Umberto Cillo

ISO-SCORE 2.0:

Traslazione clinica di un sistema di bilanciamento di principi

STATI GENERALI

20 ANNI 1999·2019

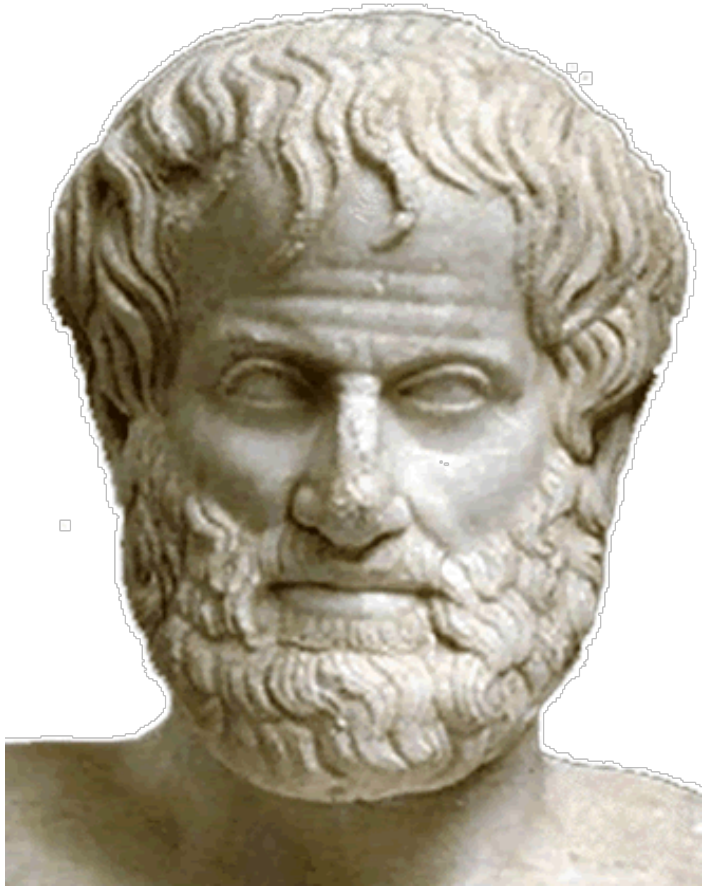
RETE NAZIONALE TRAPIANTI

6·7·8 NOVEMBRE

ROMA

Who Should Determine Allocation & Prioritization Policies?

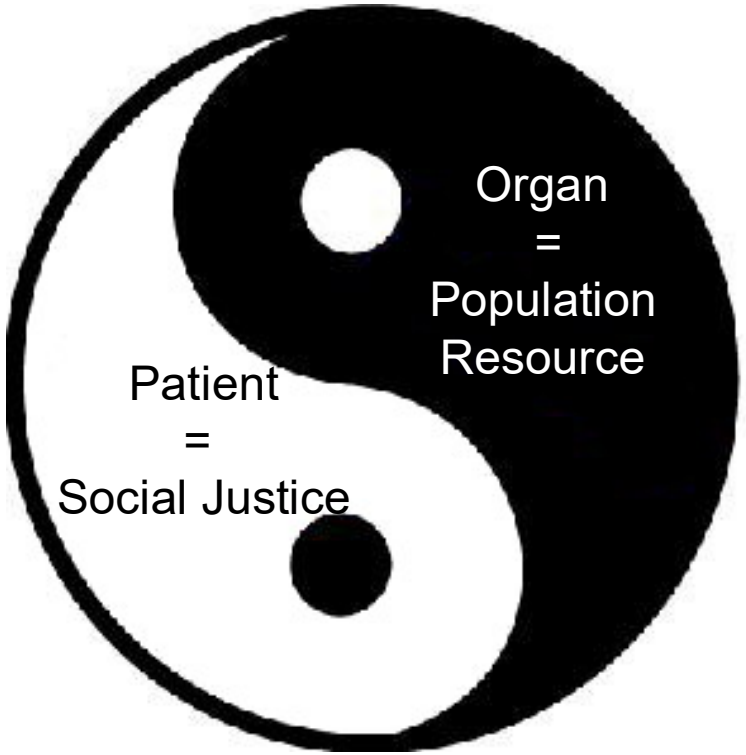
Aristotle defined justice as
“treating equal cases equally”



Who Should Determine Allocation & Prioritization Policies?

