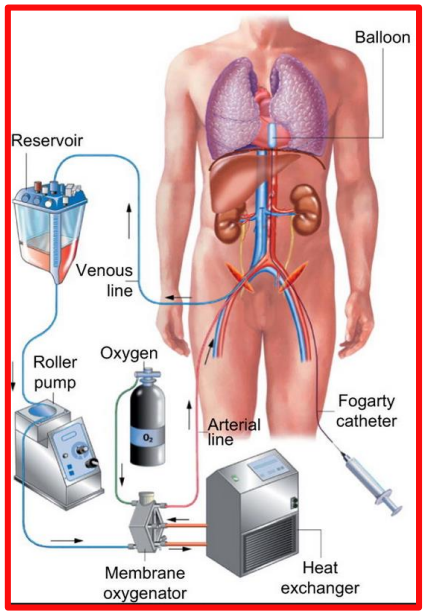
Muller et al, 2019

HOPE for the future?

Update of the French cDCD Protocol

- 2015-2021
- Well selected Donors
- Excellent outcomes



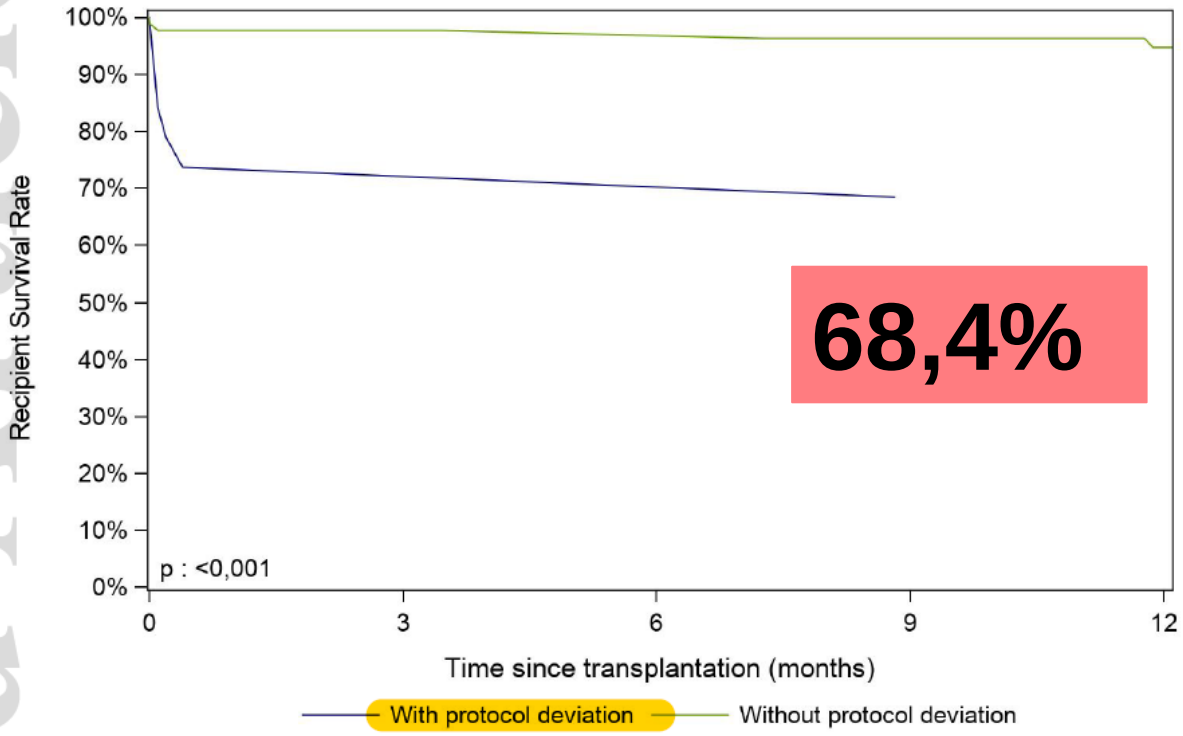
Original Clinical Science—Liver

Favorable Outcomes of Liver Transplantation from Controlled Circulatory Death Donors Using Normothermic Regional Perfusion Compared to Brain Death Donors

Savier et al, Transplantation 2020

Update of the French cDCD Protocol

Figure 2. One-year graft survival according to deviation from the national protocol

