The Effect of Extracorporeal C3A Cellular Therapy in Severe Alcoholic Hepatitis – The VTI-208 ELAD Trial

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Disclosures

- Julie A. Thompson
  - Consulting: Vital Therapies, Inc. (VTL)
- David J. Reich
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- Lewis W. Teperman
  - Clinical Advisory Board Member: VTL
- Ram Subramanian
  - Consulting: VTL
- Jan Stange
  - Consulting: VTL

The following have nothing pertinent to disclose:
Ali Al-Khafaji, Ross Mac Nicholas, Tarek I. Hassanein

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Background

- 60,000 - 90,000 patients admitted annually to US hospitals with diagnosis of alcoholic hepatitis[1,2]
- 30 - 50% mortality at 90 days with severe disease
- Most patients are not candidates for transplant
- No treatment other than transplant has been shown to reduce long term mortality

[1]Liangpunsakul, S., J Clin Gastroenterol, 2011
[2]HCUP data on number of hospital admissions for AAH in 2013

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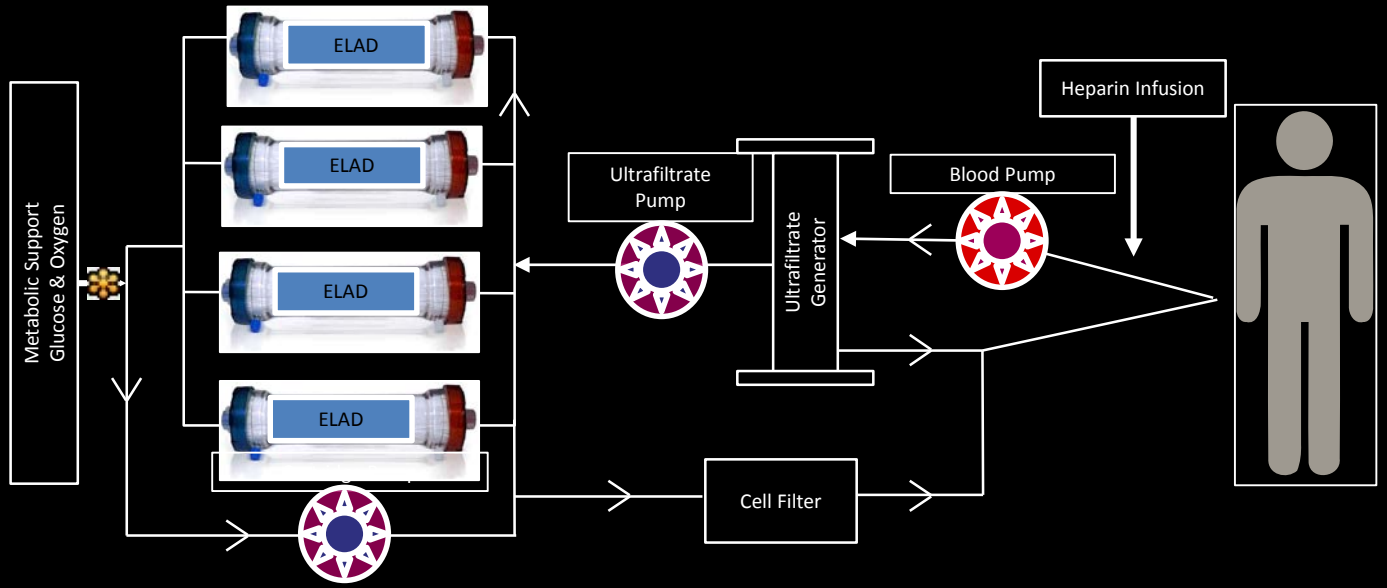
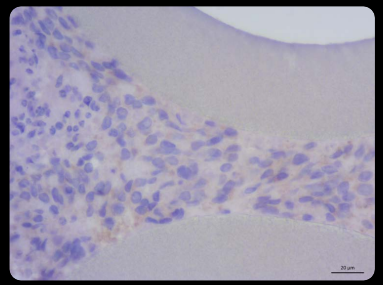
The ELAD System