The Intrinsic Ethical Dichotomy of Liver Transplantation

- Fairness
- Equity
- Urgency



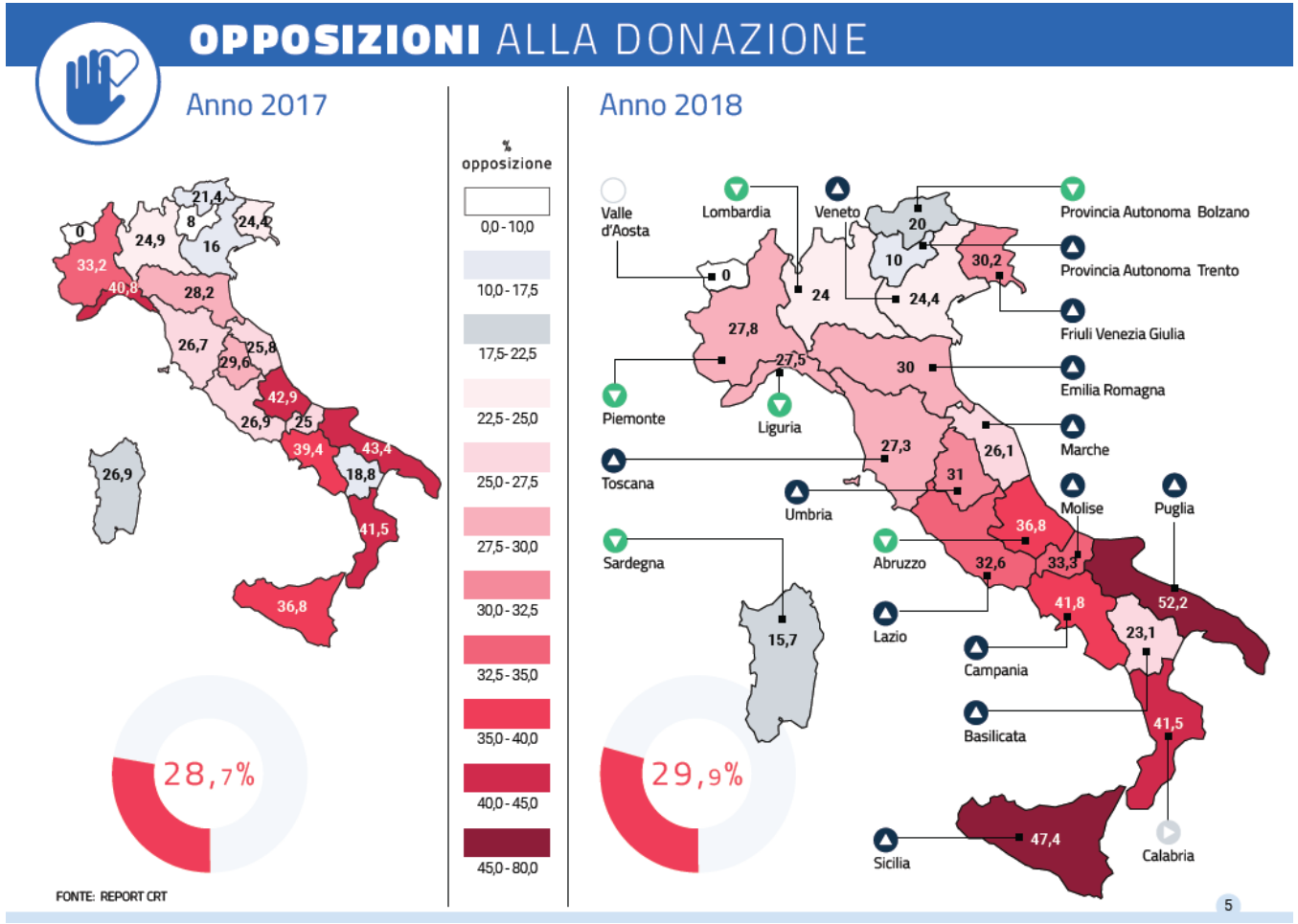
- Trasparency
- Maximization
- Utility

Allocation & Priority in Italy - Problem 1: The Geographycal Issue

HIgh costs of National Allocation: 10.000-

30.000 Euro per flight?

Allocation & Priority in Italy - Problem 2: The Socio-Cultural Issue



Centro Nazionale Trapianti

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20 ANNI 1999·2019

STATI GENERALI

RETE NAZIONALE TRAPIANTI

6·7·8 NOVEMBRE

ROMA

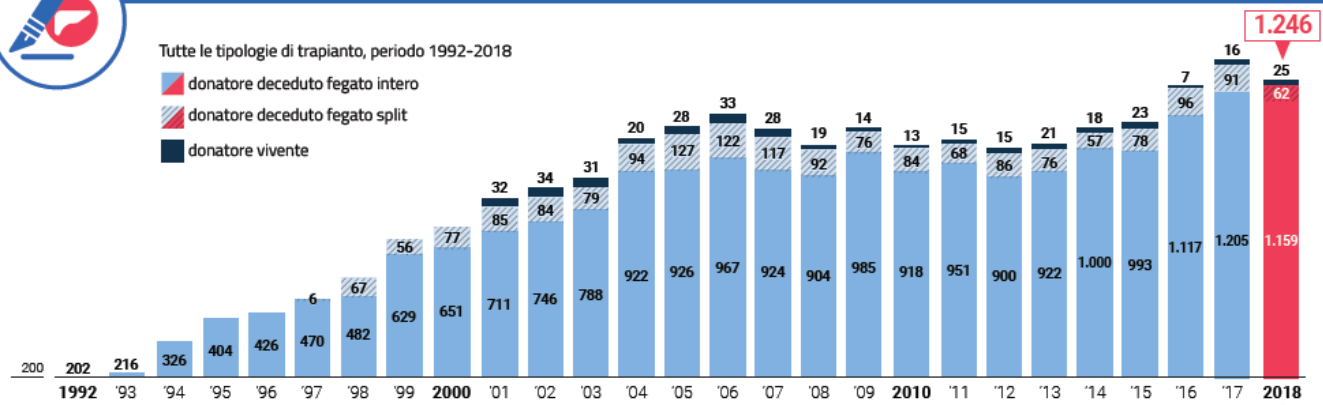
CNT data 2019

Allocation & Priority in Italy - Problem 2: The Socio-Cultural Issue

TRAPIANTI DI FEGATO

Tutte le tipologie di trapianto, periodo 1992-2018

donatore deceduto fegato intero
donatore deceduto fegato split
donatore vivente



ATTIVITÀ PER PROGRAMMA TRAPIANTO

trapianti da donatore deceduto | trapianti da donatore vivente

Pisa	161	-	Verona	47	-	Udine	26	-
Torino	152	-	Ancona	46	-	Roma - Sapienza	25	-
Milano - Niguarda*	116	1	Napoli - Cardarelli	37	-	Cagliari	23	-
Padova	101	1	Modena	37	-	Roma - Bambin Gesù	20	8
Bergamo	90	-	Milano - Tumori	36	-	Bari	20	-
Bologna	74	-	Roma - San Camillo	34	-			
Palermo - ISMETT	62	15	Roma - Gemelli	33	-			
Milano - Policlinico	52	-	Roma - Tor Vergata	29	-			

FONTE: REPORT CRT

* in collaborazione con Genova per 37 trapianti di fegato

LA MAPPA

9

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STATI GENERALI
RETE NAZIONALE TRAPIANTI
20 ANNI 1999·2019

6·7·8 NOVEMBRE
ROMA

CNT data 2019

Allocation & Priority in Italy
Differences Among Different Diseases

Liver cirrhosis: allocation according to MELD score

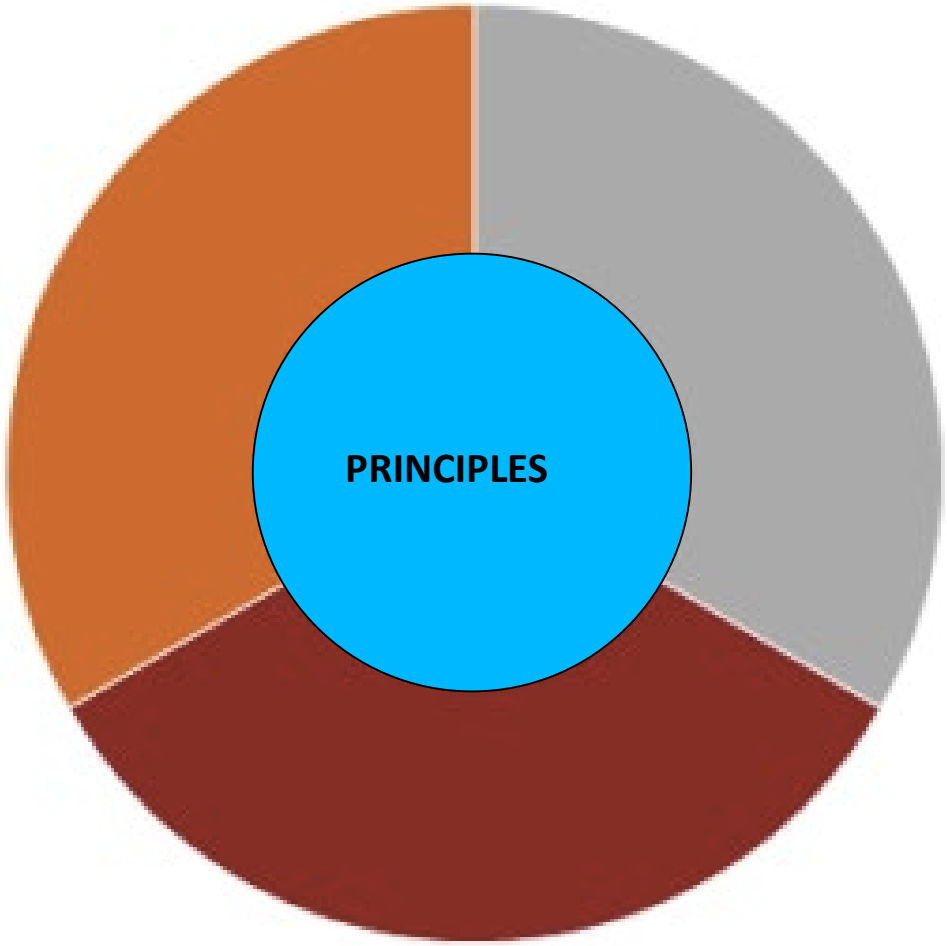
HCC:
allocation according to national waiting list prioritization

MELD-exceptions:

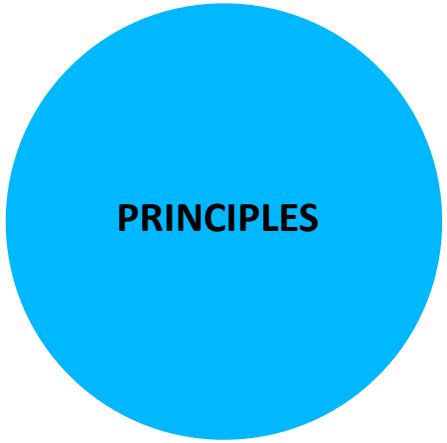
Priority and sharing	LT indication
P1 (Macro area sharing after serving those with MELD>30)*	Rendu–Osler–Weber Hepatoblastoma (young adult) Hemangioma (if Kasabach Merritt syndrome) Acute late ReLT FAP (if domino)
P2 (Sharing at regional level)	Hepato-pulmonary syndrome PPH Refractory hydrothorax Chronic late ReLT Hepato-renal syndrome (if not automatically equated to MELD) Previous severe infections
P3 (Sharing at regional level)	Refractory ascites FAP Wilson's (with compensated cirrhosis and initial neurological symptoms) NET metastases Hemangioendotheliomas
P4 (Sharing at regional level)	PSC or PBC with intractable pruritus Polycystic disease Complicated adenoma Hemangiomas
P Multidisciplinary (Center-based)	Hepatic encephalopathy Fibrolamellar HCC Liver adenomatosis (not complicated) Hilar cholangiocarcinoma CRC metastases

CNT data 2019

The allocation Process



The allocation Process



“No single principle, utility, urgency or benefit can adequately address the complexity of clinical situations, rather a blended approach is advisable” Persad 2007

Allocazione delle Risorse nel Trapianto di Fegato: I PRINCIPI

URGENCY

Criterio di URGENZA

UTILITY

Criterio della PROSPETTIVA DI SUCCESSO

Criterio di BENEFICIO

Allocazione delle Risorse nel Trapianto di Fegato: Aspetti Etici

A.I.S.F.
ASSOCIAZIONE ITALIANA PER LO STUDIO DEL FEGATO
COMMISSIONE BIOETICA PERMANENTE

Criterio di URGENZA

Privilegia chi ha la prognosi peggiore se non trapiantato e chi rischia il *drop-out* dalla lista

Guarda al *Medical Need*

Si ispira all'orientamento egualitarista del nostro orientamento

Privilegia il principio di beneficialità e di sussidiarietà

Ha la priorità sugli altri criteri per salvaguardare vita e integrità fisica dei pazienti

Allocazione delle Risorse nel Trapianto di Fegato: Aspetti Etici

Criterio della PROSPETTIVA DI SUCCESSO

Privilegia chi ha le migliori prospettive
di sopravvivenza post-trapianto

Precedentemente indicato come Principio di Utilità

Mira a massimizzare il risultato (n° di anni di vita guadagnati)
ottenuto con le limitate risorse a disposizione

Si giustifica nell'ottica del perseguimento dell'APPROPRIATEZZA
(efficacia e sicurezza per il paziente
+ efficienza dell'impiego delle risorse-organo)

NON considera il NEED

Allocazione delle Risorse nel Trapianto di Fegato: Aspetti Etici

Criterio del BENEFICIO

Incorpora e bilancia gli altri due criteri, privilegiando,
a parità di urgenza, i casi in cui il *Transplant Survival Benefit* sia maggiore

Mira a massimizzare il risultato (n° di anni di vita guadagnati)
ottenuto con le limitate risorse a disposizione TENENDO CONTO DELLE ALTERNATIVE

Può rivelarsi estremamente utile ed appropriato
specialmente in fase di valutazione dell'idoneità del paziente
per l'iscrizione in lista d'attesa

Sarà necessario esplicitare con chiarezza il *Time Horizon*
entro cui il *Survival Benefit* va misurato

La maggiore criticità nell'applicazione consiste nel fatto che
il calcolo di indicatori diretti di beneficio (*gain in life expectancy* del paziente)
è ancora troppo complesso e poco accurato in termini di potere predittivo

The Allocation Process in Italy: Urgency

Table 4: Proposed and agreed national waiting list prioritization policies and geographical distribution of organ allocation for patients with or without HCC and those considered MELD exceptions.

Priority	PTS Category	Points ISO	Allocation area
Super-Urgent	FHF, early reLT	(first come, first served)	Nationwide
Urgent	MELD >30	Biochemical MELD	Macro area
Urgent	EXCEPTIONS P1	30	Macro area
Standard	EXCEPTIONS P2	25 + 1/month	Region
Standard	Bioch MELD 15–29	Biochemical MELD	Region
Standard HCC	HCC: TT_{DR}-TT_{PR} (downstaged patients or partial responders to bridge	HCC-MELD[19] + extra points for time or MELD 22 at entry + extra points for time (at regional board's discretion)§ Cap at 29	Region
	or late	HCC-MELD[19]	Region
		Criteria for awarding extra points for longer waits and priority class migration on disease progression will be set regionally (regional board approval)#	
		Biochemical MELD	Region
		20 + 1 every 2 months	Region
		15 + 1 every 2 months	Region

URGENCY PRINCIPLE

Cillo U et I-BELT, Am J Transpl; 2015 Vol 20: 1-10

The Allocation Process in Italy: Benefit

Table 4: Proposed and agreed national waiting list prioritization policies and geographical distribution of organ allocation for patients with or without HCC and those considered MELD exceptions.

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Standard HCC Stratum 2	HCC: TT_{FR} (first presentation or late recurrence)	HCC-MELD[19] Criteria for awarding extra points for longer waits and priority class migration on disease progression will be set regionally (regional board approval)#	Region
[illegible]	[illegible]	Biochemical MELD	Region
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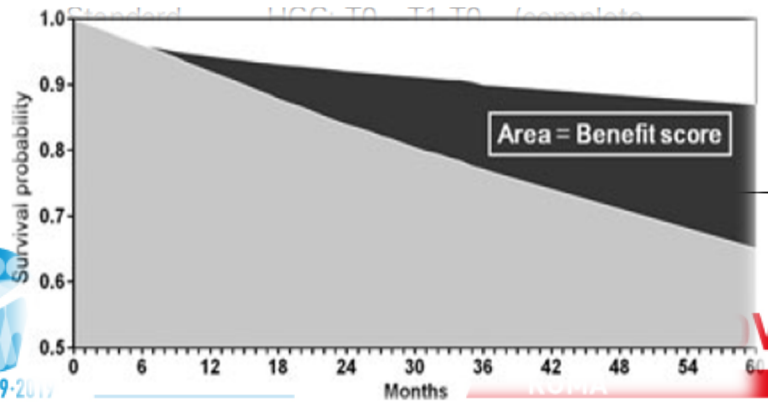