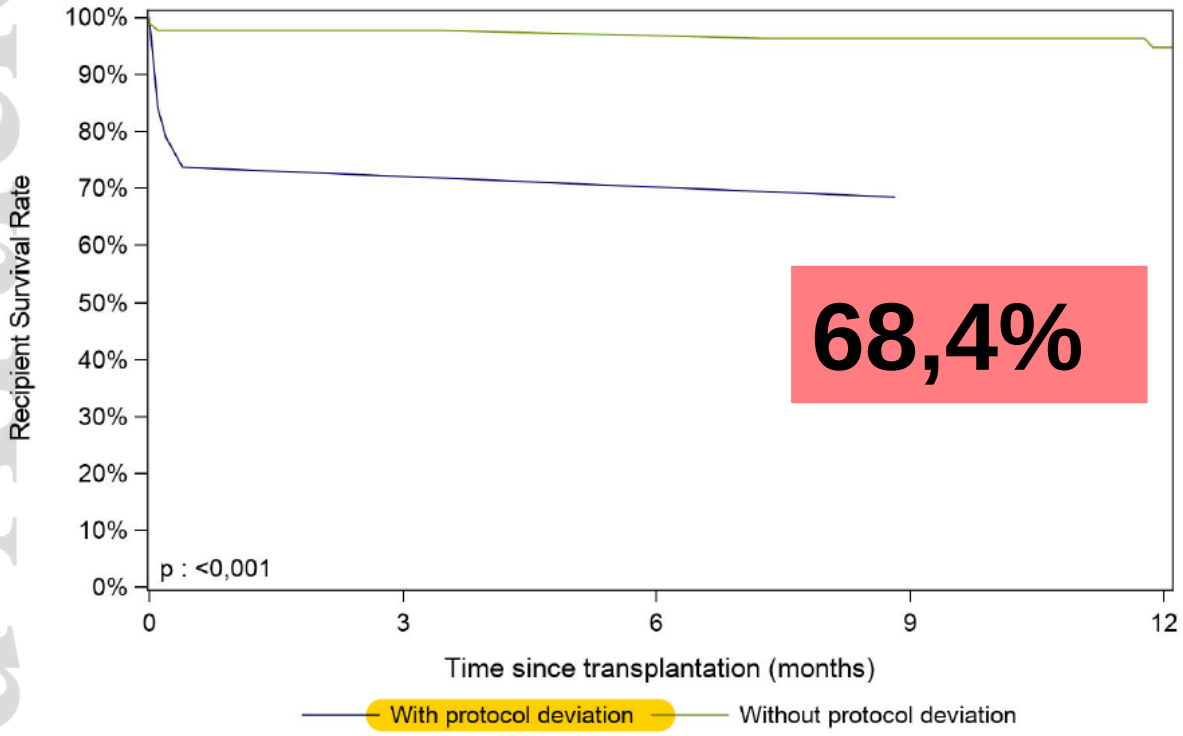


68,4%

Antoine et al, Liver Transplantation 2020

Update of the French cDCD Protocol

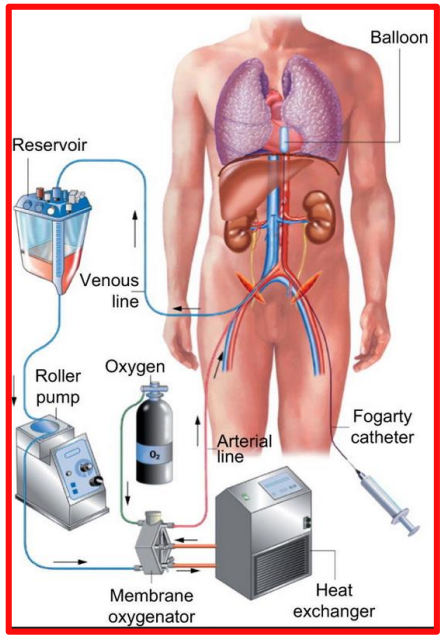
Figure 2. One-year graft survival according to deviation from the national protocol



