Home-Based Care of Complex Patients Before and In Crisis

Nelson J. Chao, MD, MBA

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Professor of Medicine and Immunology

Chief, Div. Hematologic Malignancies and Cellular Therapy

Duke University

Overview

- Microbiome and human health
- Microbiome and HCT
- Home HCT Methods
- Phase 1 Results
- Phase 2 Studies
- Home HCT and COVID-19
- Future Directions

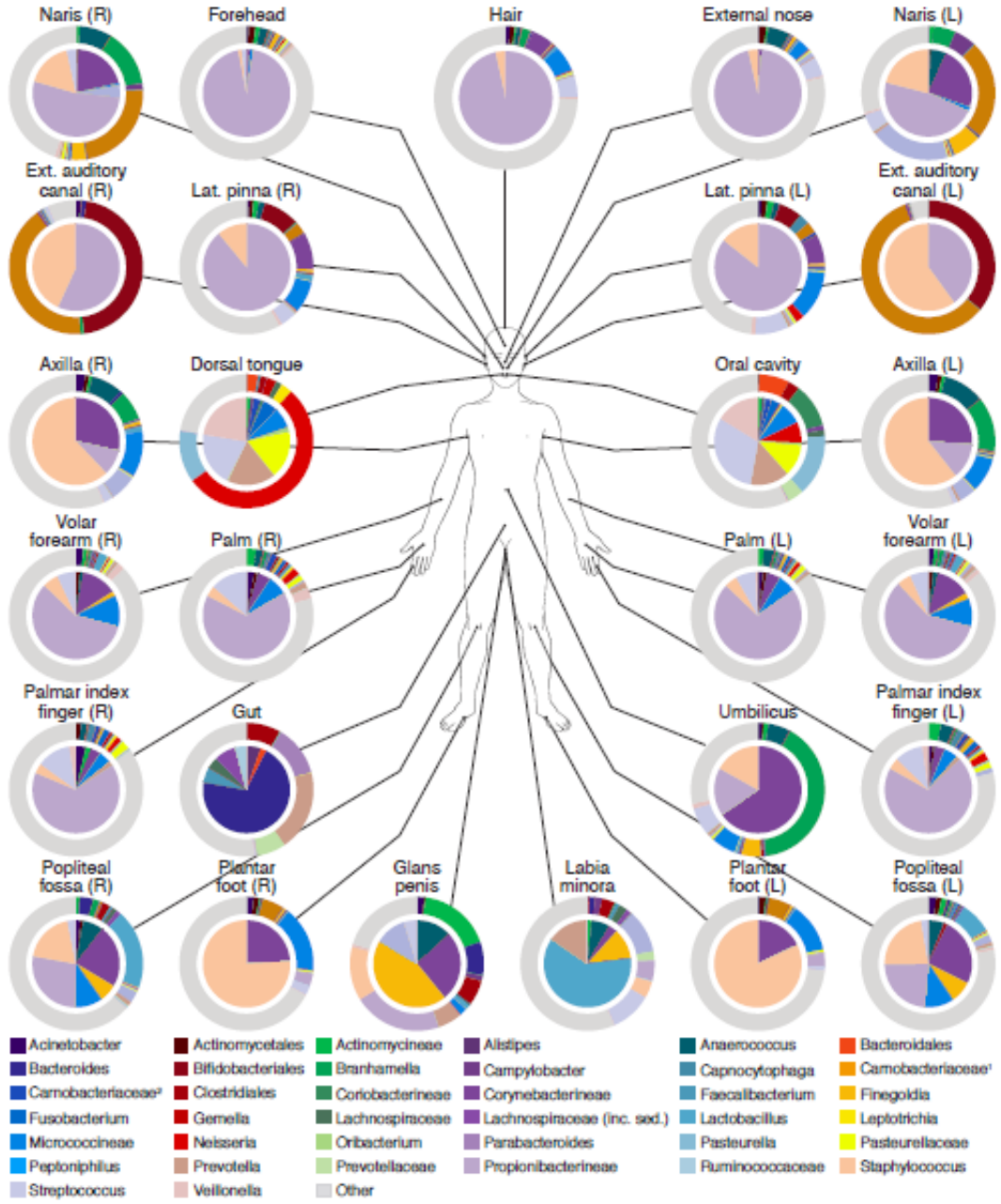
The Microbiome

100 trillion microbes

3% human body mass

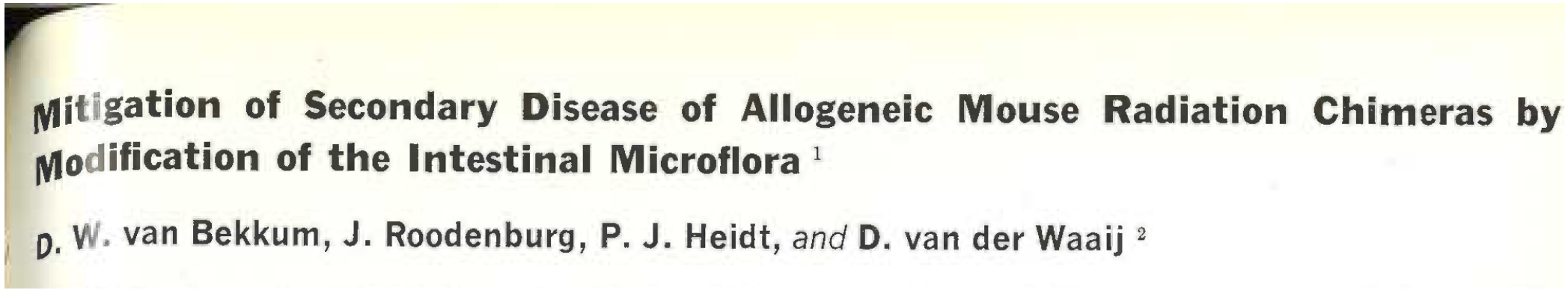
10x microbes : human cells

100x microbial : human genes



Costello *et al.*, *Science*. 2009

An Old Story…



Mitigation of Secondary Disease of Allogeneic Mouse Radiation Chimeras by Modification of the Intestinal Microflora [1]

D. W. van Bekkum, J. Roodenburg, P. J. Heidt, *and* D. van der Waaij [2]

1974

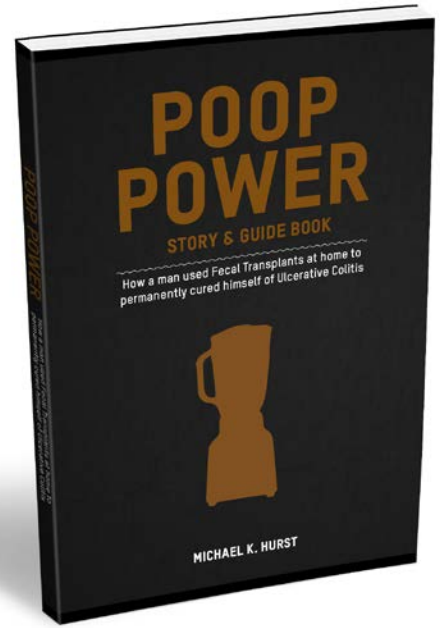
An Even Older Story…

Yellow Soup:
Fermented stool to treat abdominal diseases

Li Shizhen
1518 - 1593

Slide courtesy of Ian Carroll, UNC

Becomes a New Story…



The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D.
Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D.
Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Sp
Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M

ABSTRACT

BACKGROUND
Recurrent Cl
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METHODS
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RESULTS
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infusion gro

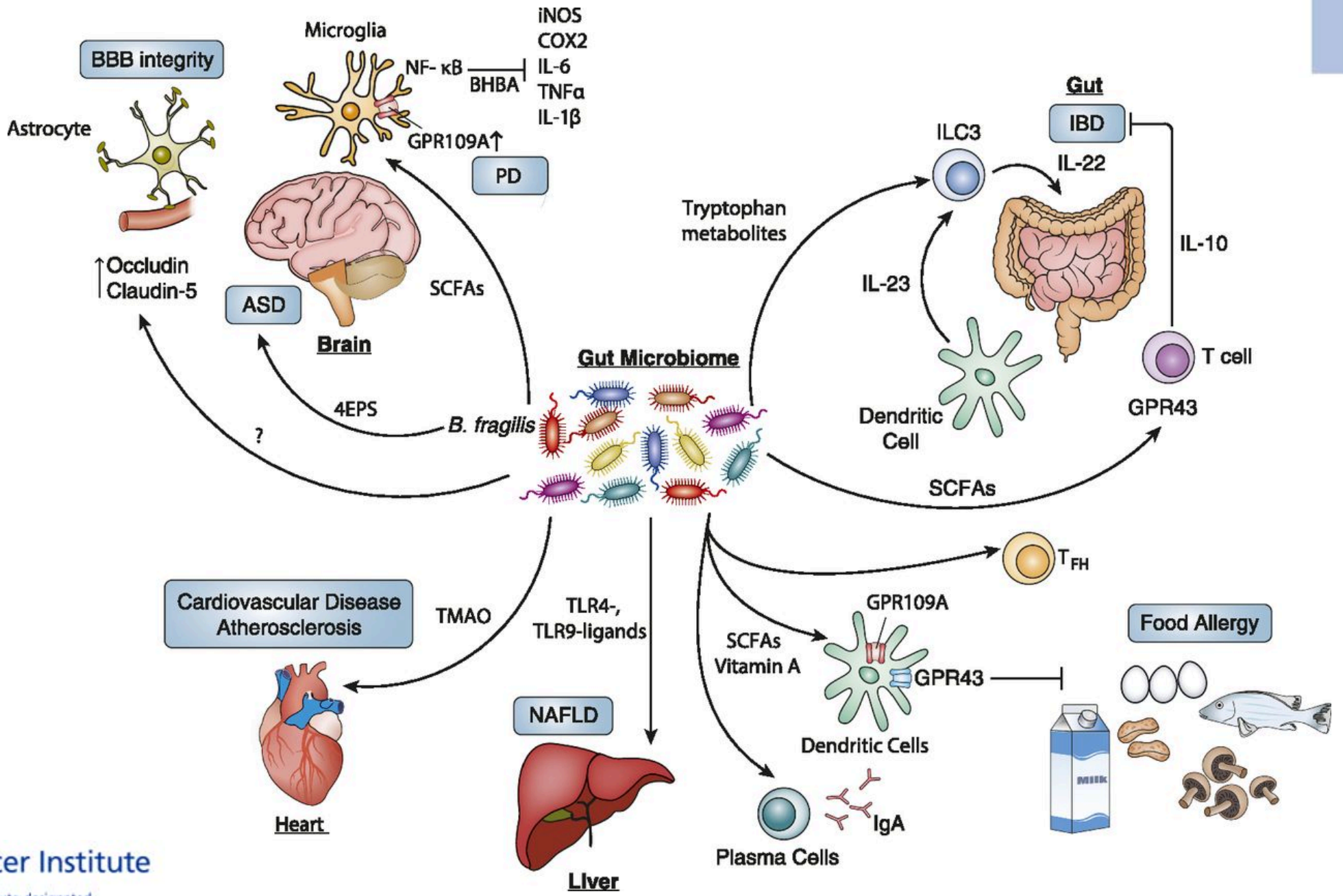
Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome

THE POWER of POOP
HAPPY MICROBES - HEALTHY BODY

START HERE! FMT BEST PRACTICES

Home › ePatients › Fecal Transplant At Home – DIY Instructions

Fecal Transplant At Home – DIY Instructions



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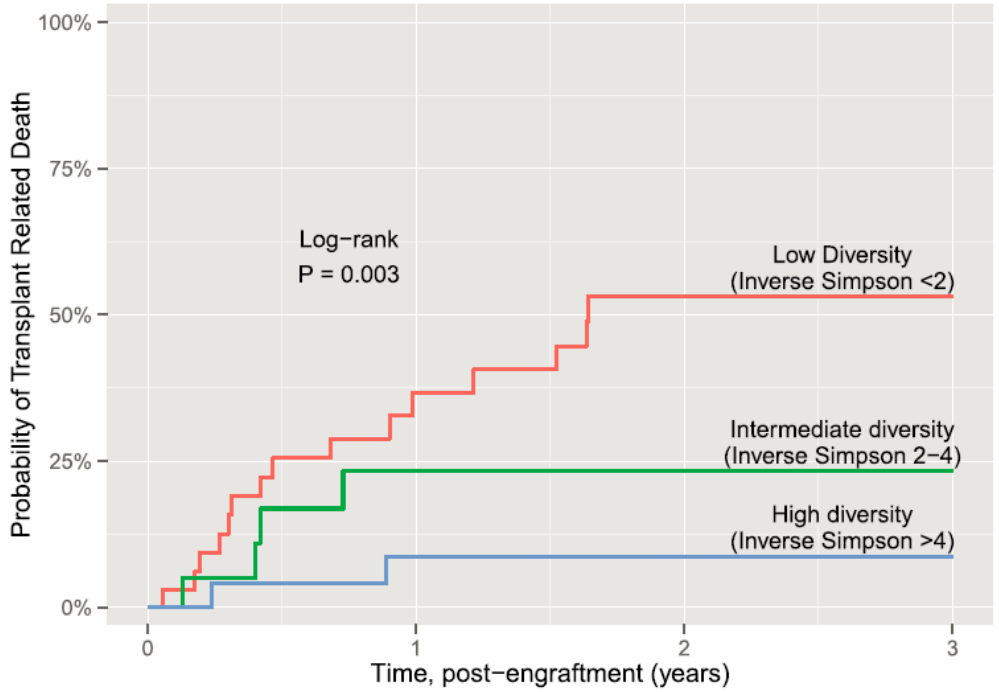
Blacher et al., J Immunol 2017

