

Appendix:

Nutritional support in hospitalized patients with diabetes and risk for malnutrition

A secondary analysis of an investigator initiated, Swiss, randomized controlled multi-center trial

Bettina Keller^{1,2*}, Carla Wunderle^{1*}, Pascal Tribolet^{1,3,4}, Zeno Stanga⁵, Nina Kaegi-Braun⁶, Beat Mueller^{1,2}, and Philipp Schuetz^{1,2}

1 Medical University Department, Division of General Internal and Emergency Medicine, Kantonsspital Aarau, Aarau, Switzerland

2 Medical Faculty of the University of Basel, Basel, Switzerland

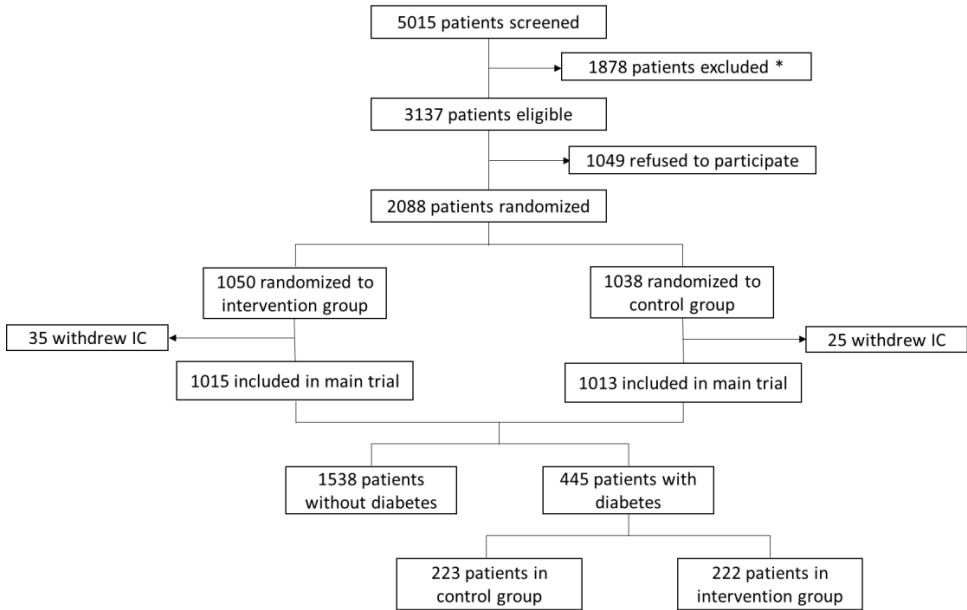
3 Department of Health Professions, Bern University of Applied Sciences, Bern, Switzerland

4 Faculty of Life Sciences University of Vienna, Vienna, Austria

5 Division of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Bern University Hospital and University of Bern, Bern, Switzerland

6 Department of Bioscience and Nutrition, Karolinska Institutet, 17177 Stockholm, Sweden

20 **Supplemental Figure 1: Trial Flow Chart**



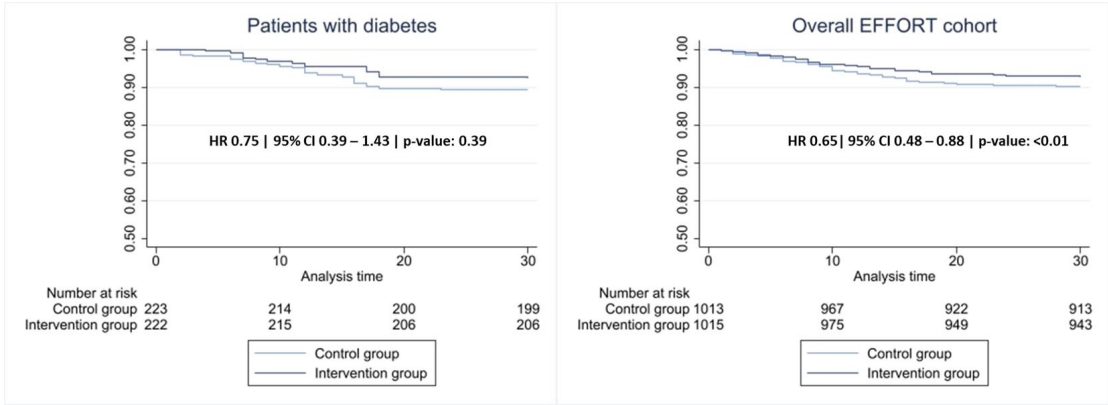
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22 *Figure 1: Study flow chart. Abbreviations: IC; informed consent. * Reasons for exclusion: 145 surgical*
23 *patients, 268 unable to ingest oral nutrition, 158 with a terminal condition, 719 patients already*
24 *receiving nutritional therapy upon admission, 31 hospitalized because of anorexia nervosa, 161 with*
25 *acute pancreatitis, 81 with acute liver failure, 6 with cystic fibrosis, 11 with stem cell transplantation, 27*
26 *with malnutrition after gastric bypass surgery, 43 with contradiction against nutritional therapy and 228*
27 *previously included in the trial.*