68,4%

- From September 2021
- **Extended criteria Donors**

HOPE



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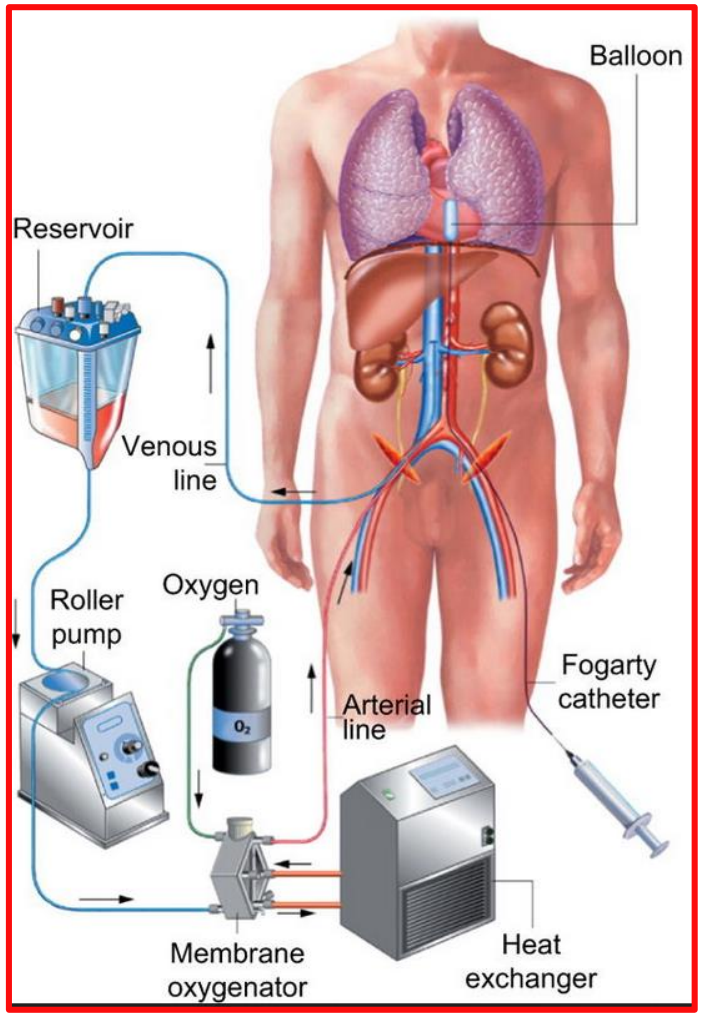
Antoine et al, Liver Transplantation 2020

NRP + HOPE for marginal grafts

Donor ALAT > 8x N during NRP



NRP + HOPE for marginal grafts

Donor ALAT > 8x N

-Warm ischemia: 36 min

-Static Cold Storage : 308 min

-HOPE : 60 min

NRP + HOPE for marginal grafts

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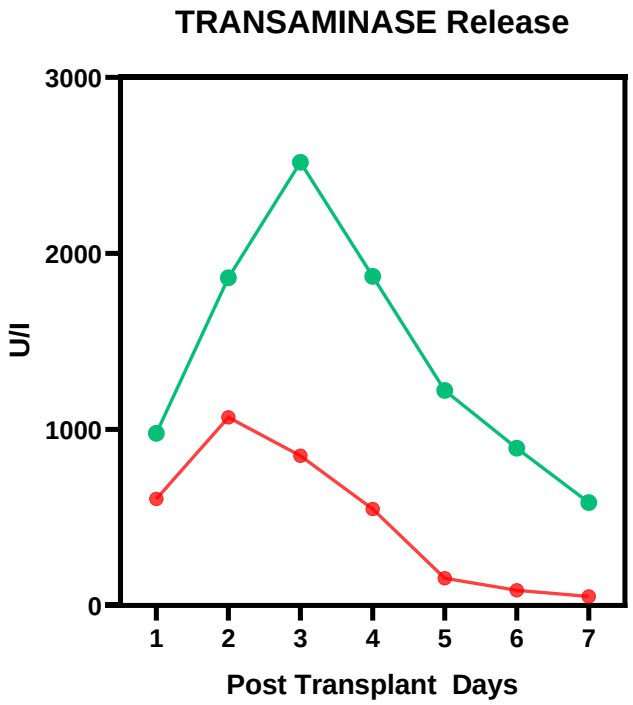