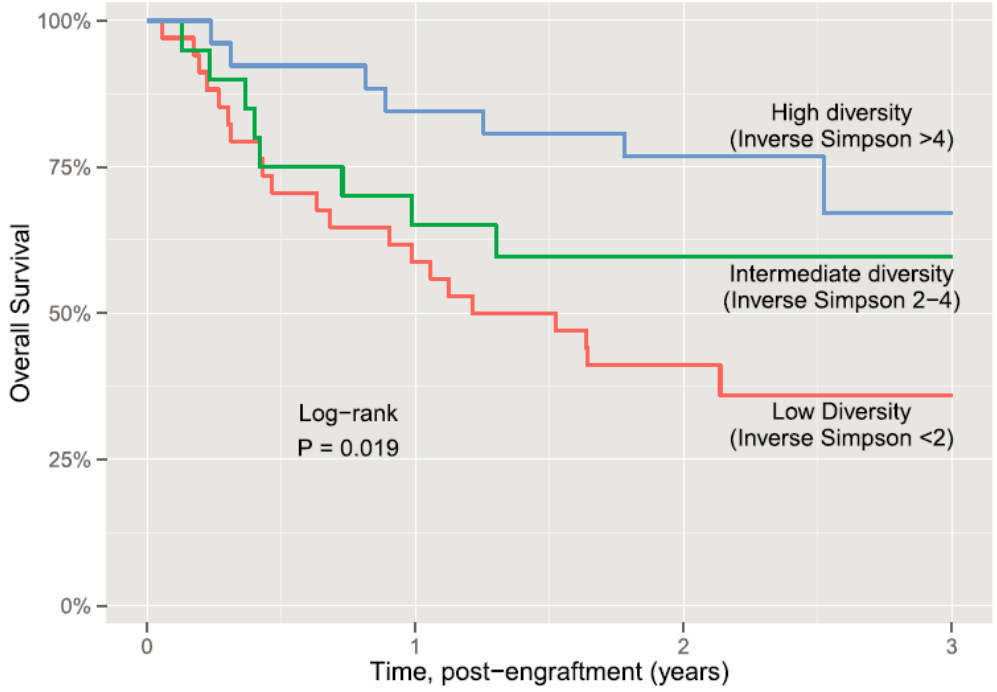
So what about transplant?

HCT and the Microbiome

- Transplant Related Morality (HR 5.25), Overall Survival (HR 3.13)



Number at Risk				
High diversity	26	21	17	4
Intermediate diversity	20	12	10	3
Low Diversity	34	17	7	2

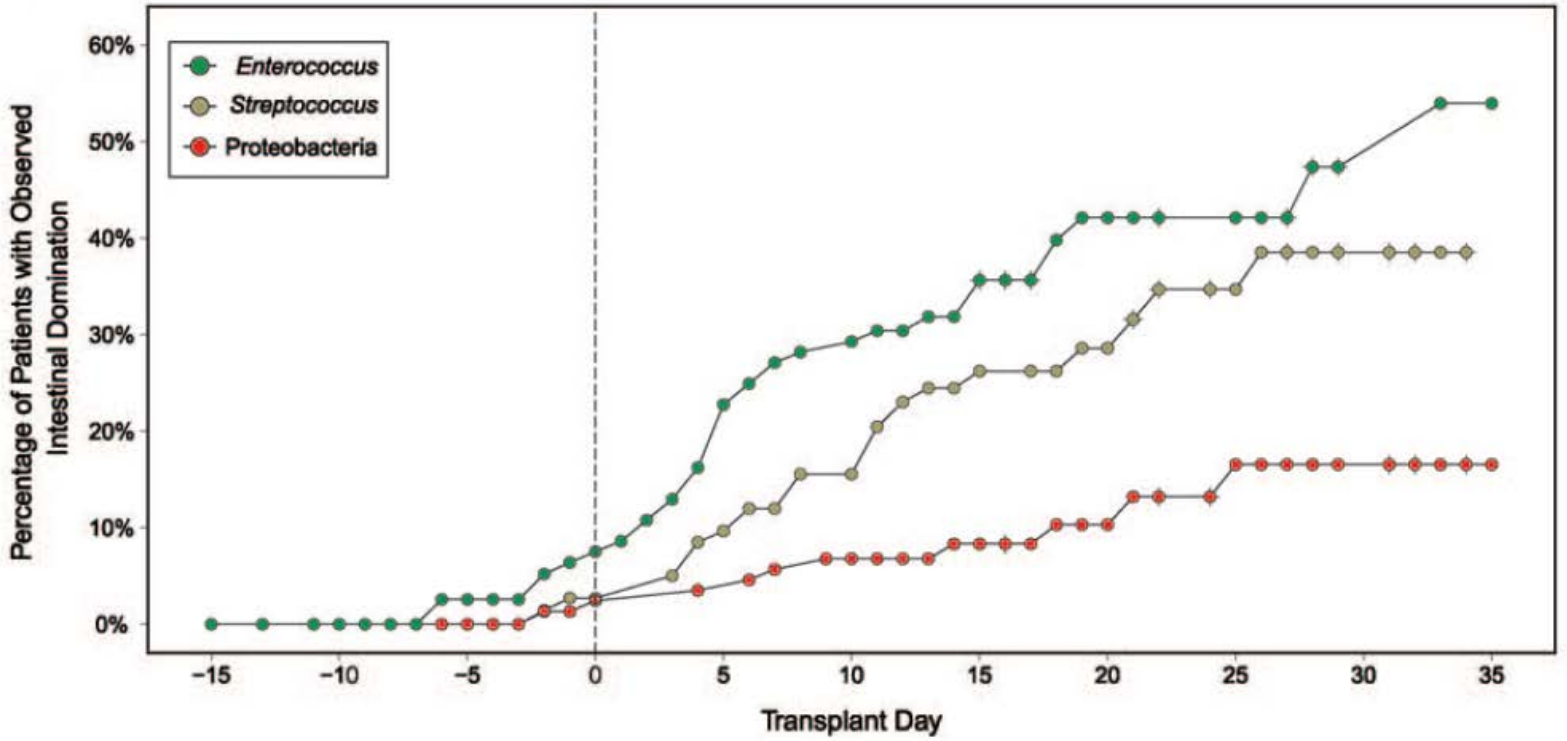


Number at Risk				
High diversity	26	23	18	4
Intermediate diversity	20	14	10	3
Low Diversity	34	21	10	2

Taur Blood 2014

HCT and the Microbiome

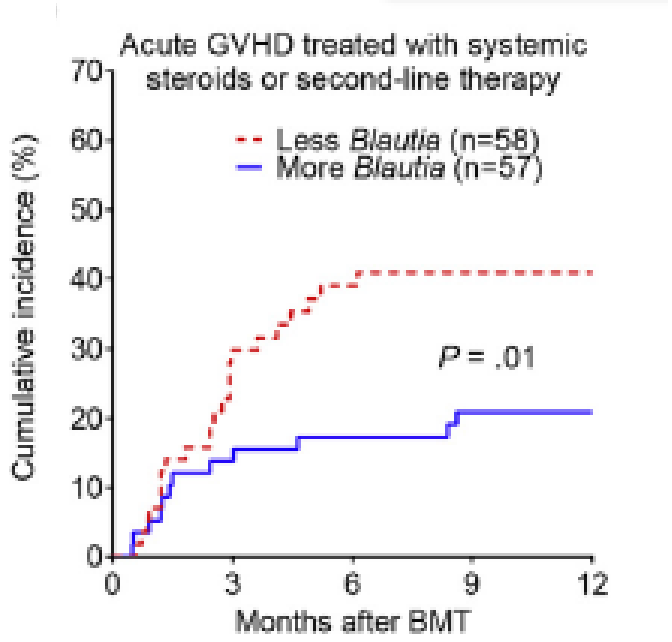
- Transplant Related Morality (HR 5.25), Overall Survival (HR 3.13)
- Bacteremia (HR 9.35)

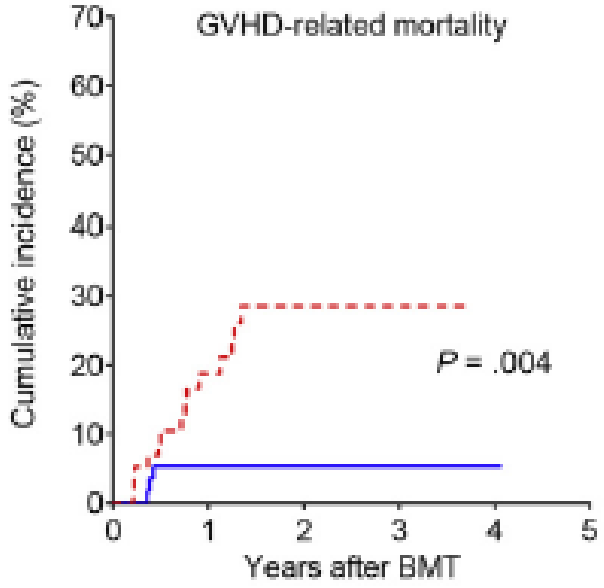


Taur Blood 2014
Taur CID 2012

HCT and the Microbiome

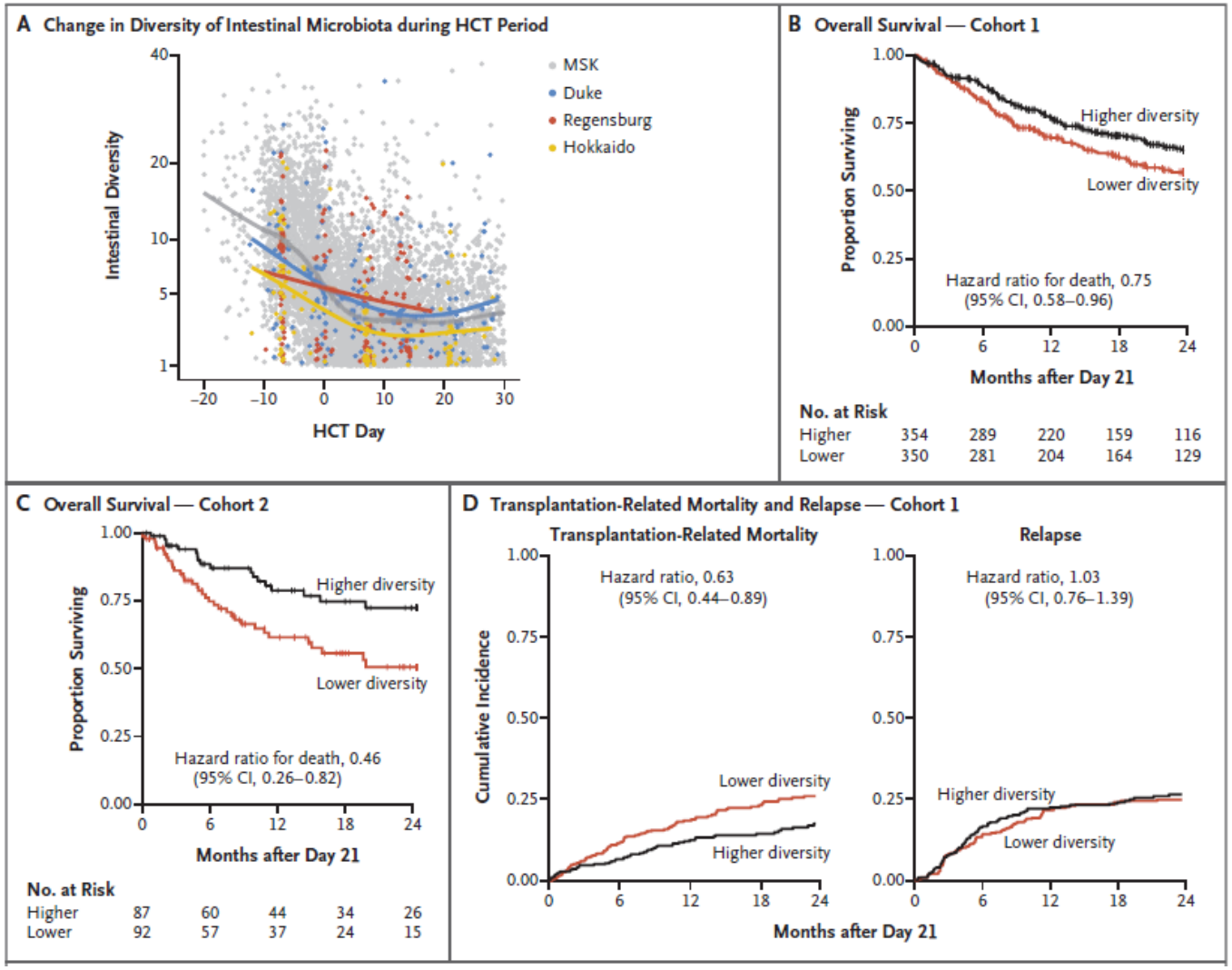
- Transplant Related Morality (HR 5.25), Overall Survival (HR 3.13)
- Bacteremia (HR 9.35)
- GVHD (HR 3.33) and GVHD-related mortality (HR 5.55)