BENEFIT
Pre-LT +
Post-LT
Utility

Cillo U et I-BELT, Am J Transpl; 2015 Vol 20: 1-10

The Allocation Process in Italy: Utility

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Standard HCC Stratum 2	HCC: TT_{FR} (first presentation or late recurrence)	HCC-MELD[19] Criteria for awarding extra points for long migration on disease progression will board approval)#	
Standard HCC Stratum 3	HCC: $T0_C$–T1-$T0_L$ (complete responders or T1 tumors)	Biochemical MELD	Region
Standard	EXCEPTIONS P3	20 + 1 every 2 months	Region
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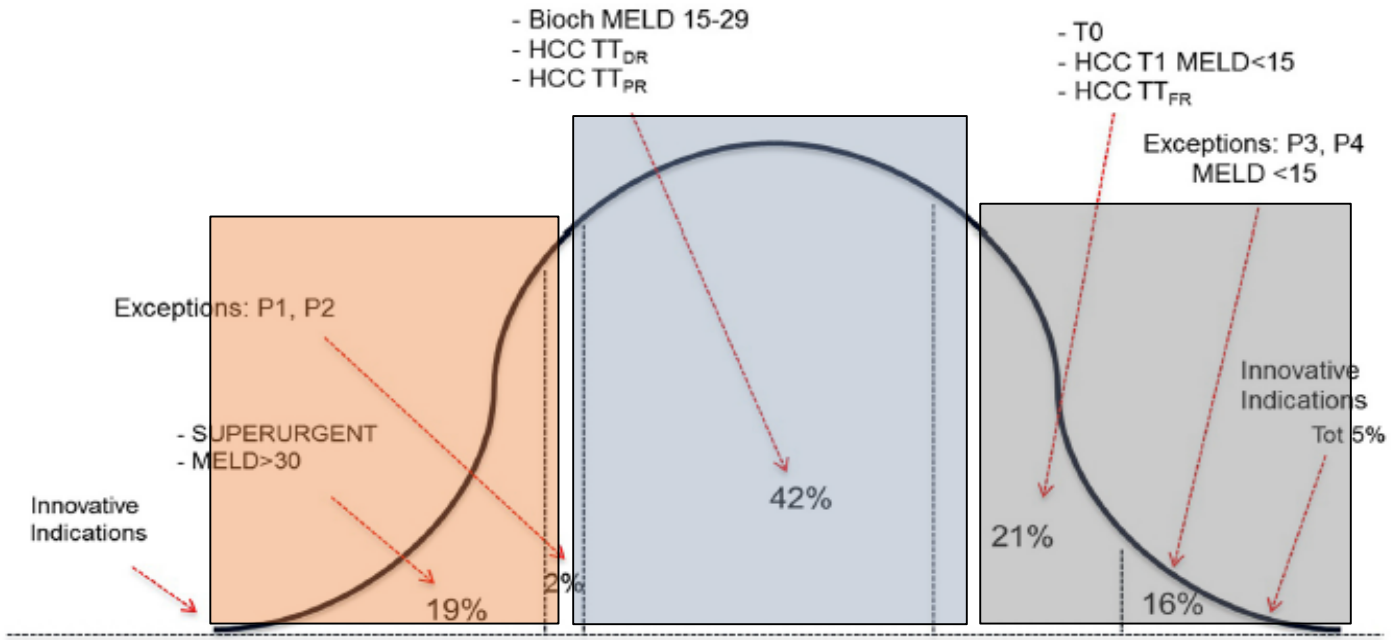
POST-LT UTILITY

Cillo U et I-BELT, Am J Transpl; 2015 Vol 20: 1-10

BALANCING PRINCIPLES



PRINCIPLE	FUTURE BENEFIT	Pure URGENCY HIGH BENEFIT	Low ALTERNATIVES HIGH BENEFIT	Post OLT UTILITY LOW BENEFIT	FUTURE BENEFIT
PRIORITY	Multidisc	Sickest first	Greater benefit	Waitlist time	Multidisc
PREDICTOR	-----	MELD/time bonus	MELD, HCC-MELD	MELD + time bonus	-----
PREVAL 2014	-----	21%	42%	37%	------
FUTURE AIM	Up to2.5%	To be reduced	To be increased	Not greater than 40%	Up to2.5%

- **Increase cost effectiveness**
- **Tx earlier reducing urgent Tx**
- **Reduce Tx for Pts with alternatives**

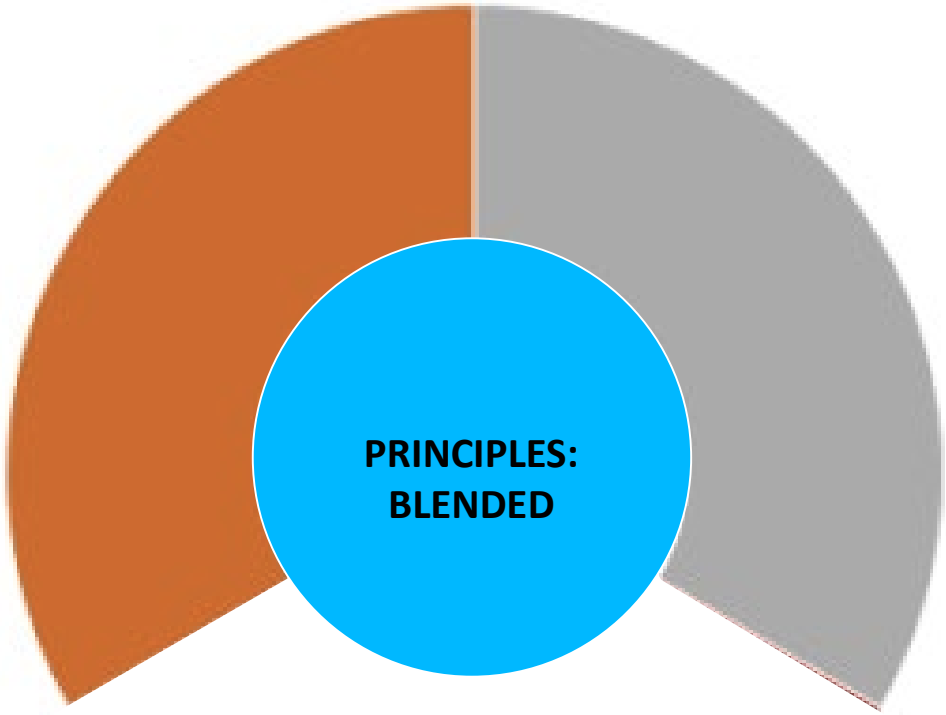
Cillo U et I-BELT, Am J Transpl; 2015 Vol 20: 1-10

The allocation Process

SELECTION

Upper Threshold:
Minimal PT utility
60% surv 5 yrs

Lower thershold:
Minimal benefit
MELD 15, HCC T2



PRIORITY

The Allocation Process in Italy

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URGENCY PRINCIPLE

BENEFIT Pre-LT + Post-LT Utility

POST-LT UTILITY

Cillo U et I-BELT, Am J Transpl; 2015 Vol 20: 1-10

Allocation Principles: Geographycal Distribution

Table 4: Proposed and agreed national waiting list prioritization policies and geographical distribution of organ allocation for patients with or without HCC and those considered MELD exceptions.

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Cillo U et I-BELT, Am J Transpl; 2015 Vol 20: 1-10

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Cillo U et I-BELT, Am J Transpl; 2015 Vol 20: 1-10

Allocation Principles: Geographycal Distribution

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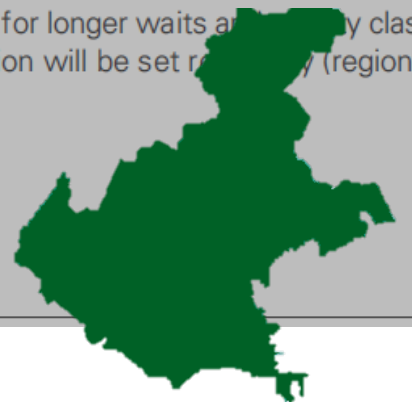
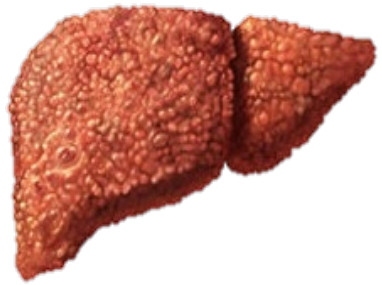
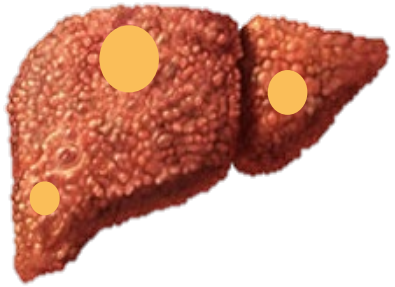
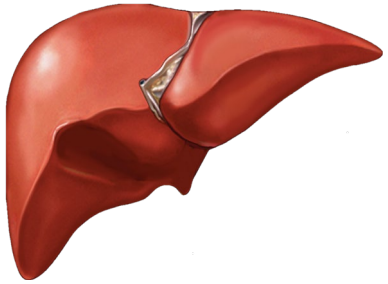