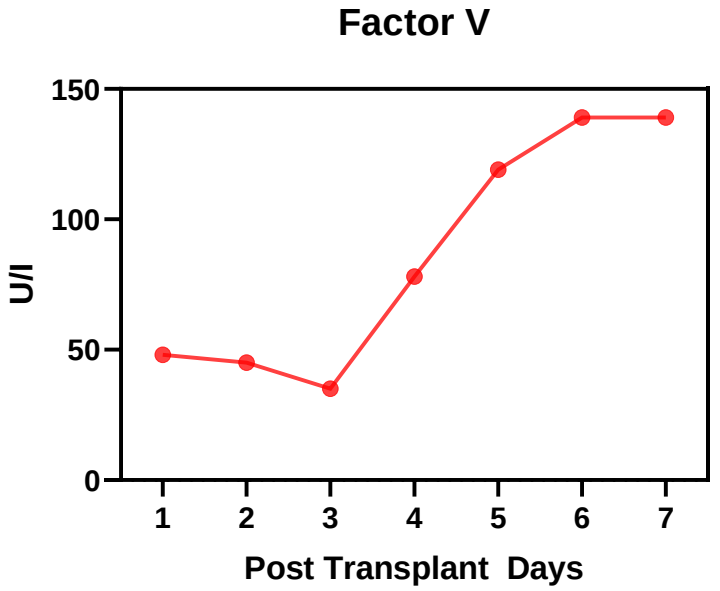

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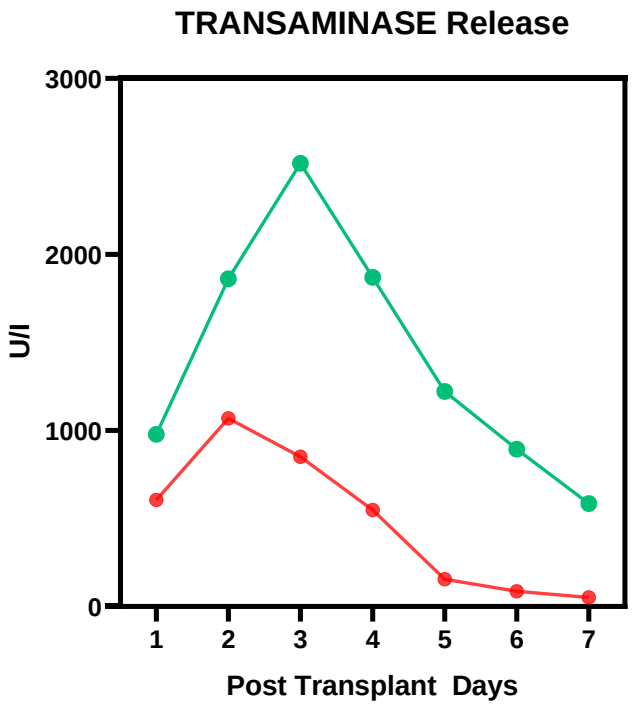
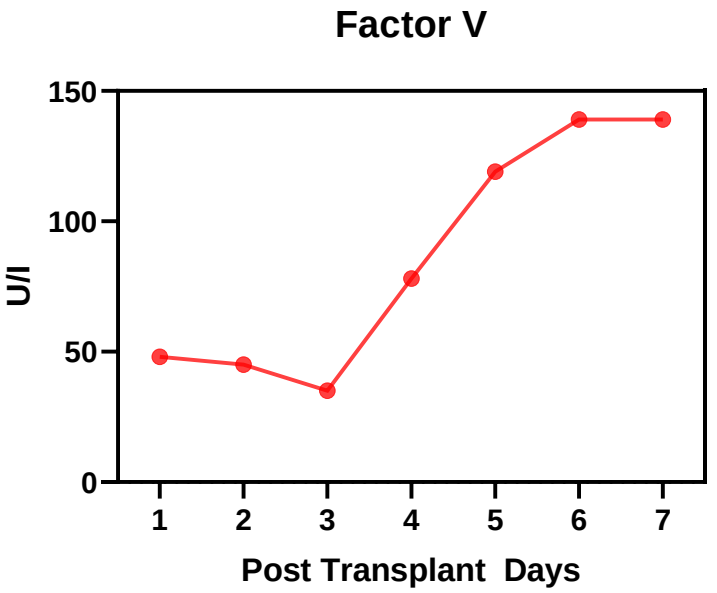
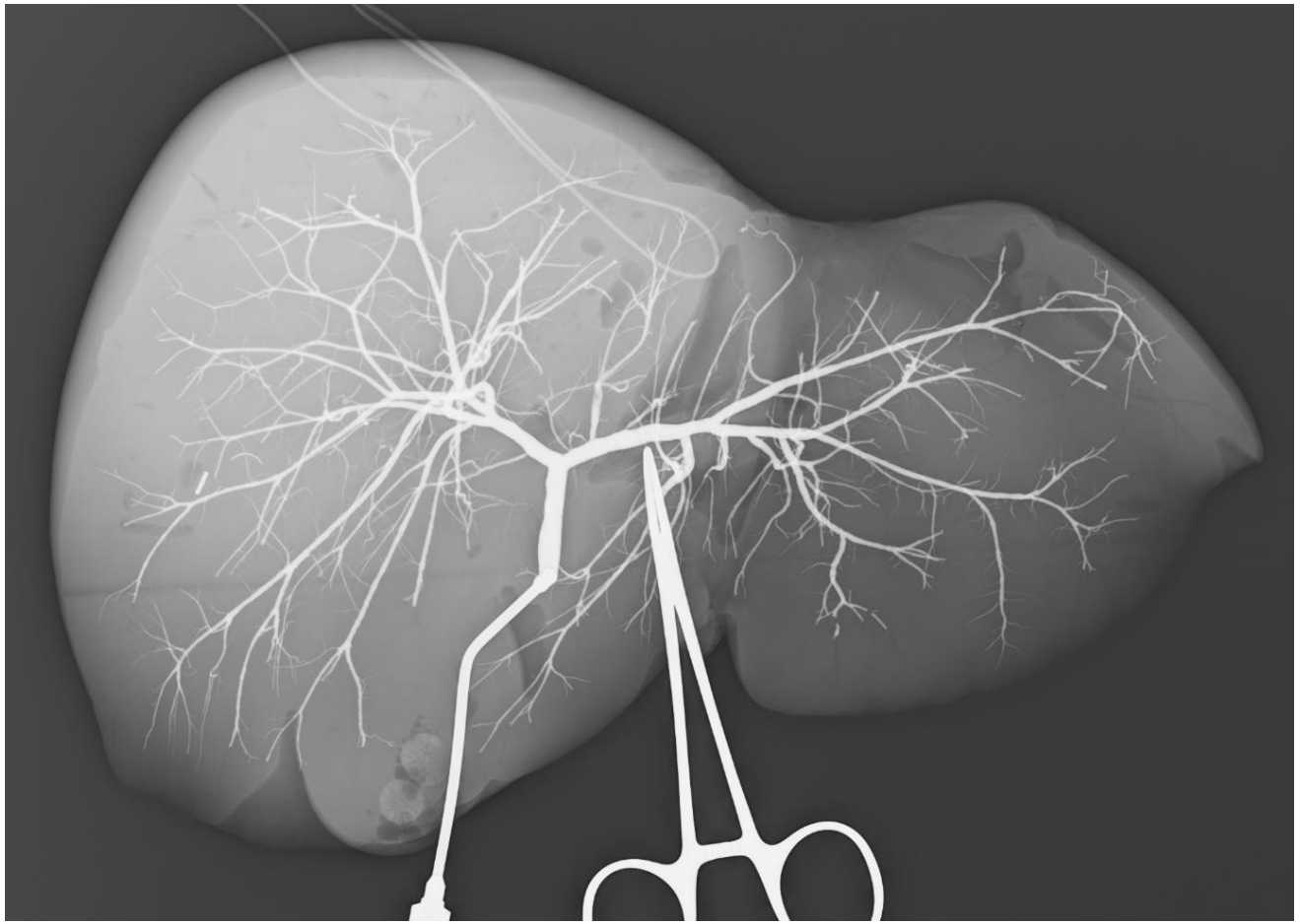




ICU Stay 4 Days
Hospital Stay 10 Days

Ex Vivo Liver Splitting and Hypothermic Oxygenated Machine Perfusion: Technical Refinements of a Promising Preservation Strategy in Split Liver Transplantation

Jean-Yves Mabrut, MD, PhD,[1,2] Mickaël Lesurtel, MD, PhD,[1,2] Xavier Muller, MD,[1,2] Rémi Dubois, MD,[3] Christian Ducerf, MD, PhD,[1] Guillaume Rossignol, MD,[2,3] and Kayvan Mohkam, MD, PhD[1,2,3]