Taur Blood 2014
Taur CID 2012
Jenq BBMT 2015

Not just single-center



Peled N Engl J Med 2020

Epithelial breakdown and inflammation

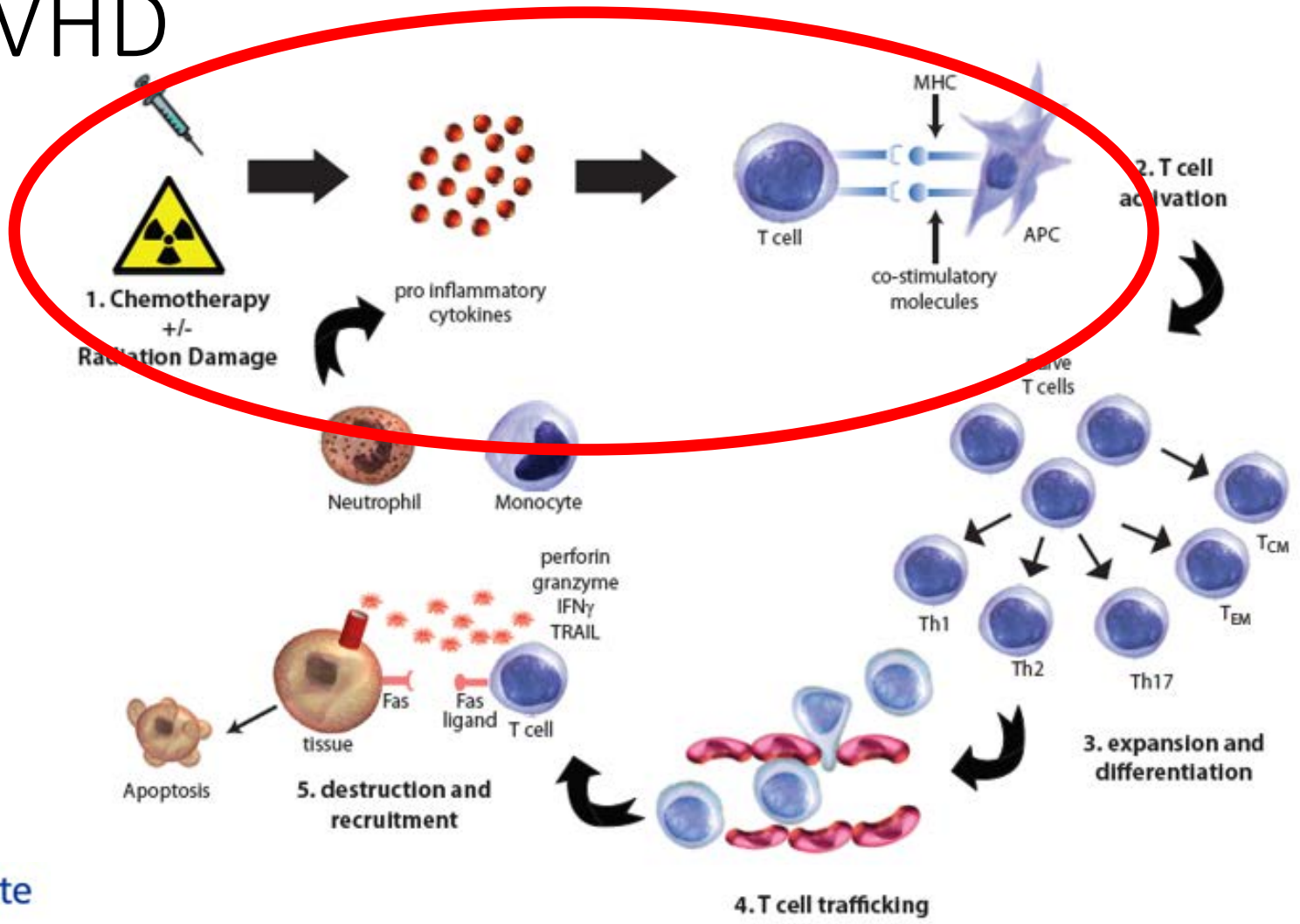
GASTROENTEROLOGY 2011;141:959–971

Enterococcus faecalis Metalloprotease Compromises Epithelial Barrier and Contributes to Intestinal Inflammation

NATALIE STECK,* MICHA HOFFMANN,* IRINA G. SAVA,* SANDRA C. KIM,[‡,§] HANNES HAHNE,[‖] SUSAN L. TONKONOGY,[§,¶] KATRIN MAIR,[#] DAGMAR KRUEGER,[**] MIHAELA PRUTEANU,[‡‡] FERGUS SHANAHAN,[‡‡] ROGER VOGELMANN,[#] MICHAEL SCHEMANN,[**] BERNHARD KUSTER,[‖] R. BALFOR SARTOR,[‡,§] and DIRK HALLER*

**Chair for Biofunctionality, ZIEL–Research Center for Nutrition and Food Science, CDD Center for Diet and Disease, [‖]Chair for Proteomics and Bioanalytics, and [**]Chair for Humanbiology, Technische Universität München, Freising-Weihenstephan, Germany; [‡]Department of Medicine and [§]Center for Gastrointestinal Biology and Disease, University of North Carolina, Chapel Hill, North Carolina; [¶]College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina; [#]Klinikum rechts der Isar, II. Medizinische Klinik und Poliklinik, Technische Universität München, München, Germany; and [‡‡]Alimentary Pharmabiotic Centre, University College Cork, National University of Ireland, Cork, Ireland*

Endothelial breakdown and inflammation and GVHD



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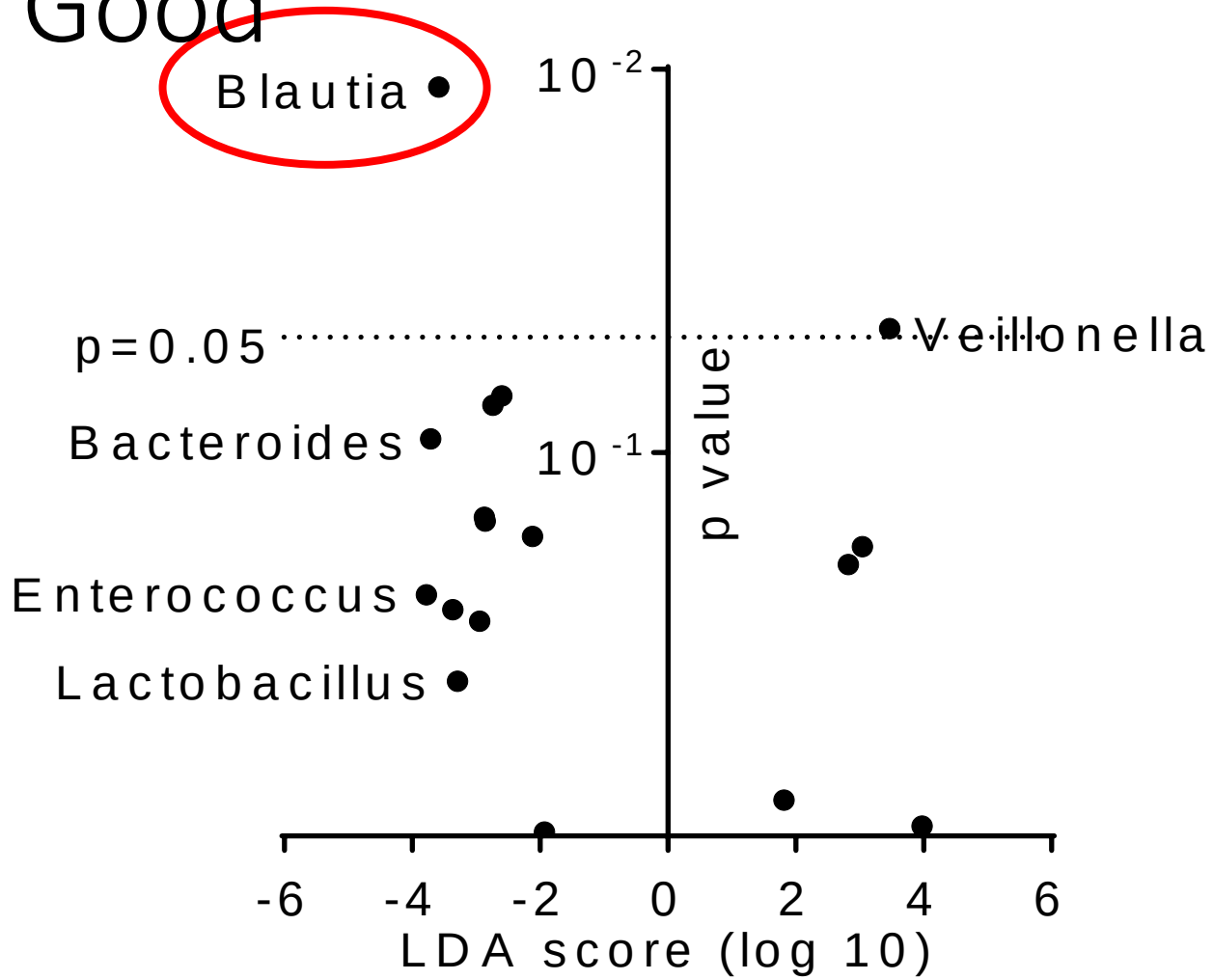
Sung AD, Chao NJ. Stem Cells Trans Med 2012

So why not get rid of all bacteria?

Data are mixed –

- Initially total decontamination seemed beneficial (Storb et al., 1983)
- Then it seemed to have no benefit (Peterson et al., 1987; Passweg et al., 1998; Russell et al., 2000)
- Then it seemed all about eliminating the anerobes with the addition metronidazole (Beelen et al., 1999)
- But then you increase VRE (Taur et al., 2012)
- And maybe anerobes are actually helpful (Jenq et al., 2015)
- And some argue going back to full circle with total decontamination (Vossen et al., 2014)

Blautia is Good



Favors no GVHD-related mortality

Favors GVHD-related mortality

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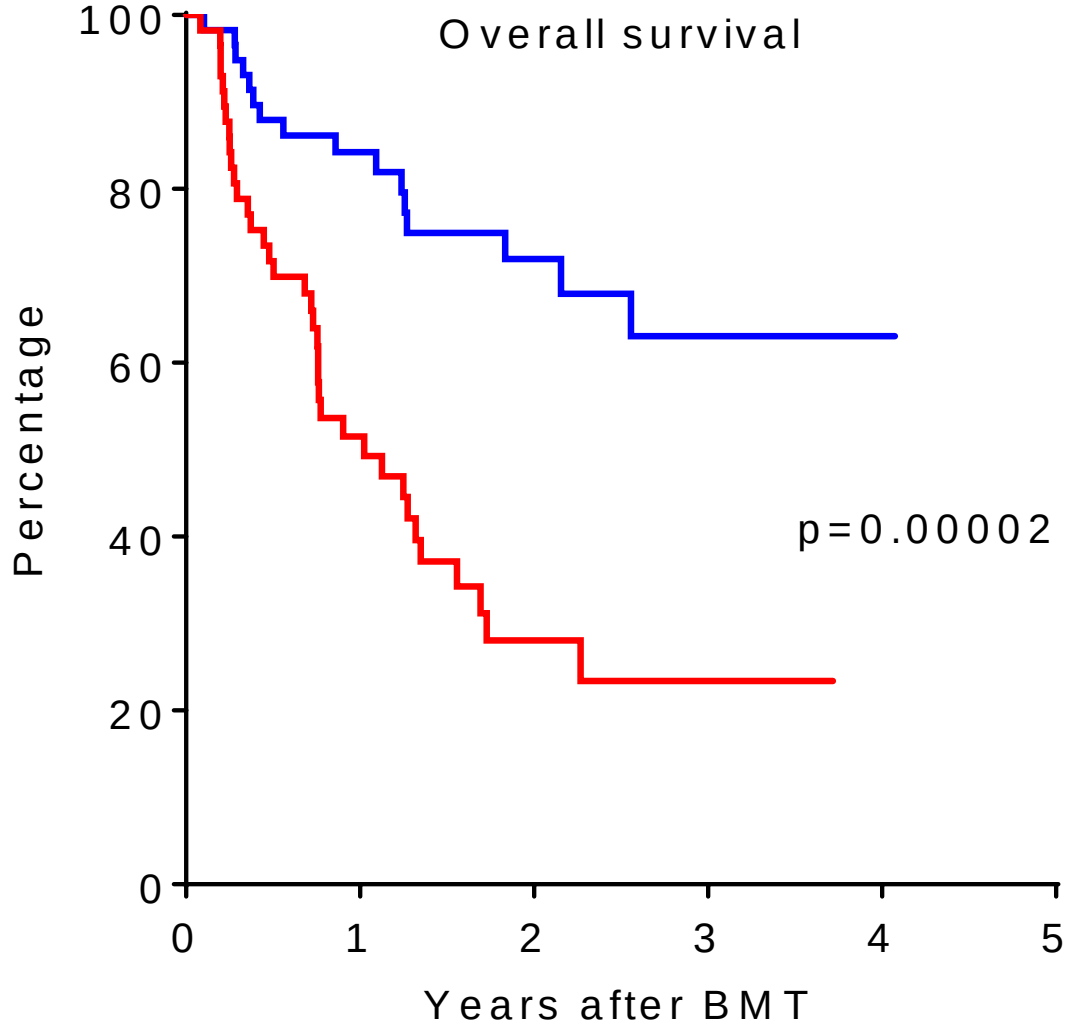
Jenq et al, BBMT 2015