4 ELAD® Cartridges
With Immortal
C3A Human Liver Cells



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C3A Cells Express Numerous Proteins Relevant to Liver Function

- Anti-inflammatory proteins[1]
  - IL-1 receptor antagonist
  - Alpha-1-antitrypsin
  - Gelsolin
- Growth factors[2]
  - Amphiregulin
  - TGFα
  - VEGF
- Anti-apoptotic factors[2]
  - EGFR signaling ligands
- Coagulation factors[3]
  - Pro/anti-coagulation
  - Anti-fibrinolysis
- Cytochrome P450 isoenzymes[4]
  - e.g. CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5

References:
[1] Landeen, 2015, ILTS, P249
[2] Bedard, 2015, AASLD, P1770
[3] Riley, Experimental Biology, *in submission*
[4] Landeen, 2015, J Hepatology 62:S764

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Aim

To evaluate:

- Safety and efficacy of ELAD treatment on overall survival in subjects with severe alcoholic hepatitis
- Influence of pre-specified baseline parameters (e.g. MELD, MELD components, age) on outcome

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Design

- International, prospective, randomized, controlled, open-label Phase III trial
- 200 subjects
- 1:1 randomization:
  - ELAD (5 days continuous therapy) plus protocol-mandated standard of care (SOC) or
  - SOC alone
- Weekly home health visits post-discharge
- Primary endpoint:
  - Kaplan-Meier analysis of overall survival
- Secondary endpoints:
  - Proportion of survivors at 28 and 91 days

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Major Inclusion / Exclusion Criteria

Inclusion

- Age >18
- Total bilirubin ≥8 mg/dL
- EtOH within 6 weeks of onset of symptoms
- Group A (sAAH)
  - Maddrey DF ≥32
  - Liver biopsy <u>or</u>
  - At least 2 out of:
    - Hepatomegaly
    - AST>ALT
    - Elevated WBC
    - Ascites
- Group B (AILD)
  - MELD 18 – 35
  - Histological / laboratory / medical evidence of underlying disease

Exclusion

- Platelets <40,000/mm^3
- INR >3.5
- MELD >35
- AST >500 IU/l
- Bilirubin reduction of >20% in prior 72 hours
- Uncontrolled infection, bleeding or hemodynamic instability
- Small liver size (by imaging)
- Chronic dialysis

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Summary of Analysis Populations

Screened (n=341)

Screen Failure (n=138)

Randomized (n=203)

ELAD (n=96)
Received ≥72 hrs on ELAD (n=82)

Control (n=107)

Analyzed:
- **ITT: ELAD (n=96)**
- Safety: ELAD 94, Control 2

Analyzed:
- **ITT: Control (n=107)**
- Safety: Control 106; ELAD 1

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Baseline Characteristics

	ELAD (n=96)	Control (n=107)
Severe acute alcoholic hepatitis (Group A)	92	101
Alcoholic hepatitis superimposed on underlying liver disease (Group B)	4	6
Days between last alcohol and hospital admission (mean +/- SD)	19.8 ± 14.15	19.3 ± 16.18
Days between site admission and randomization (mean +/- SD)	10 ± 6.1	9.4 ± 7.8
Age (mean +/- SD)	46.5 ± 9.06	44.8 ± 10.66
Age 18 – 35 ($p<0.05$)	12	25
Age ≥35	84	82
Males	55	65
Females	41	42
≥2 episodes of dialysis in last week	2	0
Intubated	8	3
On vasopressor	18	20
Bilirubin (mean +/- SD)	26.21 ± 9.7	24.07 ± 8.3
INR (mean +/- SD)	2.01 ± 0.6	2.05 ± 0.5
Creatinine (mean +/- SD)	1.09 ± 0.9	0.93 ± 0.5
MELD (mean +/- SD)	27.6 ± 3.9	27.1 ± 3.8
On steroids	44	53
On pentoxifylline	33	34