Cillo U et I-BELT, Am J Transpl; 2015 Vol 20: 1-10

Priority & Disease Eterogeneity







Liver cirrhosis: allocation according to MELD score

HCC:
allocation according to national waiting list prioritization

MELD-exceptions:

Priority and sharing	LT indication
P1 (Macro area sharing after serving those with MELD>30)*	Rendu–Osler–Weber Hepatoblastoma (young adult) Hemangioma (if Kasabach Merritt syndrome) Acute late ReLT FAP (if domino)
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P4 (Sharing at regional level)	PSC or PBC with intractable pruritus Polycystic disease Complicated adenoma Hemangiomas
P Multidisciplinary (Center-based)	Hepatic encephalopathy Fibrolamellar HCC Liver adenomatosis (not complicated) Hilar cholangiocarcinoma CRC metastases

20 ANNI 1999·2019

Priority for Different Diseases

Italian Consensus Conference to Create a common Priority Scale for Exceptions

Table 2: Agreed priority strata for MELD exceptions and corresponding organ-sharing areas

Priority and sharing	LT indication
P1 (Macro area sharing after serving those with MELD>30)*	Rendu–Osler–Weber
	Hepatoblastoma (young adult)
	Hemangioma (if Kasabach Merritt syndrome)
High benefit, Urgency	Acute late ReLT
	FAP (if domino)
P2 (Sharing at regional level)	Hepato-pulmonary syndrome
	PPH
High benefit	Refractory hydrothorax
	Chronic late ReLT
	Hepato-renal syndrome (if not automatically equated to MELD)
	Previous severe infections
P3 (Sharing at regional level)	Refractory ascites
	FAP
Benefit	Wilson's (with compensated cirrhosis and initial neurological symptoms)
	NET metastases
	Hemangioendotheliomas
P4 (Sharing at regional level)	PSC or PBC with intractable pruritus
	Polycystic disease
Utility	Complicated adenoma
	Hemangiomas
P Multidisciplinary (Center-based)	Hepatic encephalopathy
	Fibrolamellar HCC
	Liver adenomatosis (not complicated)
	Hilar cholangiocarcinoma
	CRC metastases

