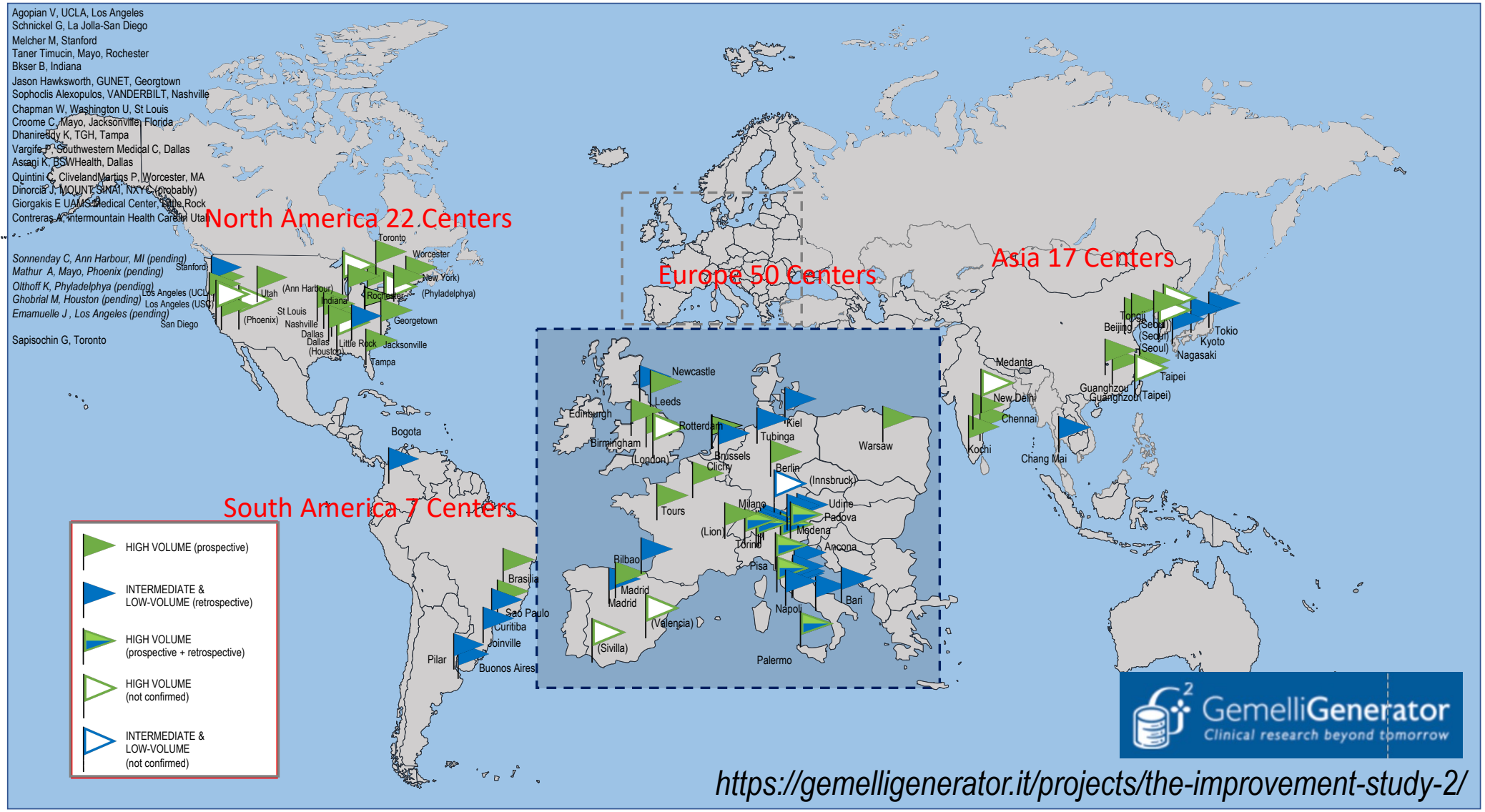
International, Multicenter, Prospective, Non-competitive, Observational study to Validate and Optimize prediction models of 90-day and 1-year allograft failure after Liver Transplantation.

The IMPROVEMENT study

The IMPROVEMENT study - Map of Centers (updated March 6, 2022)



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International Multicenter Prospective, Non-competitive, Observational study to Validate and Optimize kinetic prediction models of 90-day and 1-year allograft failure after liver transplantation

*The **IMPROVEMENT** study*

Promoters:

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International: previous studies were not performed on an international basis.