Blautia is Good



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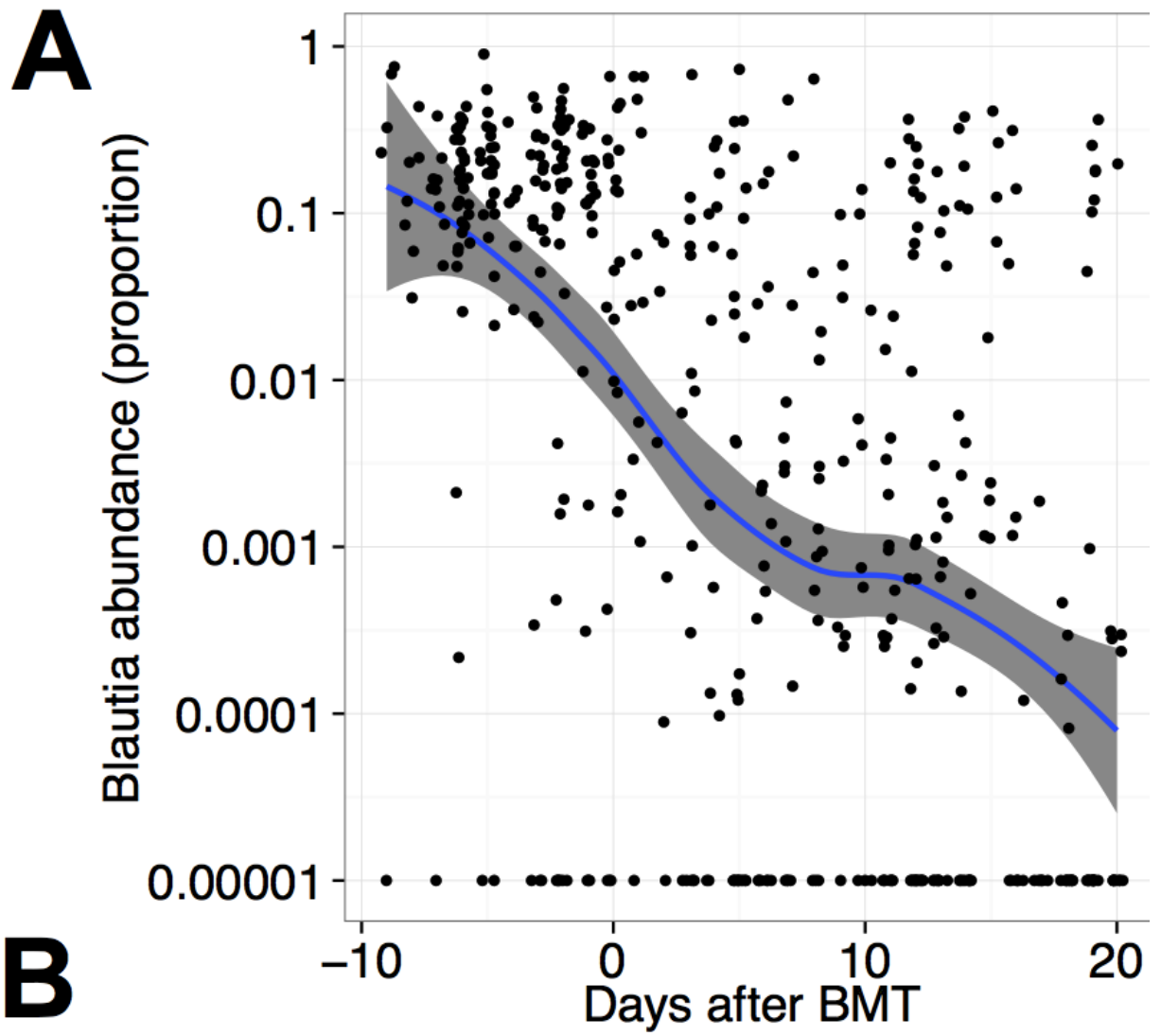
Jenq et al, BBMT 2015

Blautia during HCT



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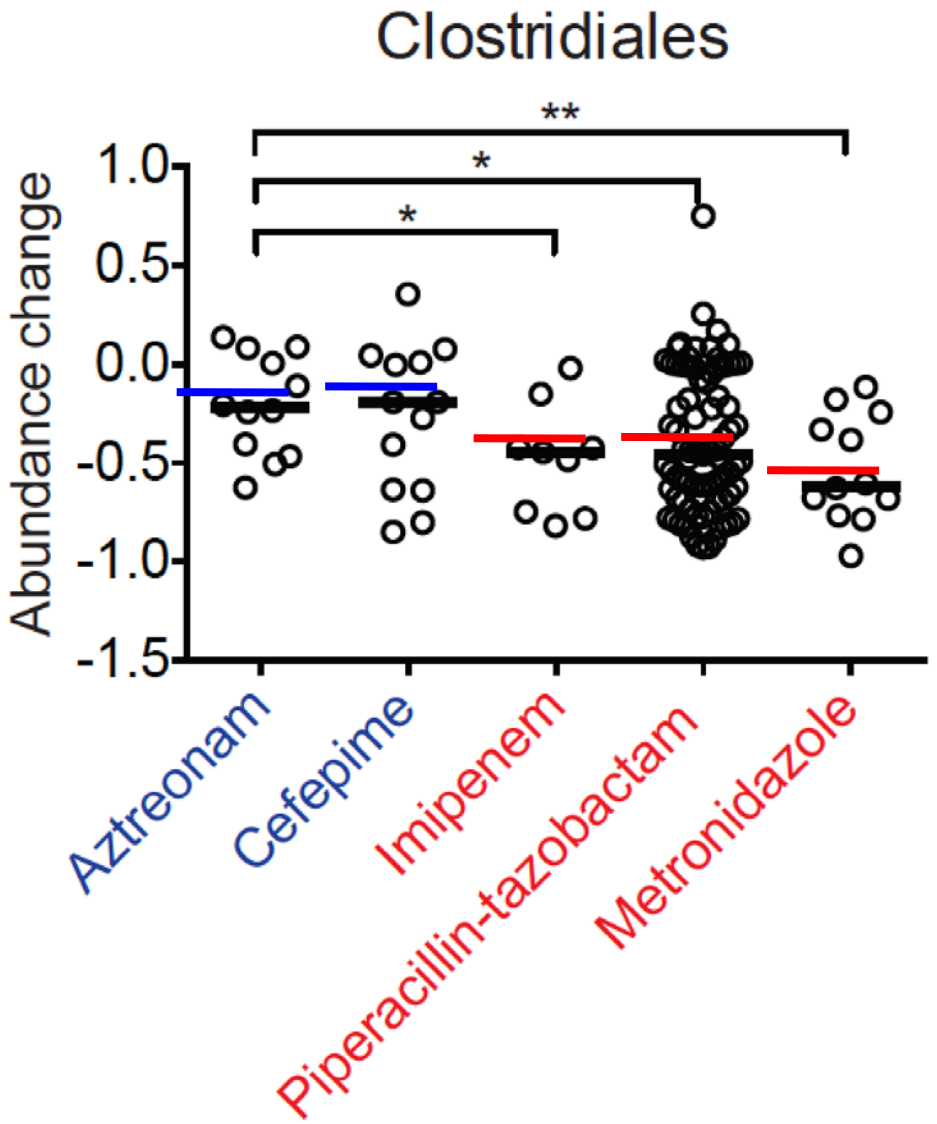
Jenq et al, BBMT 2015

What causes Blautia to go down?



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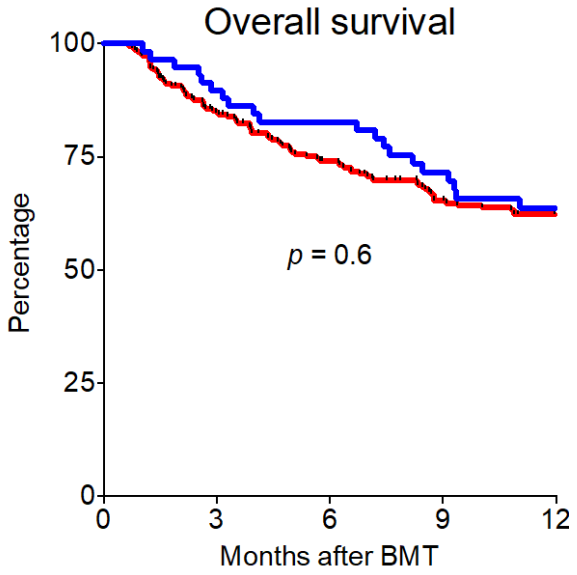
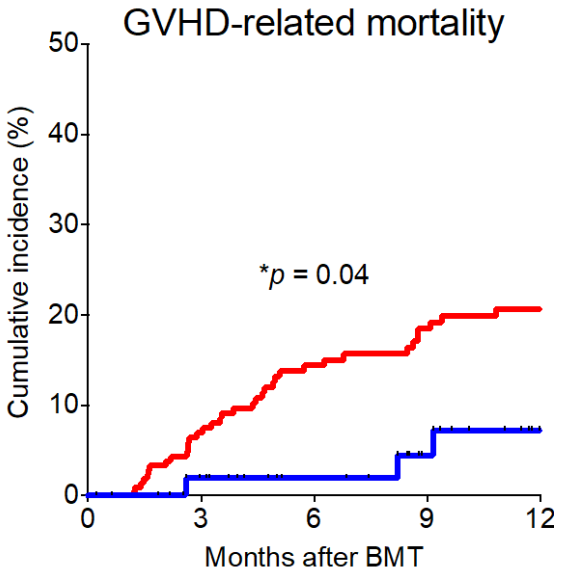
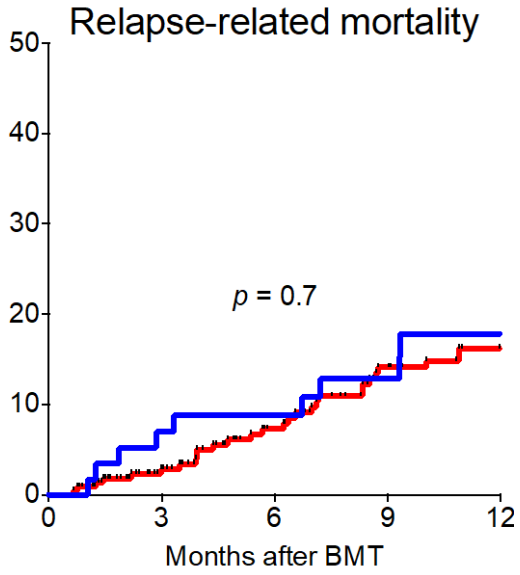
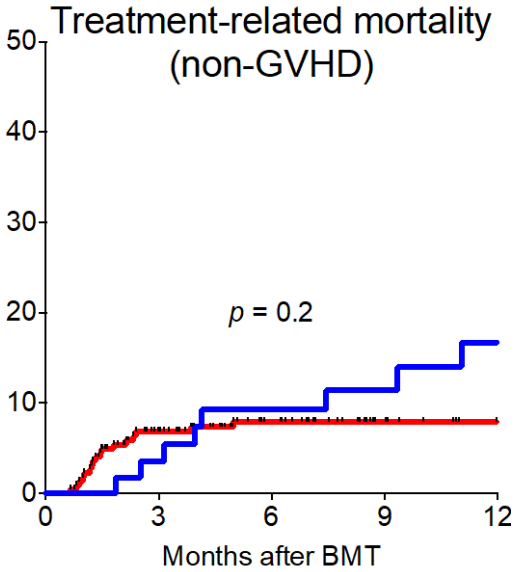
Slide courtesy of Rob Jenq, MD Anderson