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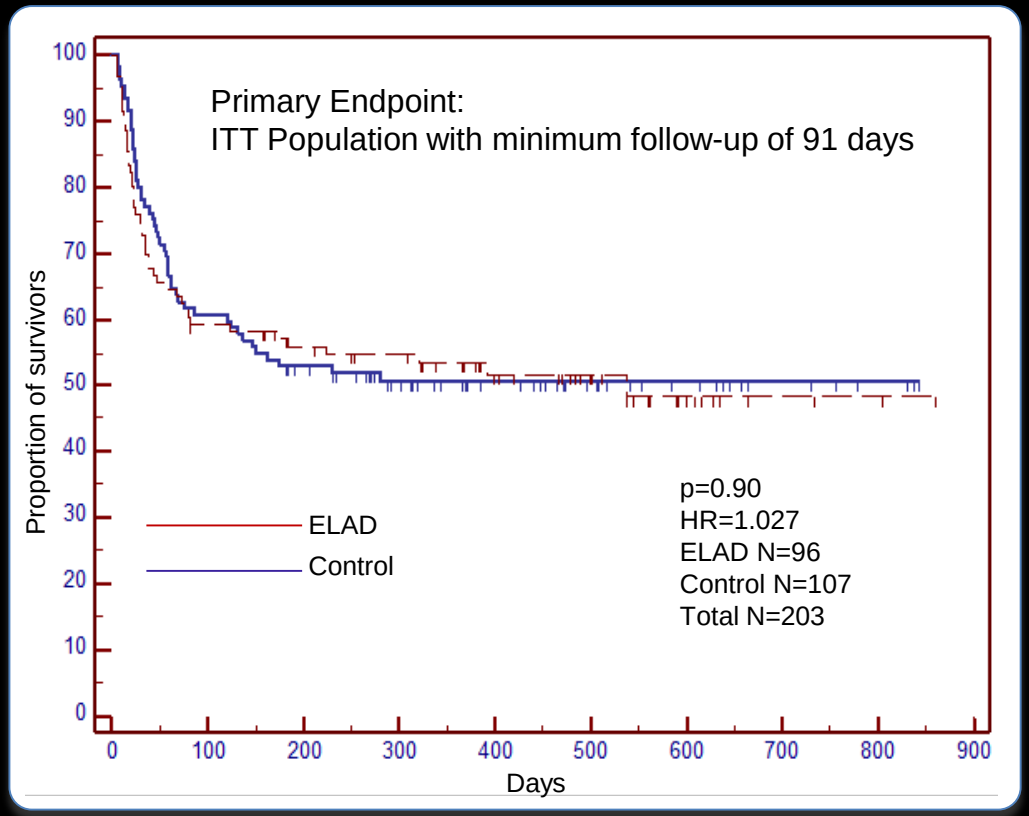
Study Endpoints



Secondary Endpoints: Proportion of Survivors			
	ELAD (%)	Control (%)	p-value (Pearson's chi-squared)
28 days	76.0	80.4	0.46
91 days	59.4	61.7	0.74

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Safety

	ELAD (%) (n=95)	Control (%) (n=108)
Subjects Reporting at Least One Serious Event	**76.8**	**69.4**
SAE Type		
Renal dysfunction	16.8	21.3
Ascites	6.3	12
GI Hemorrhage	7.4	5.6
Other Hemorrhage	2.1	0.9
Hypotension	2.1	1.9
Anemia	8.4	5.6
Coagulopathy	3.2	0
Thrombocytopenia	2.1	0
Deaths (through 91 days)	39	41
Deaths attributed to ELAD	2	-

Non-serious adverse events were balanced except for:
anemia (48% vs. 18%)
thrombocytopenia (37% vs. 11%)
coagulopathy (33% vs. 12%)
hypotension (33% vs. 18%)