Mabrut et al, Transplantation 2021

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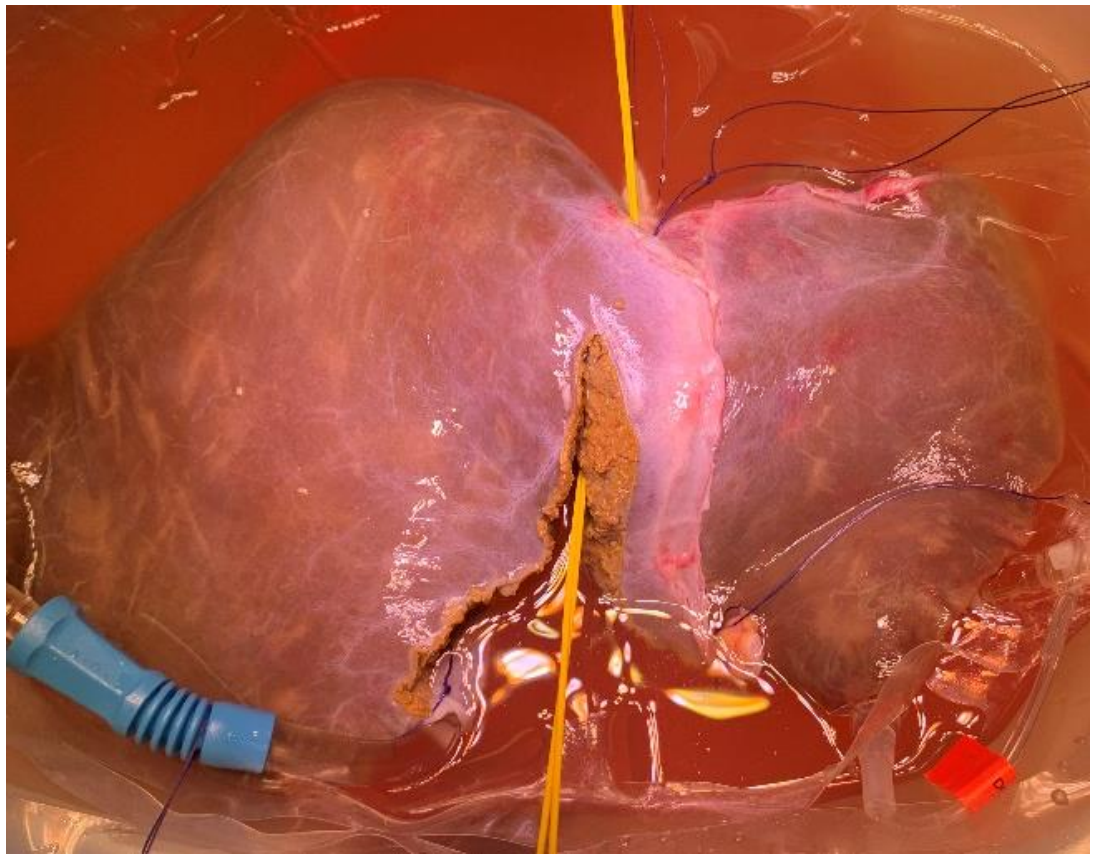
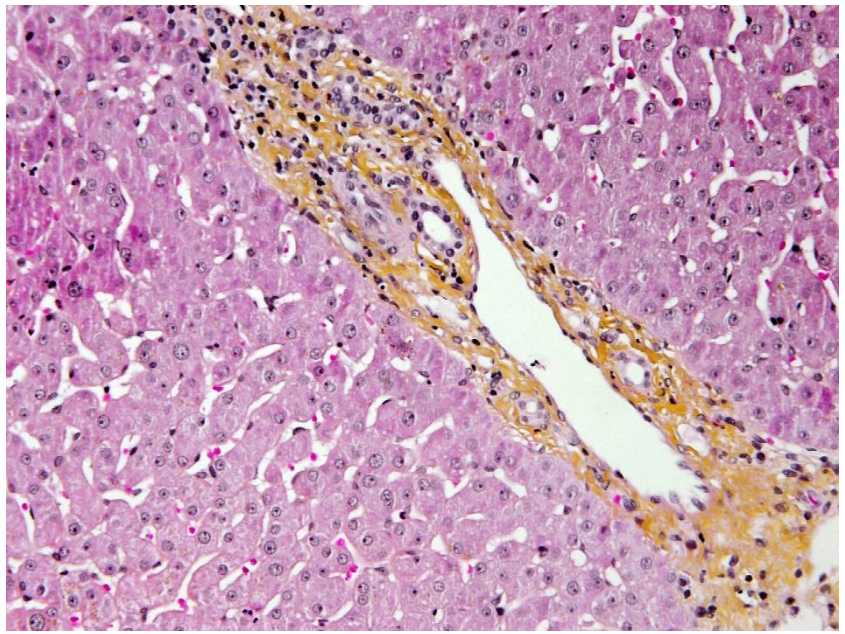