Cillo U et I-BELT, Am J Transpl; 2015 Vol 20: 1-10

MELD Adjusted Score For Exceptions

10 mesi per passare alla categoria successiva

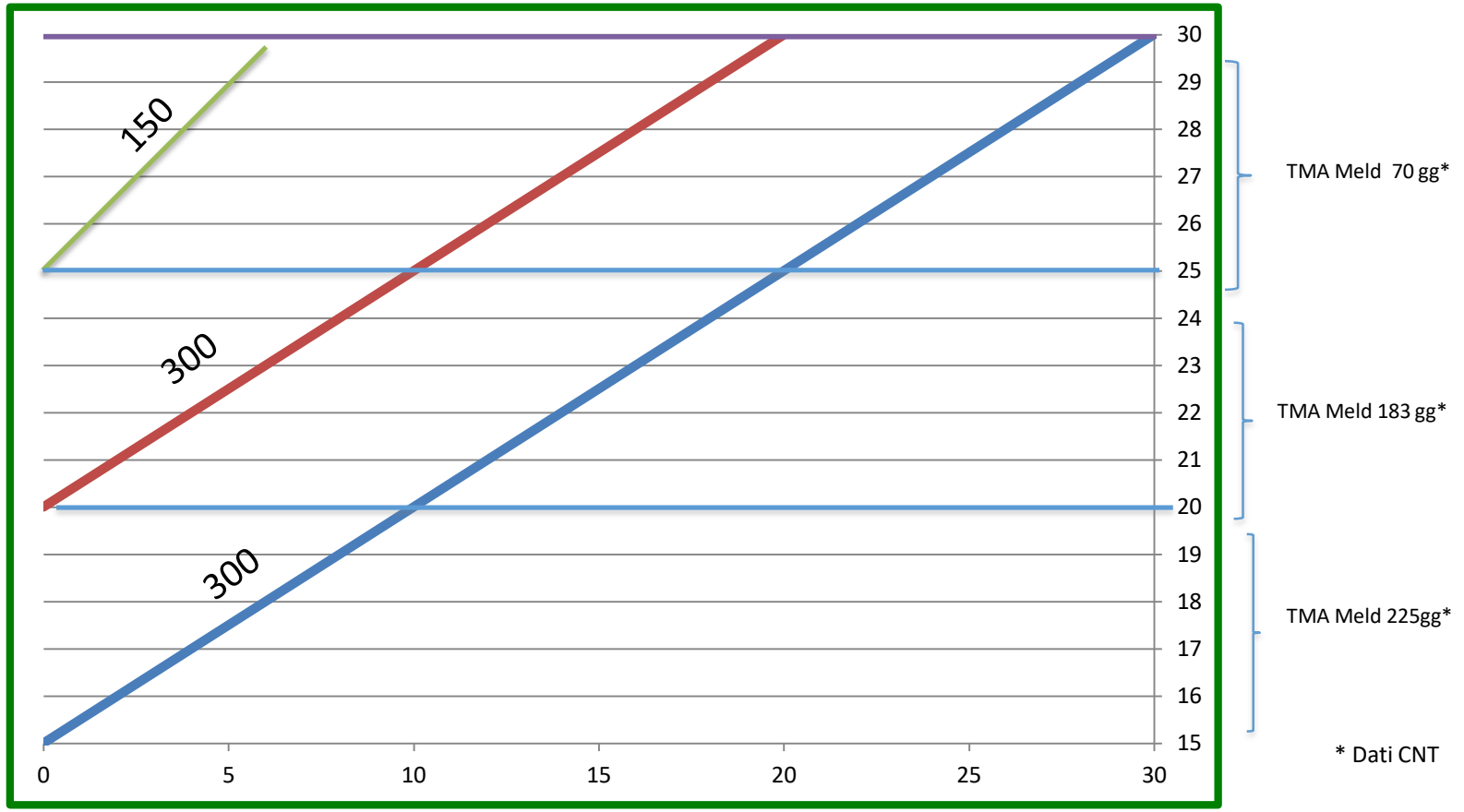
Adjusted MELD

P1 = 30

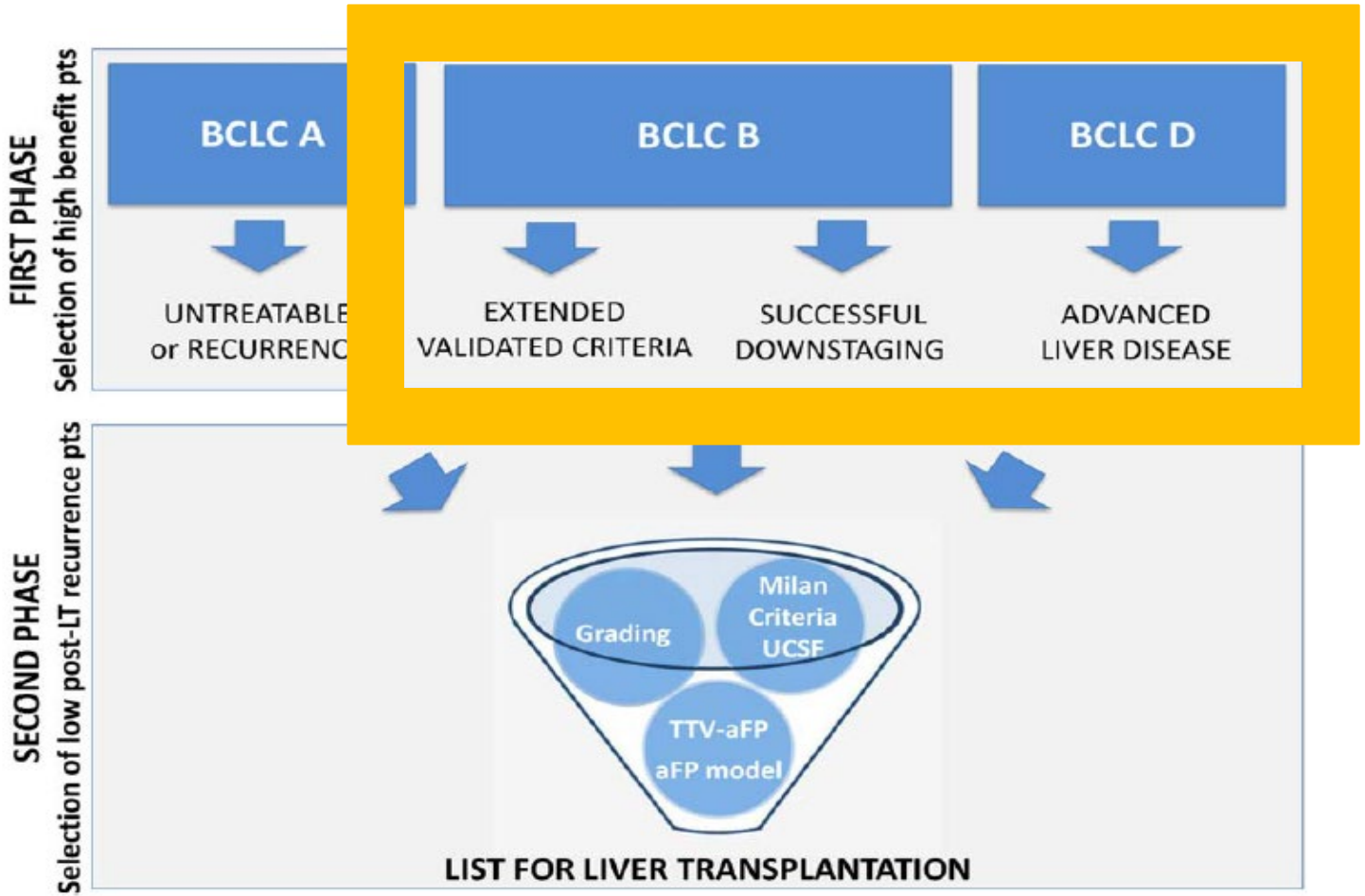
P2 = 25

P3 = 20

P4 =15



Liver Transplantation for Hepatocellular Carcinoma Through the Lens of Transplant Benefit



Cillo U et al, Hepatology. 2016 Dec 23.

Principio: BENEFIT
Predittore: HCC MELD

ST 1

- Downstaging
- Early recurrence
- Ineffective Bridge therapy → PD / SD / PR

ISO=HCC MELD, start from 22
+1 ISO/MESE

ST 2

- HCC, first diagnosis, late recurrence

ISO=HCC MELD,
+ 1 ISO/MESE after 3 months

ST 3

- HCC T1 or complete response

ISO= BIOCHEMICAL MELD

ISO SCORE 2.0

- Torino 2011, Padova 2014, Cagliari 2017: ISO SCORE 1.0,
- Firenze 2018, Bologna 2018, Roma 2019: ISO SCORE 2.0

- Gruppo di lavoro SITO Collegio CTF, AISF, CNT

- OBIETTIVI:

  Implementare il sistema ISO per:

  - Migliorare la capacità del sistema di catturare i pazienti a rischio
  - Rendere il sistema più fruibile per ridurre la disomogeneità nazionale ancora presente
  - Incrementare la leggibilità dei dati da parte del CNT
  - Sanare alcune inefficienze per chi è strettamente aderente a ISO
  - Rendere il sistema più flessibile

ISO SCORE 2.0

Disomogeneità tra le dimensioni di lista, i tempi di attesa in lista in Italia ed il rischio di morte/dropout in Italia

Tema delle eccezioni in deroga

Basso utilizzo della allocazione di MACROAREA per MELD 30 o superiori

Nuove regole di allocazione Nazionale – ISO 2.0

NATIONAL time	**ReOLTX <15gg SUPERURGENZA**	
MACRO time	**P1 + NaMELD UGUALE o >29**	**NaMELD** **Rendu-Osler-Weber** **Hepatoblastoma (young adult)** **Hemangioma (if kasaback Merrit Syndrome** **FAP (if Domino)** **ReOLTX >15gg con tr.vascolari ascessi, colangiopatia con procedure invasive, DNF15-90**
REGIONAL ISO score	**P2 (Sharing at regional level)** **High priority** **NO CAP 29** **ISO 25 + 1 PUNTO/MESE**	**Hepato-pulmonary Sindrome** **PPH** **Refractory Hydrothorax** **Refractory ascites** **Re-LT >15 gg** **Hepato-renal Syndrome (..MELD)** **Previous Severe infection** **HD cronica e peggioramento epatologico (BILIRUBINA >3MG/DL)** **Malattia policistica in dialisi**
	P3 (Sharing at Regional Level) **Intermediate Priority** **NO CAP 29** **ISO 20 + 1 PUNTO OGNI 2 mesi**	**FAP** **Wilson's** **NET metastases** **Hemangioendotheliomas** ***F*/R di pz in HD cronica**
	P4 (Sharing at Center) **Low priority)** **NO CAP 29** **ISO 15 + 1 PUNTO OGNI 2 MESI**	**PSC or PBC with intractable pruritus** **Polycistic disease** **Complicated adenoma** **Hemangiomas** **PVT G3, G4 se risoluzione no priorità** ***F/R pre-emptive***

INGERSSO IN LISTA CON MELD 15 SE NON ECCEZIONI, NON PIU' CAP A 29

Nuove regole di allocazione Nazionale – ISO 2.0

HCC	**Eliminata la regola ingresso a 22** **Tutti gli HCC sono descritti come HCC MELD** **HCC risposta sostenuta:>3 mesi, NO LI-RAD4, AFP<50** **HCC curato: v. sopra >24 mesi** **Recall policy non superiore a tre mesi** **Se recidiva entro i 24 mesi Stratum 1 con ISO calcolato dalla immissione in lista** **Se ricorrenza dopo i 24 ricolcolo ISO dal tempo di ricorrenza** **Principio di progressività di attribuzione degli extra ISO scores tra i diversi strati HCC** **In generale inizio computo degli extra ISO solo dallo sviluppo dell'HCC** **HCC DW risposta sostenuta dopo 6 mesi**	
STRATUM 1 (DW PR ER)	**Entra con HCC MELD + 1 PUNTO/MESE (salvo altro modello regionale reso pubblico)**	Disponibilità regionale
STRATUM 2 (T2, LR)	**Entra con HCC MELD + 1 PUNTO/MESE DOPO 6 MESI (salvo altro modello regionale reso pubblico)**	Disponibilità regionale
STRATUM 3 (CR, T1)	**ENTRA CON HCC MELD (stretta recall policy, ricorrenza<24 mesi in Stratum 1, ricorrenza >24 mesi: extra ISO dalla nuova diagnosi) (salvo altro modello regionale reso pubblico)**	Disponibilità regionale