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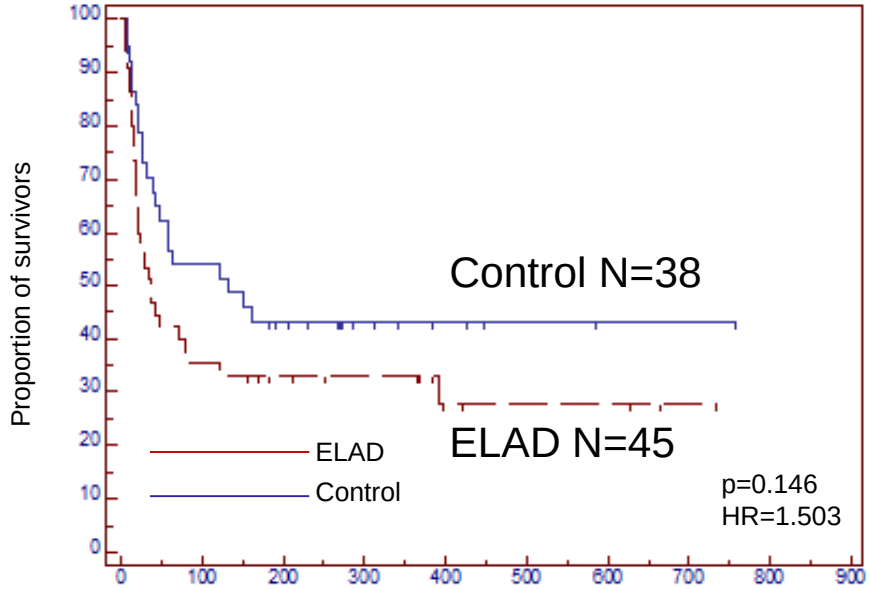
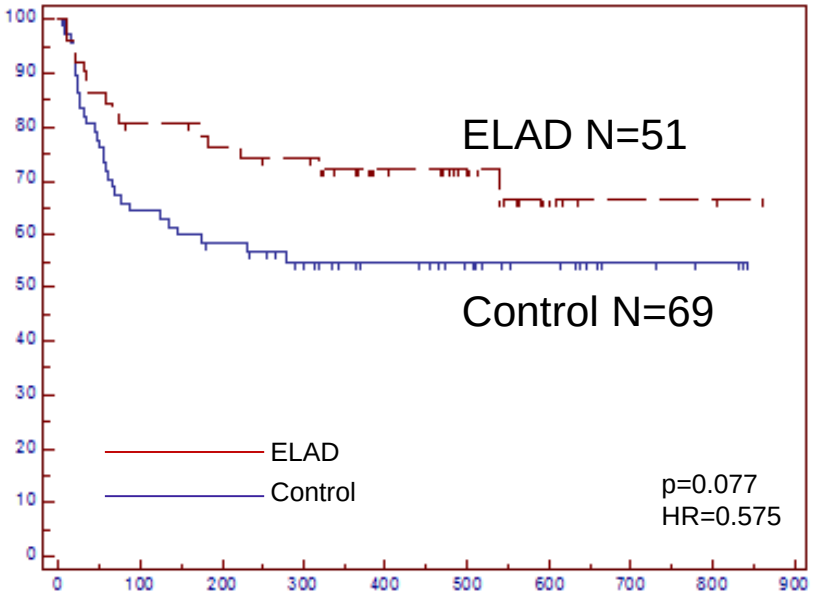
Pre-Specified Subgroup Analysis: MELD

Pre-specified subgroup analysis reveals MELD-dependent ELAD response

83 patients ITT with MELD ≥28



120 patients ITT with MELD <28



Baseline parameters were balanced between ELAD and Control in both subgroups.

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Baseline Creatinine, INR and Bilirubin

Baseline Parameter	# Subjects	Overall Survival / LTFU: ITT Population		p-value (ELAD vs Control)
		ELAD Treated	Control	
Creatinine ≥1.5mg/dL	33	27.8%	53.3%	p=0.077
Creatinine <1.5mg/dL	169	57.1%	52.2%	N.S.
INR >2.5	36	25.0%	60.0%	p<0.05
INR ≤2.5	167	57.5%	50.6%	N.S.
Bilirubin ≥25.7mg/dL	102	44.0%	44.2%	N.S.
Bilirubin <25.7mg/dL	101	60.9%	60.0%	N.S.