Anaerobic antibiotics and GVHD-mortality









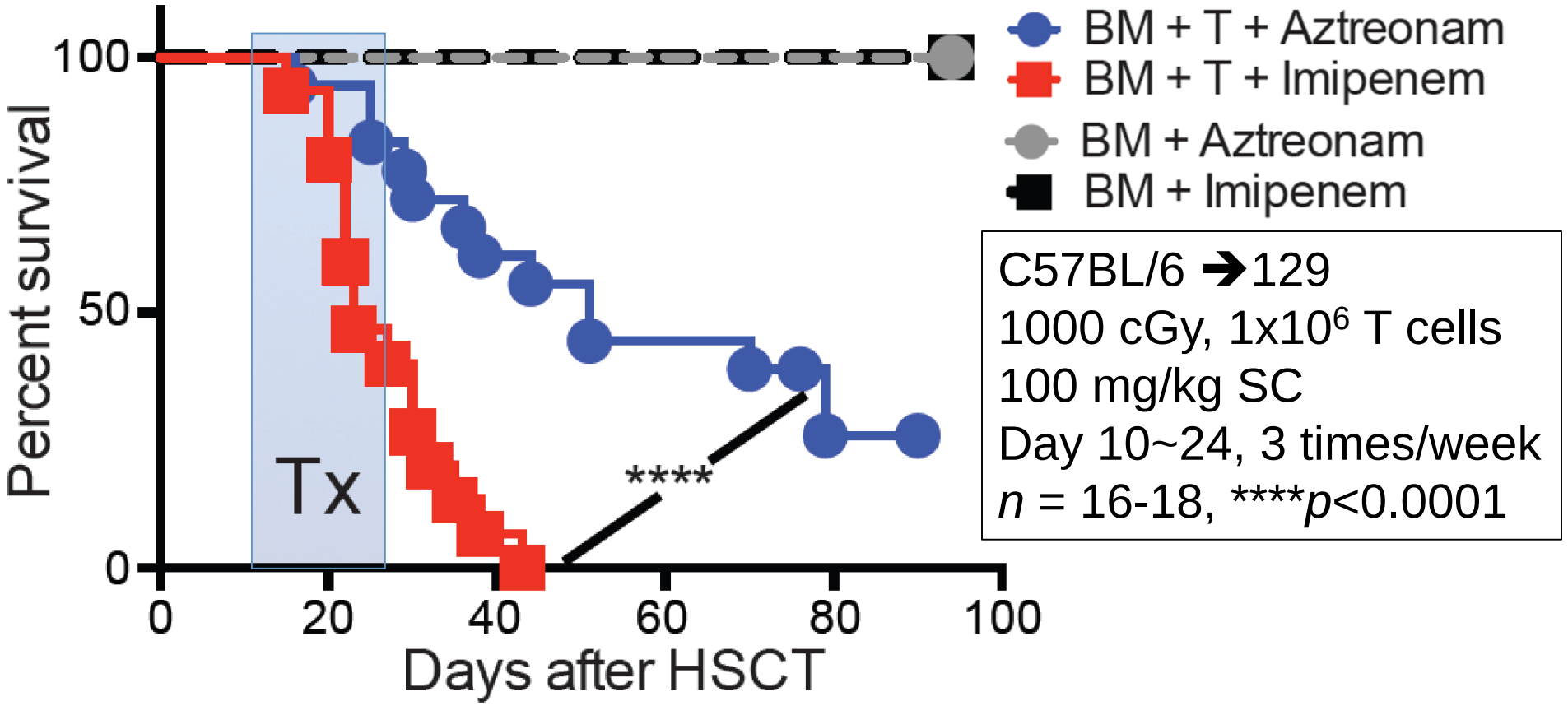
Antibiotic Treatment

w/ anaerobic coverage
(n = 225)

w/ less anaerobic coverage
(n = 58)

Slide courtesy of Rob Jenq, MD Anderson

Clostridiales-eliminating antibiotic Imipenem worsens GVHD survival

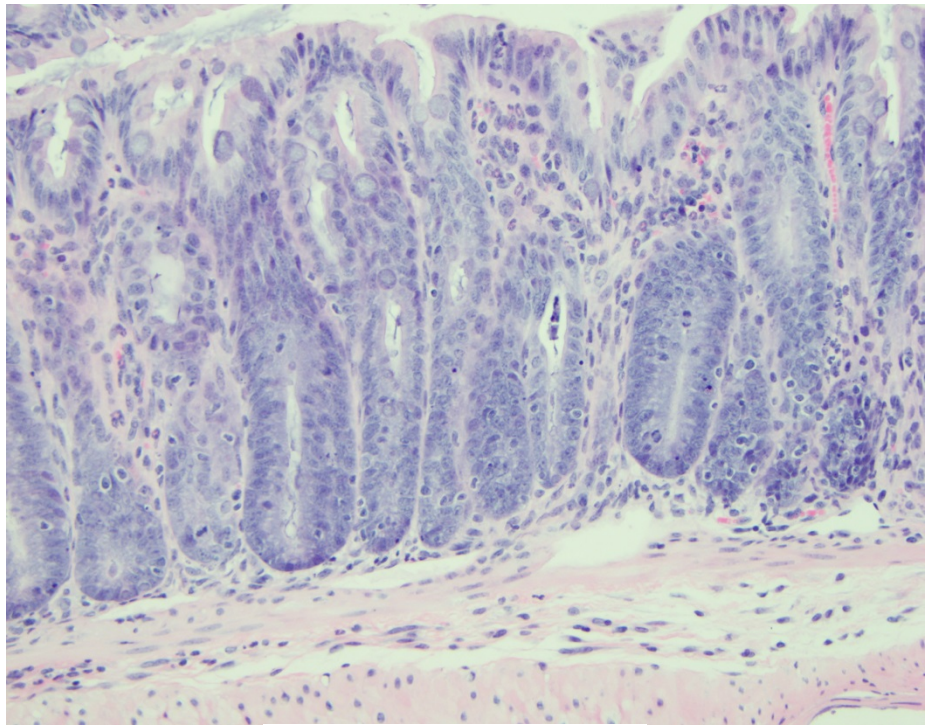


C57BL/6 ➔129
1000 cGy, 1x10^6 T cells
100 mg/kg SC
Day 10~24, 3 times/week
n = 16-18, ****p<0.0001