Multicenter: the multicenter dimension is a prerequisite for a real-life approach to the prognosis of liver transplanted patients. This approach is even more important to identify the correct indication for liver retransplantation.

Prospective: all previous studies have been performed on a retrospective modality; our study design allows the prospective data collection. Interestingly, the parameters able to investigate and quantify the indication and the contra-indication to retransplant cannot be accrued from previous databases even if many of them are prospectively registered. High-volume Centers allow the prospective enrollment of 50 cases in 3-10 months, according to Center activity.

Non-competitive: each Center will enroll the same number of cases. This is the best way to minimize the Center related bias.

Observational: although the randomized clinical trial remains the best modality of investigation, results from a well-designed large observational study are supposed to be robust and be translated into clinical practice.

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The IMPROVEMENT study

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NEW STUDY

International Multicenter Prospective, Non-competitive, Observational study to Validate and Optimize prediction models of 90-day and 1-year allograft failure after liver transplantation

*The **IMPROVEMENT** study*

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The RATIONALE of the study and the working hypothesis of the MODEL includes

three graft MACRO-types

1. **DBD (standard grafts)** **reference group**

2. **DCD (& high-risk DBD) grafts** ***high-risk group ?*** **perfusion machines**
   → ***reference group ?***

3. **Living Donor grafts** ***low-risk group ?*** **perfusion machines**
   for previously excluded grafts (steatosis >30%)

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NEW STUDY

International Multicenter Prospective, Non-competitive, Observational study to Validate and Optimize prediction models of 90-day and 1-year allograft failure after liver transplantation

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Primary objective: **to develop new algorithms for the timely prediction of Allograft Failure at 90 and 365 days** using a comprehensive prospectively collected dataset based on the current clinical practice of high-volume centers.

Secondary objectives:

1. to **validate** the already **existing predictive models** and the newly developed algorithms on a retrospective cohort of patients from low to medium-volume transplant centers;
2. to **develop** a novel **time-based dynamic algorithm**, with increasing accuracy **from the 3rd to 7th post-operative day**;
3. to **identify** the **best-time** for **re-transplant** (after stratification according to the post-operative weeks, months, trimesters);
4. to **investigate differences** in the incidence of **Allograft Failure** at 90 and 365 days according to **DBD, DCD, LD donor grafts**;
5. to **evaluate** the effect of **mitigation strategies** on the precipitating factors of Allograft Failure at 90 and 365 days;
6. to **investigate** the **association** of kinetic algorithms with development of **post-LT complications** (acute kidney injury, ischemic cholangiopathy, other complications);
7. to **identify risk factors** for **MORTALITY** that may contraindicate re-transplant.

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Inclusion Criteria

- Adult Patients (≥ 18 y.o.)
- First transplant (re-transplants allowed only if the first transplants are in the study)
- DBD grafts, DCD grafts, Living Donor grafts
- SPLIT grafts

Exclusion Criteria

- Combined transplants (liver-kidney, liver-heart, liver-pancreas)
- Domino transplants, Dual transplants
- Heterotopic transplants
- Recipient with Cholangiocarcinomas or CRLM

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	RETROSPECTIVE cohort low-VOLUME & intermediate-VOLUME (≤ 65 LTx per year)	PROSPECTIVE cohort high-VOLUME Centers (> 65 LTx per year)
Consecutive pts to be included	75	50
Sample size	3000	2000
N of Centers to be involved	40	40
Enrollment period	December 2019 → January 2017	April 2022 → November 2022
AIMs	Validation of PREVIOUS kinetic algorithms Possible Validation (?) of NEW ONE(S)	Validation of PREVIOUS kinetic algorithms DEVELOPENT of NEW ONE(S)
main KINETIC PARAMETERS	AST, PLT, BIL, INR	AST, PLT, BIL, INR
OUTCOME DATA and follow-up	Incidence of AF at 90 and 365 days Length of stay, 90d and 365d Graft Survival, 90d and 365d Patient Survival, Actuarial data at 36 months	Incidence of AF at 90 and 365 days Length of stay, 90d and 365d Graft Survival, 90d and 365d Patient Survival, Actuarial data at 12 months
PRE-OP. ASSESSMENT of FRAILTY, SARCOPENIA, MALNUTRITION, CARDIAC, RENAL RISK	NO	YES
BIOPSY of the graft (back-table, donor-hepatectomy for LD)	only when available	ALWAYS in DBD, DCD, LD
POST-OPERATIVE ASSESSMENT of FACTORS that favour or contraindicate RE-TRANSPLANT	NO	YES
Numeric parameters to be recorded	97	165

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