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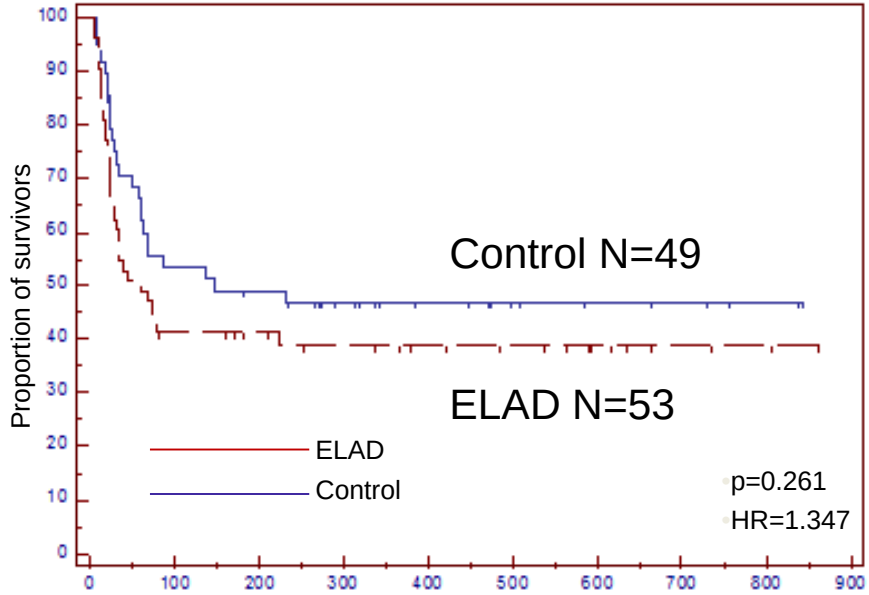
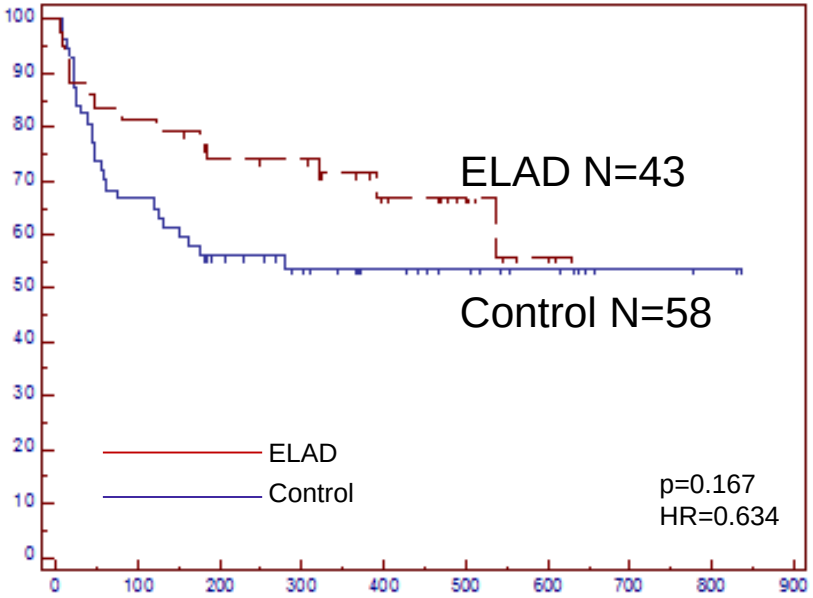
Pre-specified Subgroup Analysis: Age

Pre-specified subgroup analysis reveals age-dependent ELAD response

102 patients ITT with Age >47yrs



101 patients ITT with Age <47yrs



Baseline parameters were balanced between ELAD and Control in both subgroups.

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Conclusions

- ELAD treatment failed to meet primary and secondary survival endpoints
- Baseline parameters (including steroid use) were balanced between groups
- Serious adverse event incidence and severity was similar between groups
  - ELAD treatment arm had more non-serious adverse events of anemia, thrombocytopenia, coagulopathy and hypotension
- ELAD treatment showed trend towards overall survival in two large, pre-specified subgroups: younger subjects and lower MELD subjects