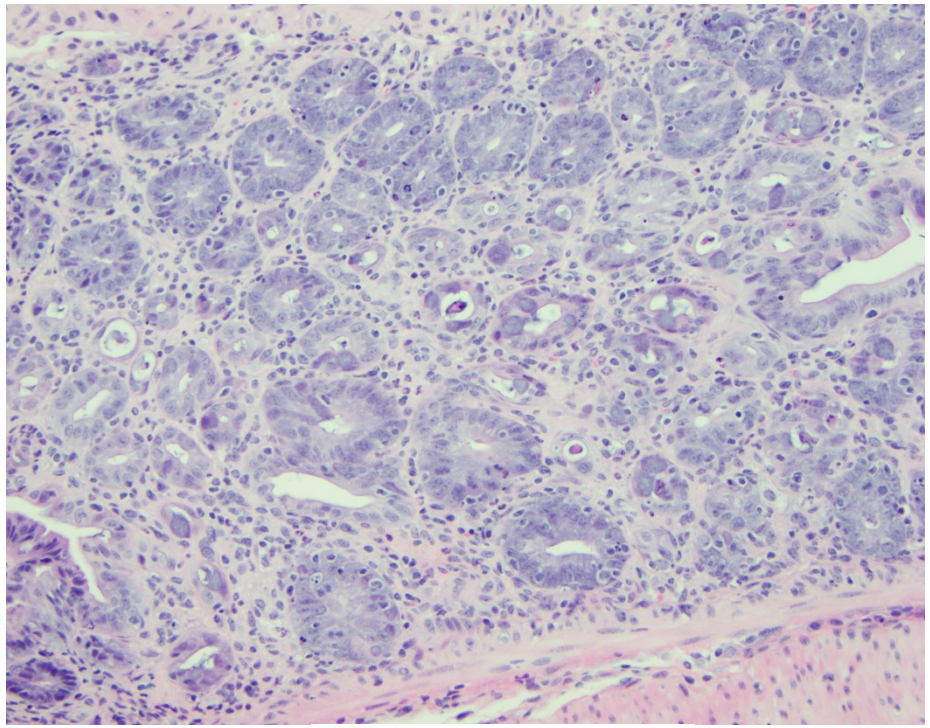
Slide courtesy of Rob Jenq, MD Anderson

Imipenem-treated mice shows higher pathologic GVHD scores in the colon

Large Intestine



Aztreonam

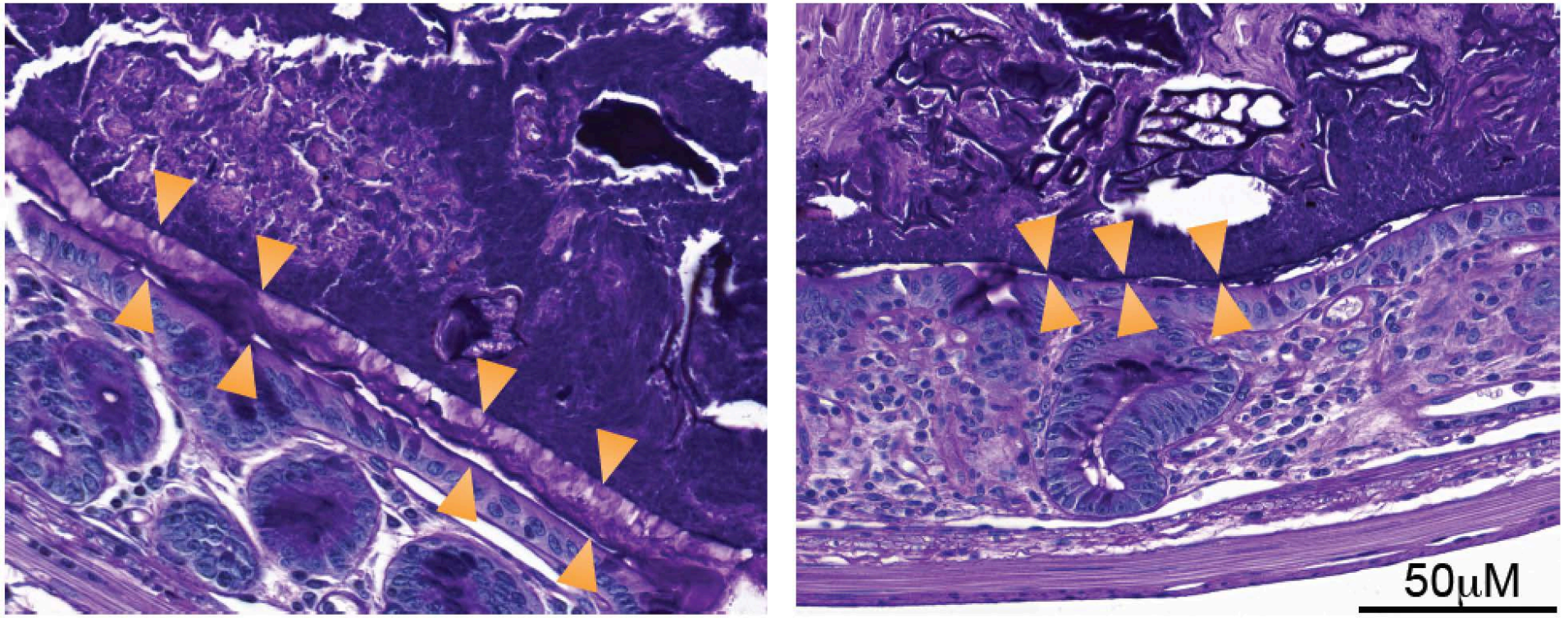


Imipenem

Slide courtesy of Rob Jenq, MD Anderson

Marked reduction of inner mucus layer in imipenem-treated mice

Periodic acid–Schiff (PAS) staining

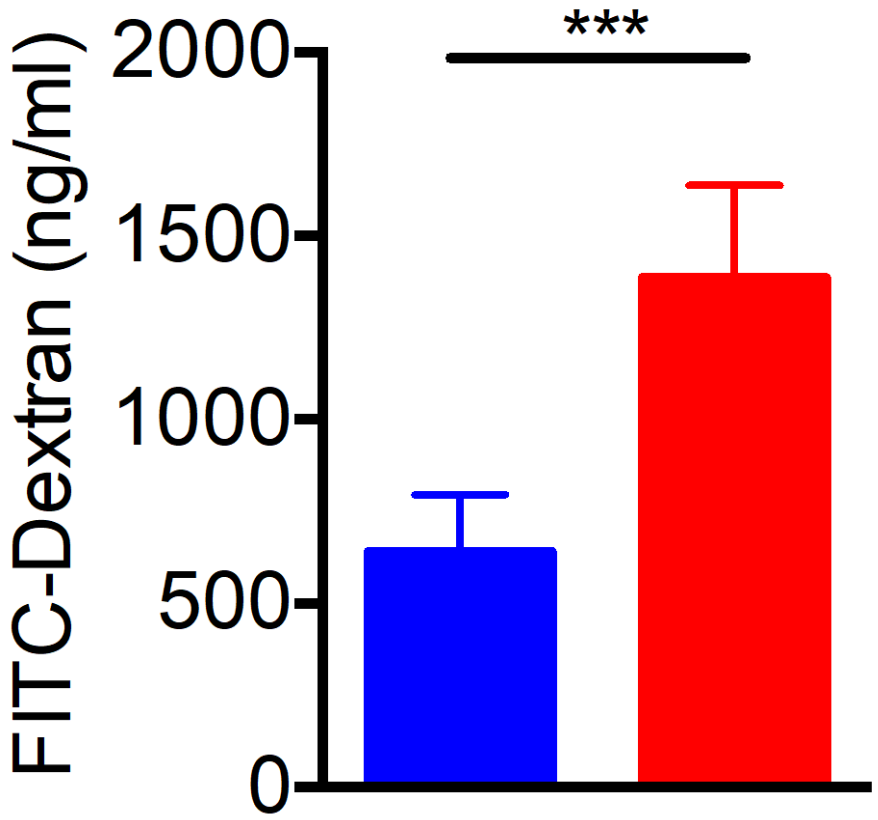


AZTREONAM

IMIPENEM

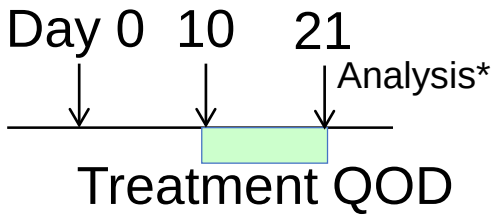
Slide courtesy of Rob Jenq, MD Anderson

Imipenem administration leads to impaired intestinal barrier function



Aztreonam

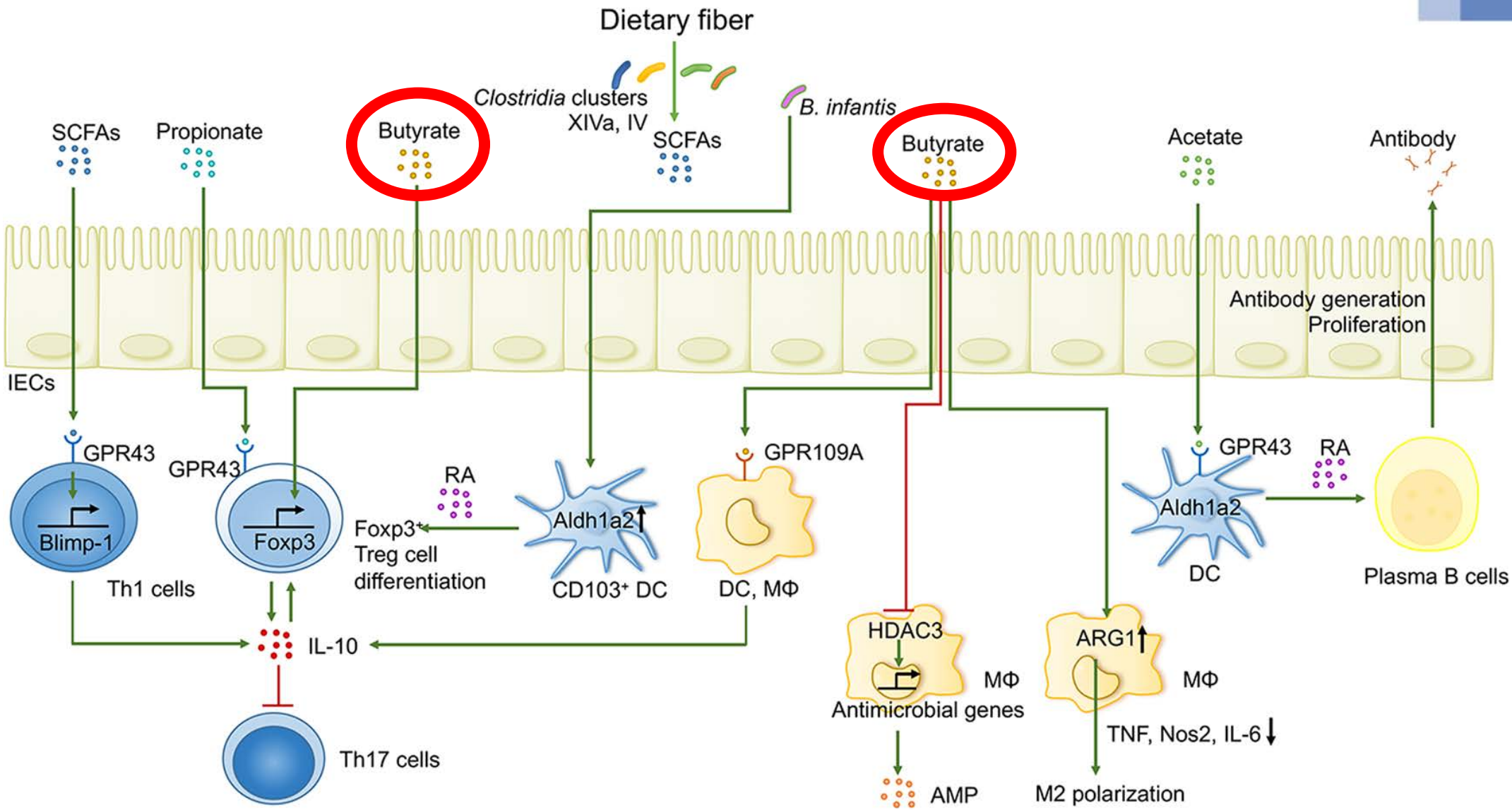
Imipenem



*800mg/kg FITC-dextran by oral gavage after 4hr NPO

Slide courtesy of Rob Jenq, MD Anderson

So is that it?
anaerobes/blautia = good



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Zhang Signal Transduct Target Ther 2019

So where do we go from here?

How does HCT affect the microbiome?

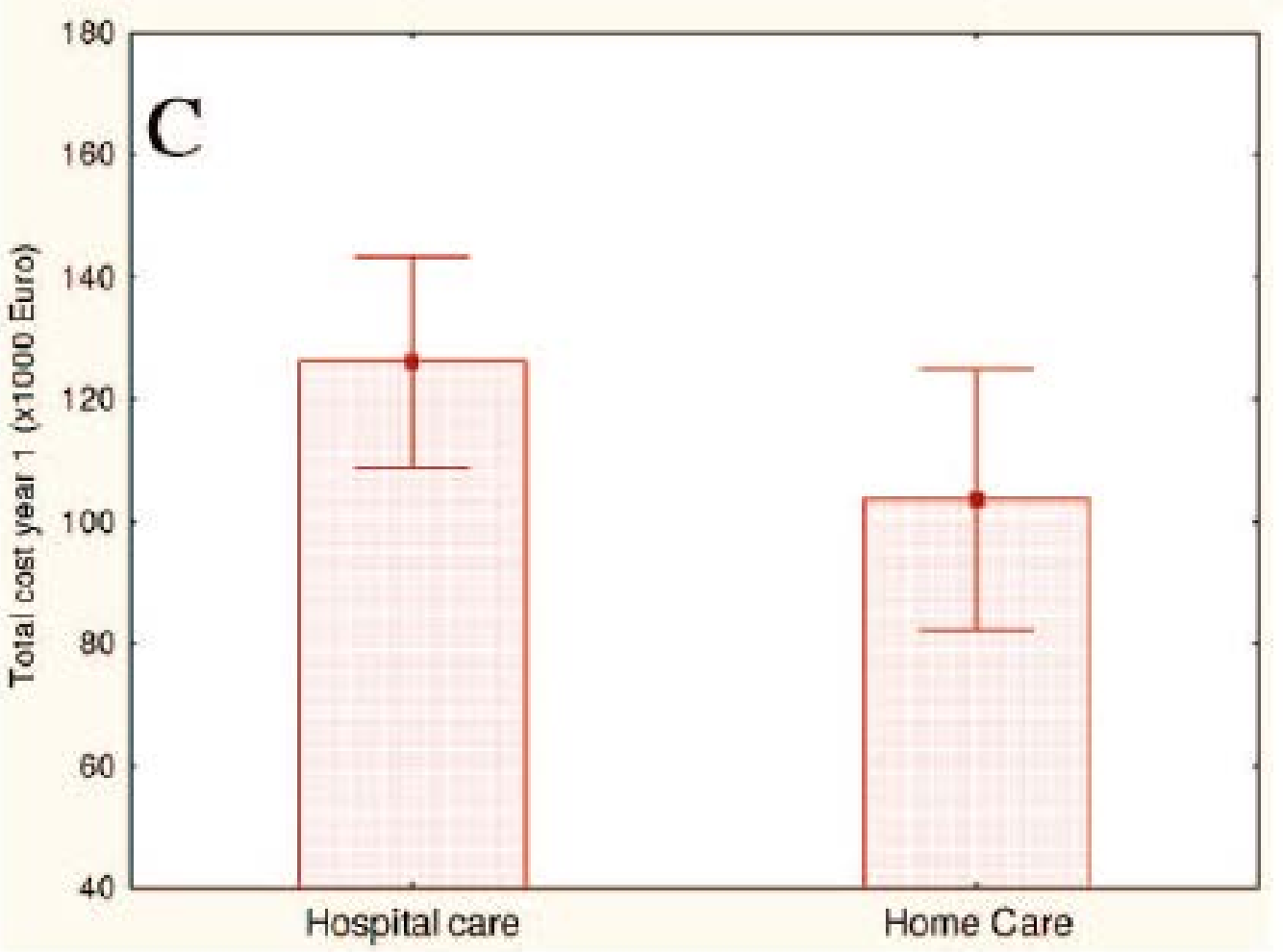
- Antibiotics
- Conditioning chemotherapy/radiation
- Diet
- Environment

Evolution of the HCT Care Environment

Inpatient (Isolation) → Outpatient (Day Hospital) → Home (House Calls)

Karolinska Experience

- Lower GVHD (RR 0.25)
- Lower TRM (RR 0.22)
- Lower costs (RR 0.37)
- Earlier discharge (RR 0.33)
- Fewer days on TPN (RR 0.24)



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Svahn Blood 2012

Methods

a. Home inspection

Methods

a. Home inspection
b. Chemotherapy +/- TBI -> home D1

Methods

a. Home inspection
b. Chemotherapy +/- TBI -> home D1
c. Typical day at home:
    a. Morning house call by APP

Methods

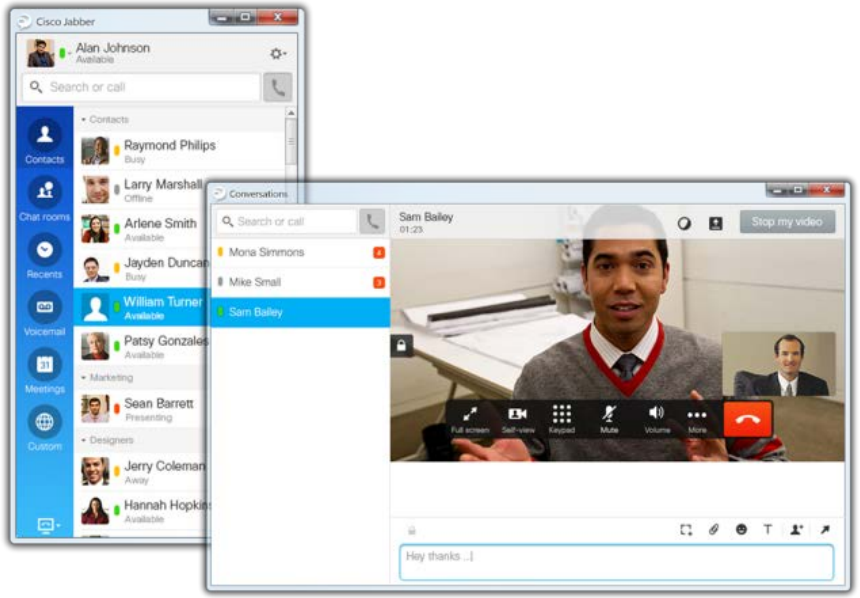
a. Home inspection
b. Chemotherapy +/- TBI -> home D1
c. Typical day at home:
    a. Morning house call by APP
    b. Labs processed at the hospital

Methods

a. Home inspection
b. Chemotherapy +/- TBI -> home D1
c. Typical day at home:
    a. Morning house call by APP
    b. Labs processed at the hospital
    c. Afternoon house call by a nurse
        a. Transfusions, antibiotics, etc., all at home

Methods

a. Home inspection
b. Chemotherapy +/- TBI -> home D1
c. Typical day at home:
    a. Morning house call by APP
    b. Labs processed at the hospital
    c. Afternoon house call by a nurse
        a. Transfusions, antibiotics, etc., all at home
    d. Video conference with MD