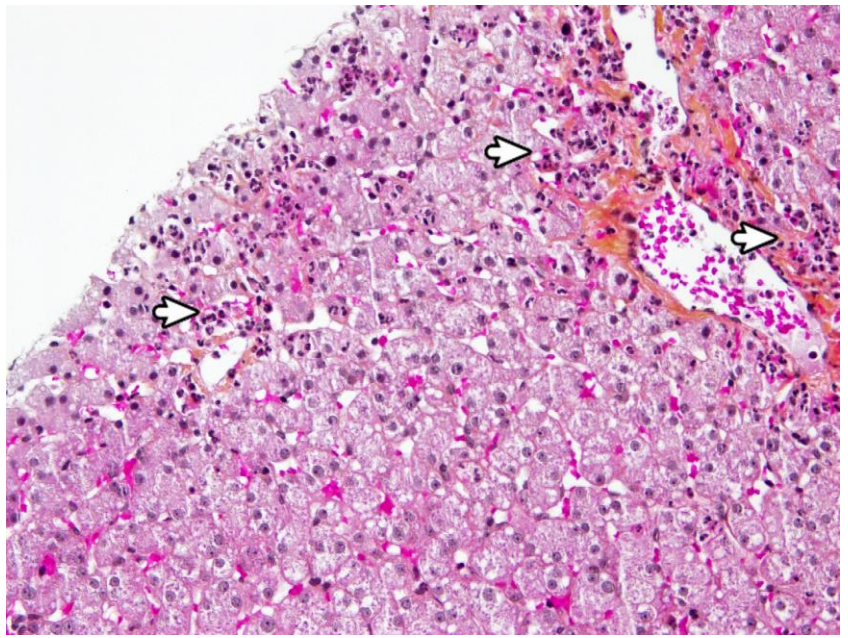
Mabrut et al, Transplantation 2021

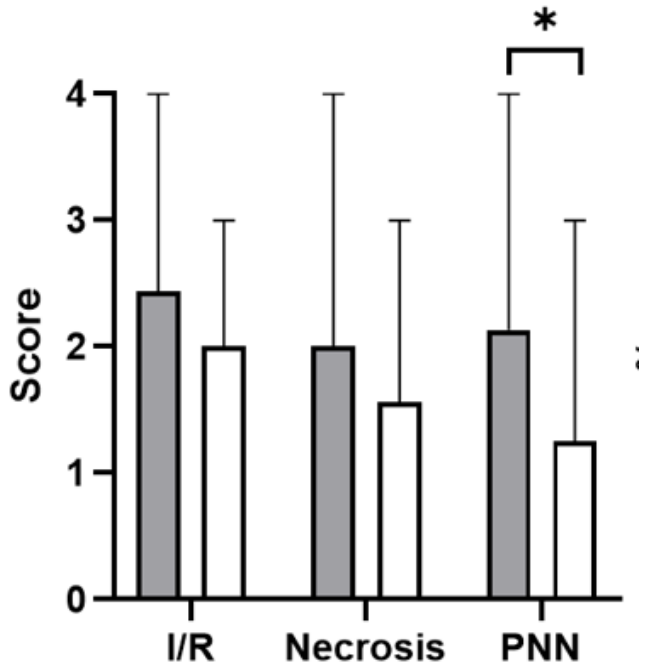
HOPE SPLIT

HOPE Split



Standard Split

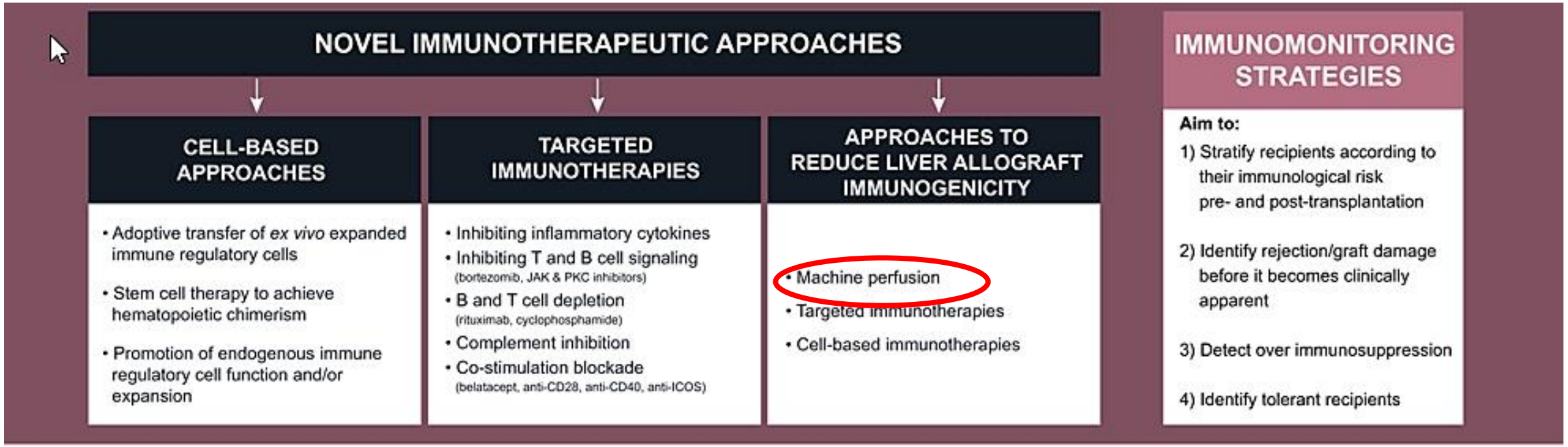




Reduction in sterile inflammation after reperfusion in the HOPE Split Group

Unpublished data

Graft Immunomodulation



Samuel D, Sanchez-Fueyo A, JHE 2018

Graft Immunomodulation

Review

Preventing Tumour Recurrence after Liver Transplantation: The Role of Machine Perfusion

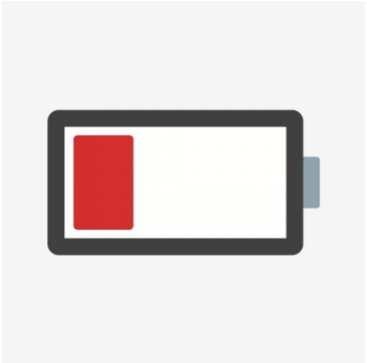
ESA PAPER

Hypothermic Oxygenated Liver Perfusion (HOPE) Prevents Tumor Recurrence in Liver Transplantation From Donation After Circulatory Death