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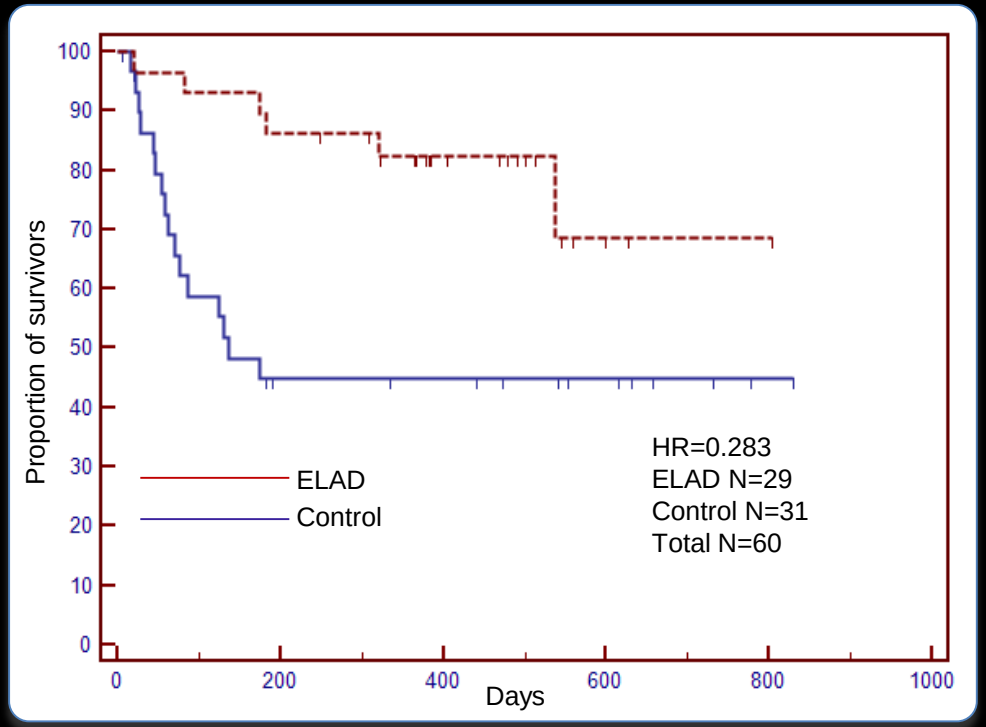
Planned Confirmatory Trial

Age <50, MELD <30, INR ≤2.5, Creatinine <1.3mg/dL, Bilirubin ≥16mg/dL



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40 Sites Enrolled Subjects

AUSTRALIA

- Flinders Medical Centre, Adelaide
- Sir Charles Gairdner, Perth
- Royal Prince Alfred Hospital, Sydney

UK

- University of Birmingham, Queen Elizabeth Hospital, Birmingham
- Royal Free Hospital, London
- Cambridge University Hospital, Cambridge
- Royal Infirmary, Edinburgh
- Kings College Hospital, London

UNITED STATES

- Albert Einstein Medical Center, Philadelphia, PA
- Baylor University Medical Center, Dallas, TX
- Beth Israel, Boston, MA
- Capital Health Medical Center, Trenton, NJ
- Cedars Sinai, Los Angeles, CA
- Cleveland Clinic, Cleveland, OH
- Cleveland Clinic Florida, Weston, FL
- Columbia University Medical Center, New York, NY
- Drexel University, Philadelphia, PA
- East Carolina University, Greenville, NC
- Emory University, Atlanta, GA
- Georgetown University, Washington DC
- Maricopa Medical Center, Phoenix, AZ
- Methodist Dallas Medical Center, Dallas, TX
- Montefiore Medical Center, New York, NY
- New York University, New York, NY
- North Shore University Hospital, Manhasset, NY
- Piedmont Atlanta Hospital, Atlanta, GA
- Rush University Medical Center, Chicago, IL
- Rutgers University, Newark, NJ
- Southern California GI Liver Centers, San Diego, CA
- Swedish Medical Center, Seattle, WA
- Tampa General Hospital, Tampa, FL
- University of Mississippi, Jackson, MS
- University of Arizona, Tucson, AZ
- University of Arkansas, Little Rock, AR
- University of California at San Diego, San Diego, CA
- University of Minnesota, Minneapolis, MN
- University of Pittsburgh Medical Center, Pittsburgh, PA
- University of Southern California, Los Angeles, CA
- University of Washington, Seattle, WA
- Westchester Medical Center, Westchester, NY

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