“One of the greatest advantages.. was the feeling of a little bit of normalcy… which is something that was so helpful and beneficial to my mental well being”

https://www.youtube.com/watch?v=ZVKLxs3M3L4

“Being able to keep G___ at home was such a blessing”

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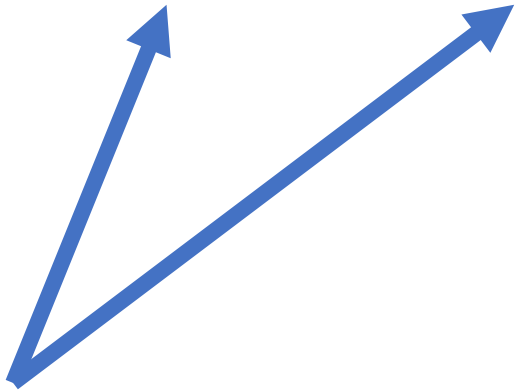
https://www.youtube.com/watch?v=ZVKLxs3M3L4

Results

	Allogeneic (n=8)	Autologous (n=17)



25 patients

Results

	Allogeneic (n=8)	Autologous (n=17)
Age (median, range)	45.5 (29-63)	60 (46-74)

74 years old

Results

	Allogeneic (n=8)	Autologous (n=17)
Age (median, range)	45.5 (29-63)	60 (46-74)
Karnofsky Performance Status (n, %)		
- 100	4 (50%)	2 (11.8%)
- 90	1 (12.5%)	5 (29.4%)
- 80	3 (37.5%)	7 (41.2%)
- 70	0 (0%)	3 (17.6%)

KPS 70: unable to carry on normal activity

Matched Control Design

- 2 matched controls (standard of care) for every home transplant patient
- Matched Variables:
  - Age
  - Gender
  - Disease
  - Type of Transplant
  - Donor Cell Type
  - Conditioning Regimen

Demographics: Allogeneic HCT

	Home-Based (N=8)	Matched Controls (N=16)	P-value
Median Age (IQR)	45.5 (29-63)	50.5 (23-72)	0.87
Gender (female)	5 (62.5%)	7 (43.8%)	0.39
Race			0.99
White	6 (75%)	12 (75%)	.
Black	2 (25%)	3 (18.8%)	.
Other	0 (0%)	1 (6.3%)	.
Ethnicity (non-Hispanic)	8 (100%)	16 (100%)	.
Karnofsky Performance Status			0.68
80 or below	3 (37.5%)	8 (50%)	.
90-100	5 (62.5%)	8 (50%)	.
Disease			0.56
Acute Leukemia (AML+ALL)	5 (62.5%)	10 (62.5%)	.
Lymphoma (HL+NHL)	1 (12.5%)	0 (0%)	.
MDS/MPN	2 (25%)	6 (37.5%)	.

Demographics: Autologous HCT

	Home-Based (N=17)	Matched Controls (N=34)	P-value
Median Age (IQR)	60 (56-64)	61.5 (55-64)	0.68
Gender (female)	4 (23.5%)	15 (44.1%)	0.15
Race			0.80
White	15 (88.2%)	26 (76.5%)	.
Black	2 (11.8%)	7 (20.6%)	.
Other	0 (0%)	1 (2.9%)	.
Ethnicity (non-Hispanic)	17 (100%)	33 (97.1%)	0.20
Karnofsky Performance Status			0.99
80 or below	10 (58.8%)	21 (61.8%)	.
90-100	7 (41.2%)	13 (38.2%)	.
Disease			0.77
Lymphoma (HL+NHL)	6 (35.3%)	14 (41.2%)	.
Plasma Cell Dyscrasia	11 (64.7%)	20 (58.8%)	.
Stem cell source			0.99
Peripheral blood	17 (100%)	33 (97.1%)	.
Bone marrow/Peripheral blood	0 (0%)	1 (2.9%)	.

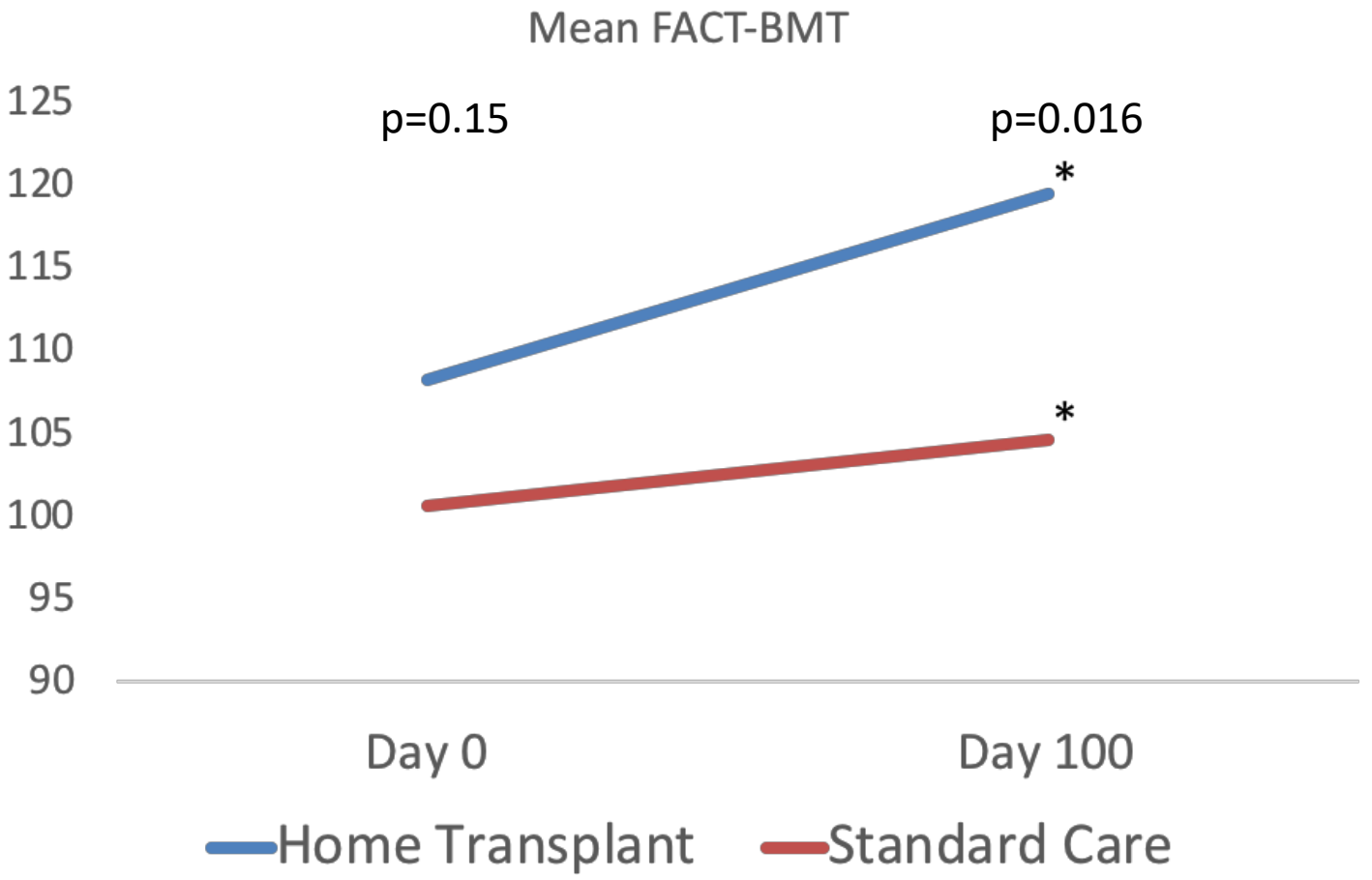
Results: Allogeneic HCT

	Home-Based (N=8)	Matched Controls (N=16)	P-value
Febrile Neutropenia	5 (62.5%)	11 (68.8%)	0.99
Bloodstream Infection	2 (25%)	4 (25%)	0.99
C. diff Infection	0 (0%)	2 (12.5%)	0.54
1-Year Relapse	2 (25%)	7 (43.8%)	0.66
1-Year Mortality	2 (25%)	5 (31.3%)	0.99

Results: Autologous HCT

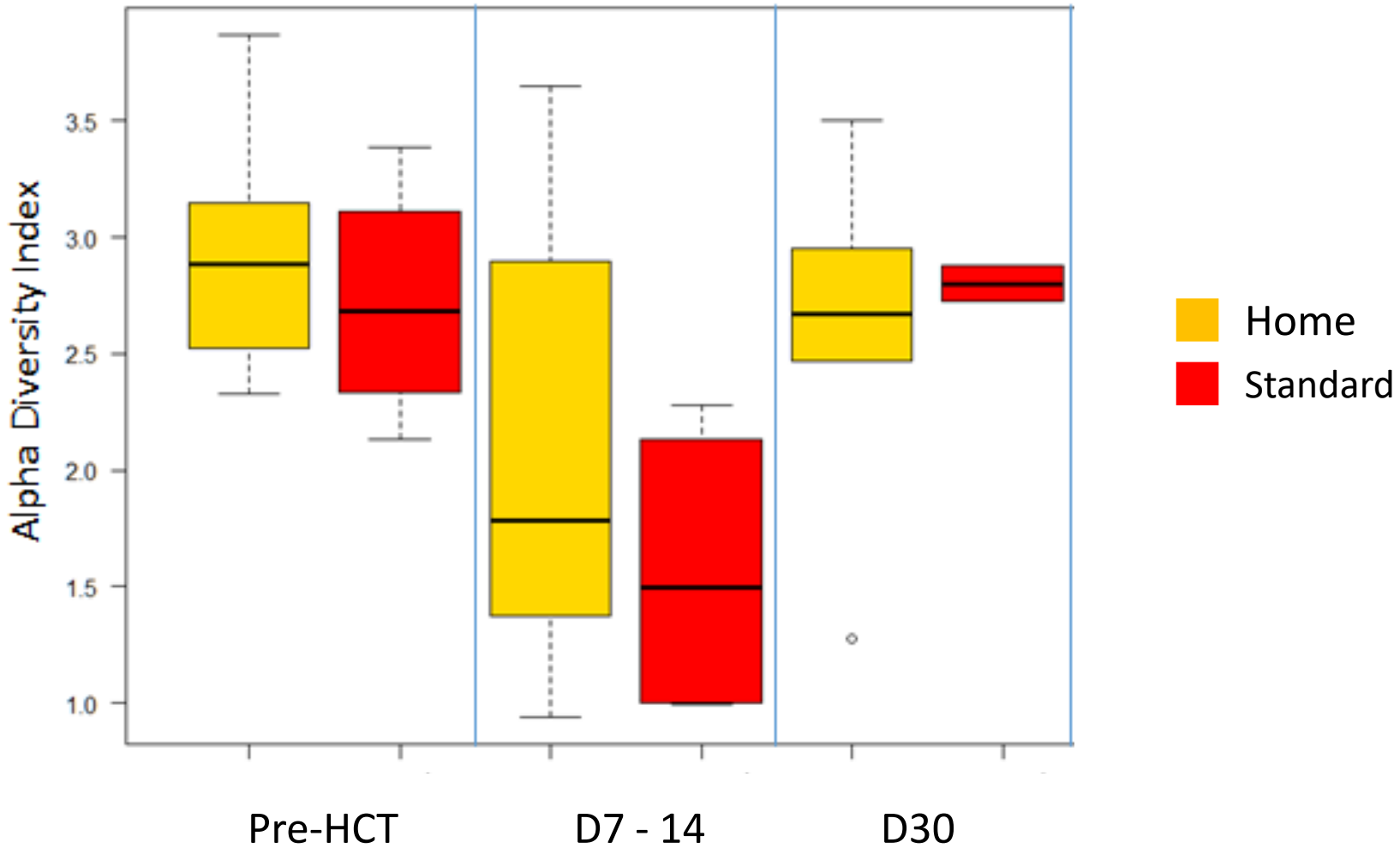
	Home-Based (N=17)	Matched Controls (N=34)	P-value
Febrile Neutropenia	11 (64.7%)	27 (79.4%)	0.31
Bloodstream Infection	5 (29.4%)	4 (11.8%)	0.14
C. diff Infection	0 (0%)	2 (5.9%)	0.55
1-Year Relapse	0 (0%)	7 (20.6%)	0.08
1-Year Mortality	0 (0%)	2 (5.9%)	0.55

Results: Quality of Life (Autologous HCT)