Nuove regole di allocazione Nazionale – ISO 2.0

FEGATO/RENE

- IL RENE SEGUE L'ALLOCAZIONE DEL FEGATO

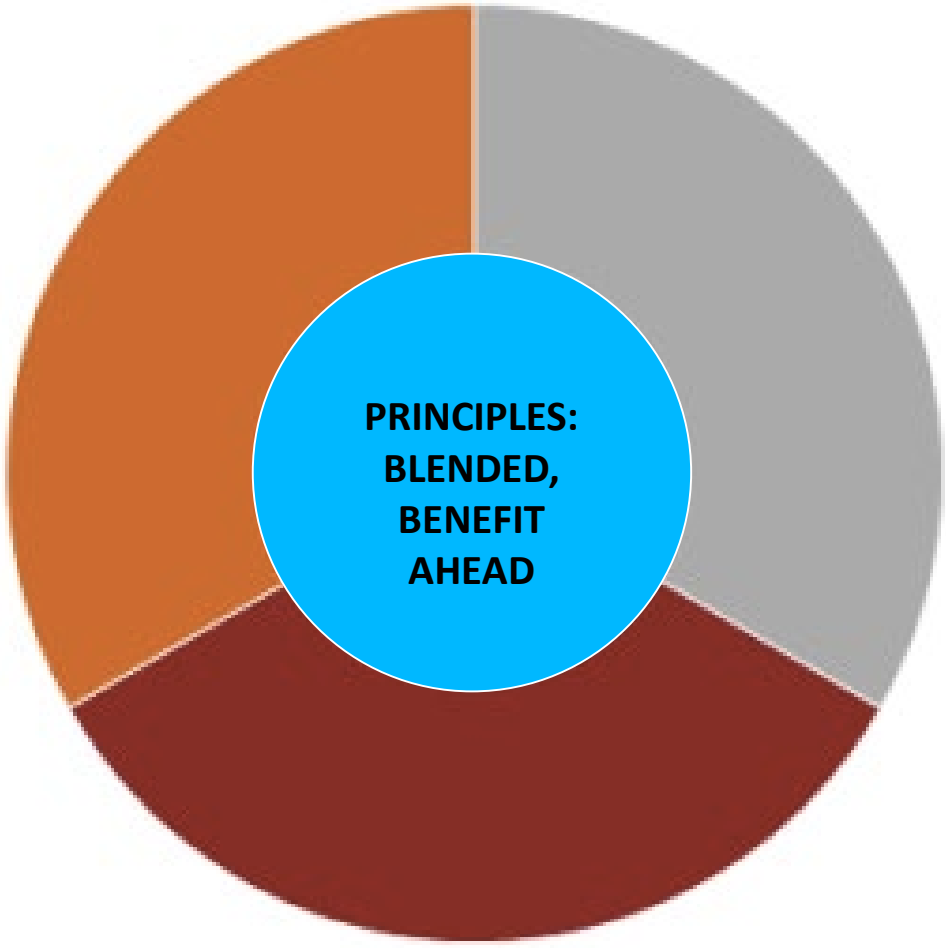
BOARD NAZIONALE TRAPIANTO FEGATO-RENE

Liver Allocation Process in Italy

SELECTION

Upper Threshold:
Minimal PT utility
60% surv 5 yrs

Lower thershold:
Minimal benefit
MELD 15, HCC T2



PRIORITY
1. Superurgent
2. Na MELD 29 o > = P1
3. ISO score

D-R MATCH
Clincal decision/ flexibility up to 30%

20 ANNI 1999-2019
STATI GENERALI
RETE NAZIONALE
TRAPIANTI

Endpoints for System Evaluation and Adjust (Performance Indicators)

PRIMARY: List mortality + dropout for disease progression
stratifyied according to
- P1-4
- HCC strata
- pure Na MELD

Expected: overlap

SECONDARY: List waiting time
- P1-4
- HCC strata
- pure Na MELD

Expected: scale

SISTEMA DI ALLOCAZIONE PADOVANO PRE ISO SCORE

Doppia lista per ciascun gruppo sanguigno

Lista MELD
Pazienti con cirrosi ordinati secondo MELD

Lista non MELD
Eccezioni – HCC con MELD <20

Epatocarcinoma – PRIMO CRITERIO = RISPOSTA ALLA TERAPIA

I.	Malattia Stabile / Progressiva*	= 6
II.	Intrattabile (sede, gravità della cirrosi)	= 5
III.	Risposta parziale**	= 4
IV.	Ricorrenza (> 6 mesi dall'ultima terapia)	= 3
V.	Nuovo tumore in attesa di stadiazione post-terapia	= 2
VI.	Risposta completa (necrosi tumorale completa)	= 1

* > 50% tumore vitale residuo; ↑ n° noduli; AFP ≥ livello pre-terapia
** < 50% tumore vitale residuo; AFP < livello pre-terapia

Epatocarcinoma - SECONDO CRITERIO = STADIO

I.	T1	1 nodulo ≤ 1.9 cm
II.	T2	1 nodulo 2-5 cm; 2-3 noduli tutti ≤ 3 cm
III.	T3	1 nodulo > 5 cm; 2-3 noduli 1 > 3 cm
IV.	T4a	≥ 4 noduli, qualsiasi taglia;
	T4b	ogni T con invasione vascolare macroscopica
	N1, M1	Metastasi

Epatocarcinoma - TERZO CRITERIO = TEMPO

Tempo (giorni) in lista d'attesa con diagnosi di epatocarcinoma.

Criteri RECIST

CRITERI DI ESCLUSIONE

- Invasione vascolare o metastasi (T4b e /o N1, M1)
- HCC scarsamente differenziato alla biopsia

ALTRE ECCEZIONI

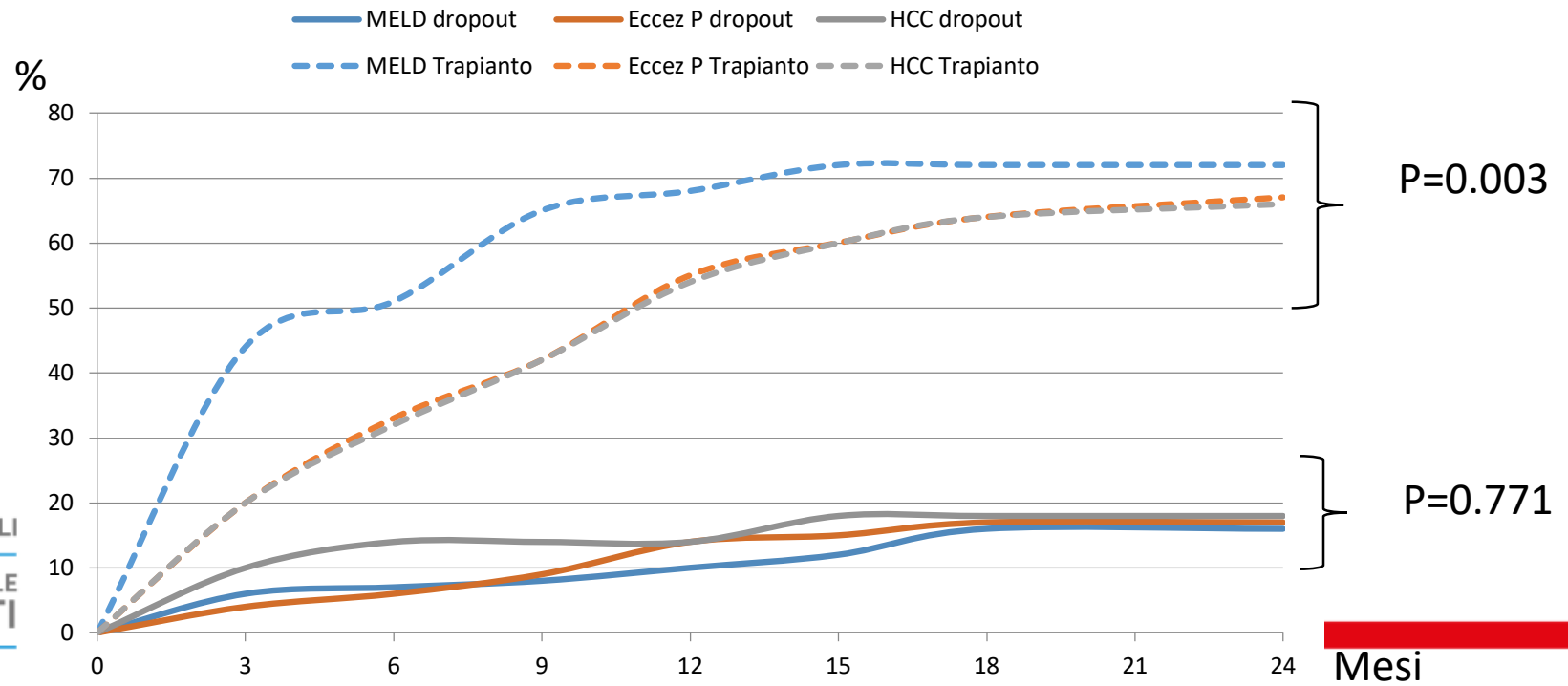
Sono posizionate in lista sulla base del giudizio clinico collegiale espresso nella riunione settimanale multidisciplinare.