Boteon et al, IJMS 2020
Mueller et al, AoS 2020

Conclusion

Marginal Liver Grafts



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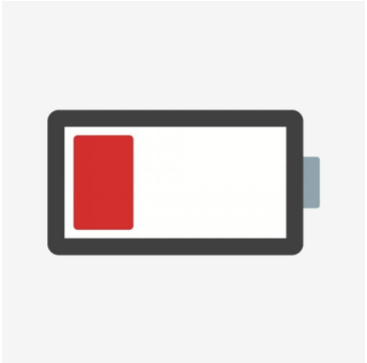


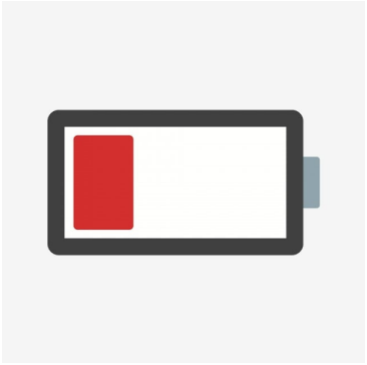
Safe

Protect

Assess Viability

Conclusion

Marginal Liver Grafts



Safe

Protect

Assess Viability

Longer Follow-up

National RCT

Financial Aspect

Logistics

MERCI

Xavier Muller, *Guillaume Rossignol,*
Antoine Breton, Joris Couillerot
Department of Surgery and Transplantation,
Croix Rousse University Hospital