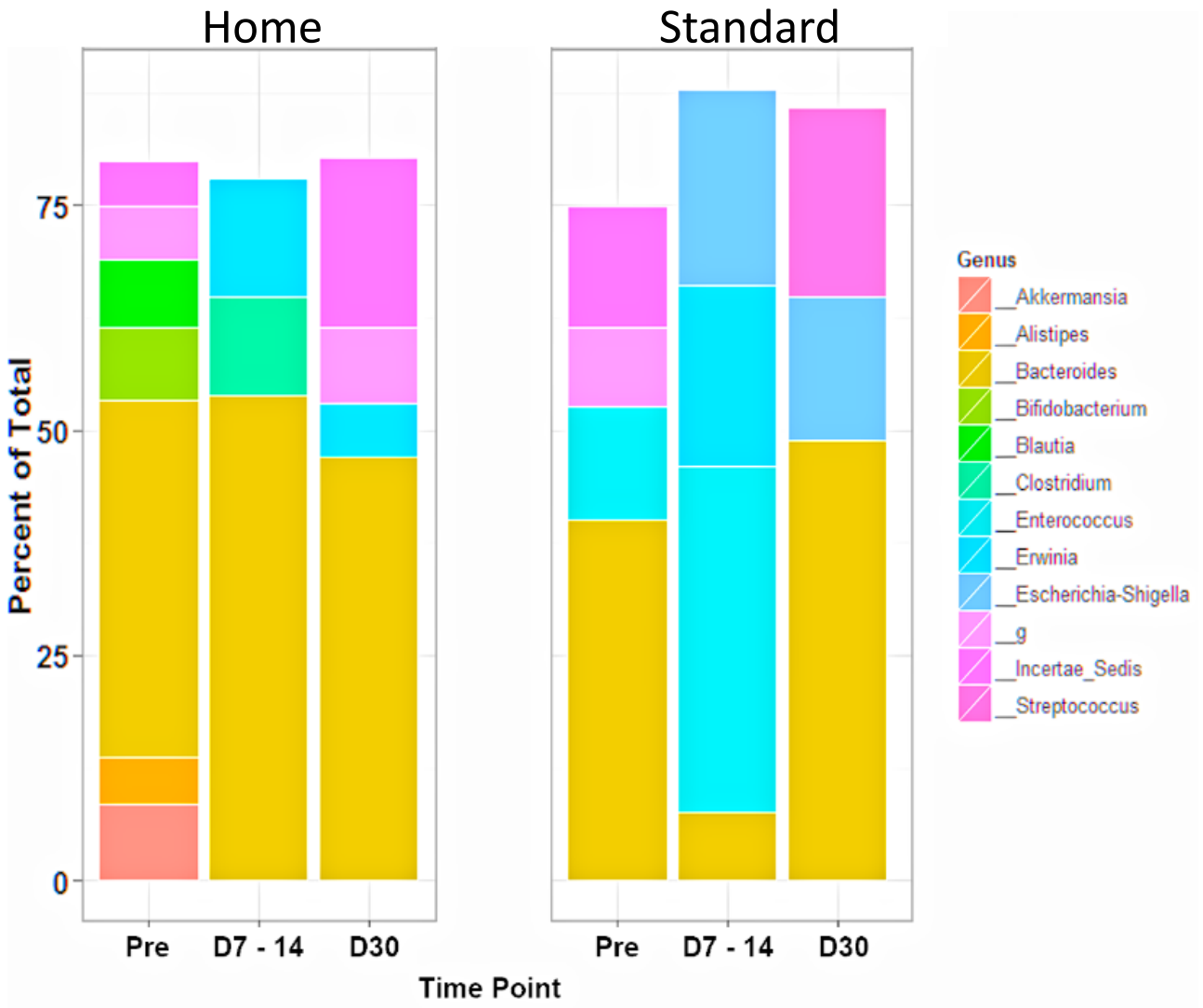


Δ +11.2 vs Δ +4.0

Results


Alpha Diversity Index
3.5
3.0
2.5
2.0
1.5
1.0
Pre-HCT
D7 - 14
D30
Home
Standard

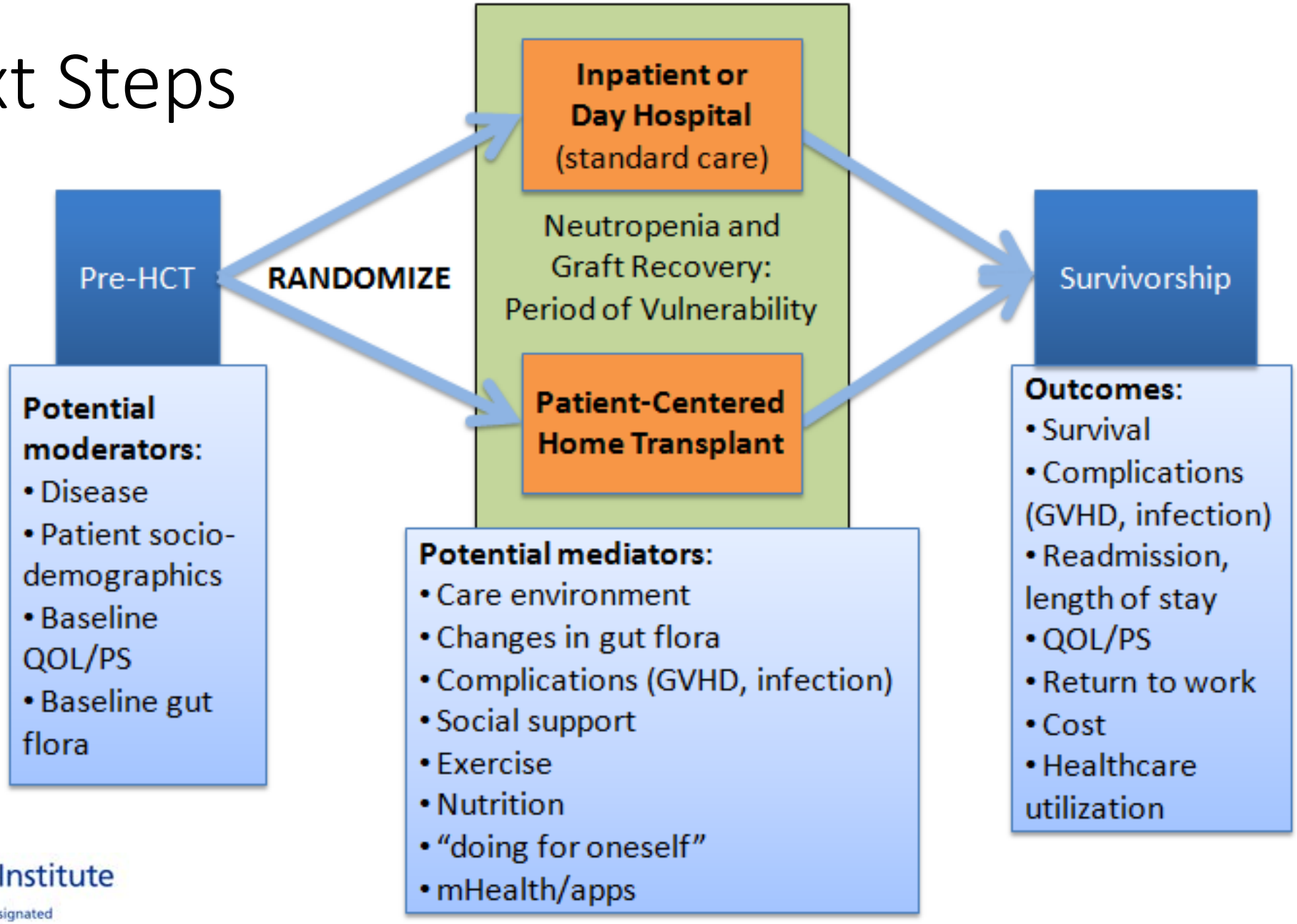
Results


Home
Standard
Percent of Total
75
50
25
0
Pre
D7 - 14
D30
Pre
D7 - 14
D30
Time Point
Genus
__Akkermansia
__Alistipes
__Bacteroides
__Bifidobacterium
__Blautia
__Clostridium
__Enterococcus
__Erwinia
__Escherichia-Shigella
__g
__Incertae_Sedis
__Streptococcus

Next Steps

- Randomized phase 2 trials of home vs. standard HCT
  - Allo (R01CA203950, PI Chao), Auto (R01AG066719, PI Sung)
  - 32 enrolled/randomized to date
- Hypotheses:
  - Improve GVHD, infections, TRM
    - Mediators (diet, activity, gut microbiome)
  - Improve quality of life
  - Lower costs

Next Steps


Pre-HCT
RANDOMIZE
Inpatient or Day Hospital (standard care)
Neutropenia and Graft Recovery: Period of Vulnerability
Patient-Centered Home Transplant
Survivorship
Potential moderators:
• Disease
• Patient socio-demographics
• Baseline QOL/PS
• Baseline gut flora
Potential mediators:
• Care environment
• Changes in gut flora
• Complications (GVHD, infection)
• Social support
• Exercise
• Nutrition
• "doing for oneself"
• mHealth/apps
Outcomes:
• Survival
• Complications (GVHD, infection)
• Readmission, length of stay
• QOL/PS
• Return to work
• Cost
• Healthcare utilization

Verizon LTE 12:11 AM 25%

Diary

Today

S M T W T F S

May 31, 2018

Your care overview is 67% complete

Exercise 1 circle represents 5 minutes

Proteins 1 circle represents 1 serving

Fruits 1 circle represents 1 serving

Vegetables 1 circle represents 1 serving

Diary Health Insights Connect

Verizon LTE 12:14 AM 24%

Health

Today

S M T W T F S

May 31, 2018

Your activity status is 75% complete

Symptoms
Tracker

General Health
Today
9
out of 10

Meals
Today
100%

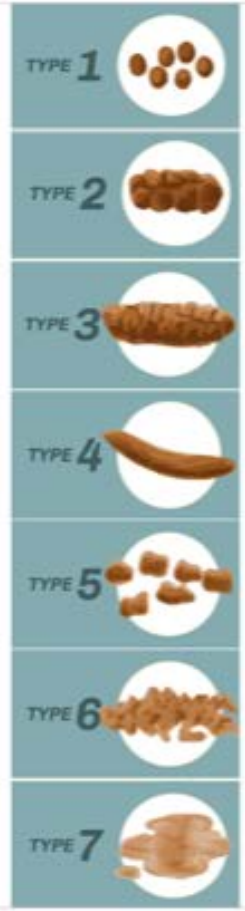
Stools
Today
2

Diary Health Insights Connect

Verizon LTE 12:14 AM 24%

Step 1 of 1 Cancel

Stool



2

Verizon LTE 12:15 AM 24%

Connect

CARE TEAM

Medical Emergency
call 911

Kristi Romero
Study Coordinator

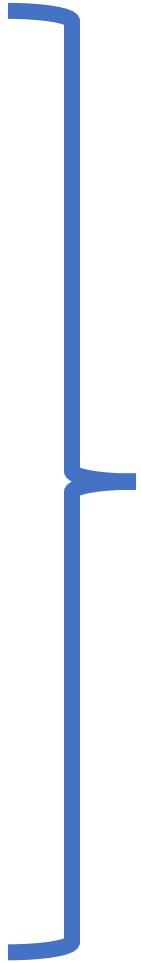
ABMT
Clinic (M-F 8-6 and S/S 8-4)....

9200
Inpatient Unit (Open 24/7). As...

Diary Health Insights Connect

Home HCT and COVID-19 and Social Distancing

Screener (1)
Front Desk (2)
Phlebotomy (3)
Medical Assistant (4)
Provider (5)
Nurse (6)
Environmental Services (7)
Other patients/caregivers (8-10)
Surfaces (???)



Provider (1)
Nurse (maybe 2)

Home HCT and COVID-19

>10-fold increase in home visits

- No longer limited to those living locally
- No longer randomized
- Now standard of care

} Herculean effort by advanced practice providers and nurses

Protocol and administrative supplement in preparation

Continue until there is a vaccine…

Conclusions

- The gut microbiota affects transplant outcomes
- Home care may maintain the gut microbiota
- Home HCT is safe, feasible, and may improve outcomes
- Randomized phase 2 studies are ongoing
- Pivot to standard of care with COVID-19 pandemic

Conclusions

“I can't say enough good things about the bone marrow at home program. While going through an extremely difficult situation where so many things are out of your control and can be very scary, to have the comfort of being in your own space, sleeping in the comfort of your own bed, and having your own things certainly helped ease some of the stress of a very stressful situation.”

Acknowledgments

- Home Transplant Team: Krista Rowe Nichols, Jennifer Frith, Martha Lassiter, ABMT nurses and APPs, patients and caregivers
- Gut Microbiome: Liz Sito, Ashley Potter, 9100/9200/ABMT nurses, Megan Baker, Amy Bush, Meg Lew, Lauren Bohannon, Jill Thompson, Julia Messina, Alex Sibley
- Collaborators: Olle Ringden, Britt-Marie Svahn (Karolinska), Rob Jenq (MD Anderson), Tsoni Peled, Marcel van den Brink (MSKCC)
- Funding:
  - NIH 5KL2TR001115-03
  - NIH 1R21AG066388-01
  - NIH 1R01CA203950-01
  - ASH Scholar Award
  - Duke Institute for Health Innovation Pilot Award
  - Damon Runyon Innovation Award
  - Gateway for Cancer Research