Confronto della probabilità di DROPOUT e di TRAPIANTO stratificata per classe di priorità nel periodo ISO 1.0 (2016-2019) – Università di PADOVA

% ASSOLUTE NON TEMPO DIPENDENTI

VARIABILI	P0	P1	P2	P3	P4	Stratum1	Stratum 2	Stratum 3
Dropout	12 (11%)	1 (9%)	3 (14%)	14 (17%)	1 (7%)	7 (14%)	7 (17%)	1 (10%)
Trapianto	69 (64%)	8 (73%)	12 (55%)	46 (56%)	9 (64%)	26 (50%)	23 (55%)	6 (60%)

COMPETING RISK ANALYSIS



STATI GENERALI
RETE NAZIONALE TRAPIANTI
20 ANNI 1999-2019

Cambiamento nella stratificazione dei pazienti in lista e del valore di ISO nel passaggio da ISO 1.0 ad ISO 2.0 – Università di PADOVA

VARIABILI		ISO 1.0 Giu 2019		ISO 2.0 Lug 2019		
		N° (%)	Valore ISO	N° (%)		Valore ISO
PO		36 (38.3)	16 (13-21)	40 (43.5)		15 (13-21)
P1		2 (2.1)	30 (30-30)	2 (2.2)		30 (30-30)
P2	*	6 (6.4)	29 (29-29)	14 (15.2)		29 (27-34)
P3	*	12 (12.8)	22 (20-26)	3 (3.3)		29 (20-54)
P4		3 (3.2)	26 (21-28)	-		-
HCC STRATUM 1		17 (18.1)	23 (23-29)	16 (17.4)	*	17 (15-20)
HCC STRATUM 2		6 (6.4)	26 (20-29)	7 (7.6)	*	20 (19-24)
HCC STRATUM 3		12 (12.8)	9 (7-13)	10 (10.9)	*	17 (14-24)

- > ISO in P2-P3 per rimozione CAP
- > % P2 per ascite refrattaria da P3 A P2

- < ISO in Str 1-2 per HCC-MELD (non più 22)
- > ISO in Str 3 per HCC MELD (non più MELD bioch)

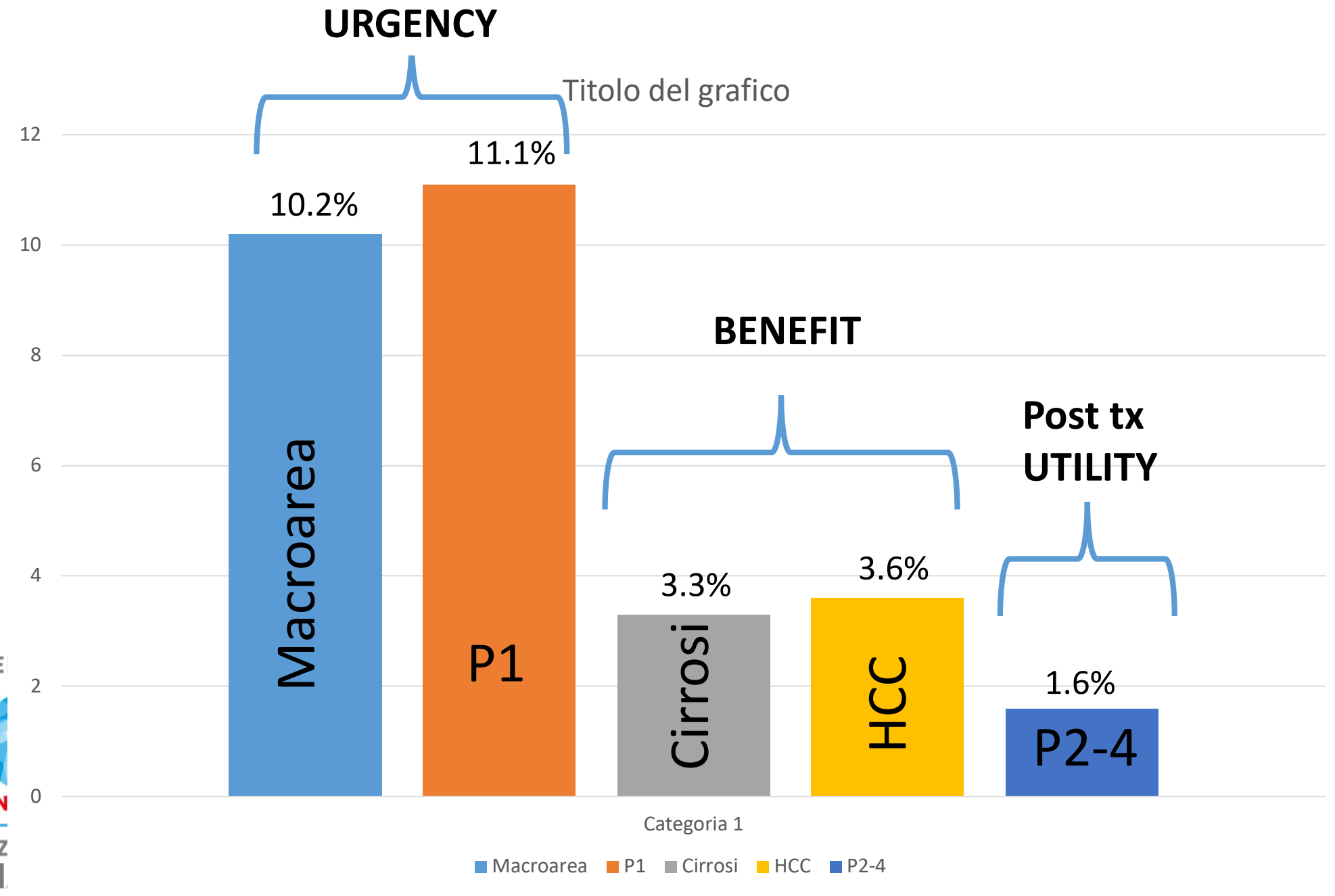
* P<0,05

Dati nazionali ISO SCORE 2.0

DROP-OUT «VERI» NEL PERIODO PER CATEGORIA 01/07/2019 – 30/09/2019

% DROP-out per categoria							
	Pediatrico	Super-urgenza	Macroarea	Eccezioni P1	Cirrosi	HCC	Eccezioni P2-4
Decessi	1	0	4	1	9	5	4
Non idoneità	3	0	2		6	12	1
Totale transitato in lista	**70**	**24**	**59**	**9**	**451**	**467**	**306**
% DROP-out per categoria	**5,7**		**10,2**	**11,1**	**3,3**	**3,6**	**1,6**

Courtesy of Sivia Trapiani & Andrea Ricci - CNT


URGENCY
Titolo del grafico
12
10
8
6
4
2
0
10.2%
11.1%
Macroarea
P1
BENEFIT
3.3%
3.6%
Cirrosi
HCC
Post tx
UTILITY
1.6%
P2-4
Categoria 1
Macroarea
P1
Cirrosi
HCC
P2-4

Who Should Determine Allocation & Prioritization Policies?

Aristotle defined justice as
“treating equal cases equally”

Need for:

- Big data analysis
- Benchmarking processes
- Regional ethical evaluations
- Public appraisals