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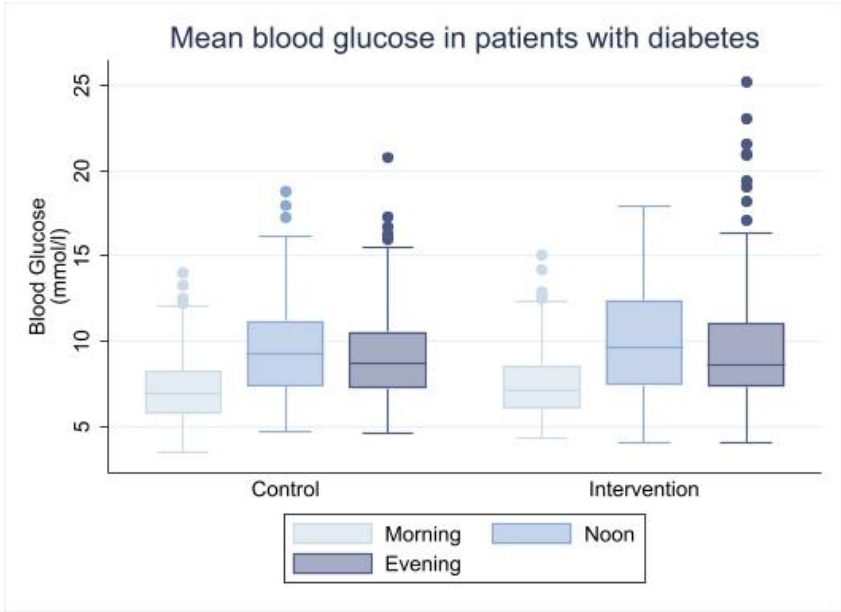
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30 **Supplemental Figure 2: 30-day Kaplan-Meier survival estimates**



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32 *Figure 2: Survival analysis in patients with diabetes (left) and the total cohort (right): HR, Hazard ratio; CI,*
33 *Confidence interval*

35 **Supplemental Figure 3: Mean blood glucose values**



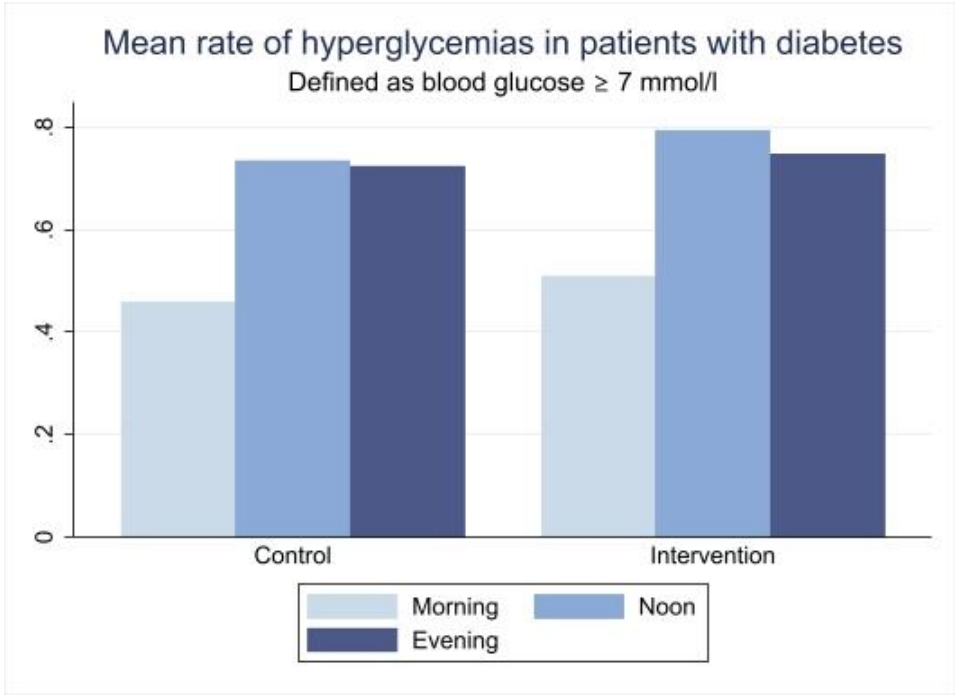
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37 *Figure 4: Box plot illustrating mean glucose values of patients with diabetes according to*
38 *randomization. (Whiskers indicating 25% and 75% of values, median indicated within the box)*

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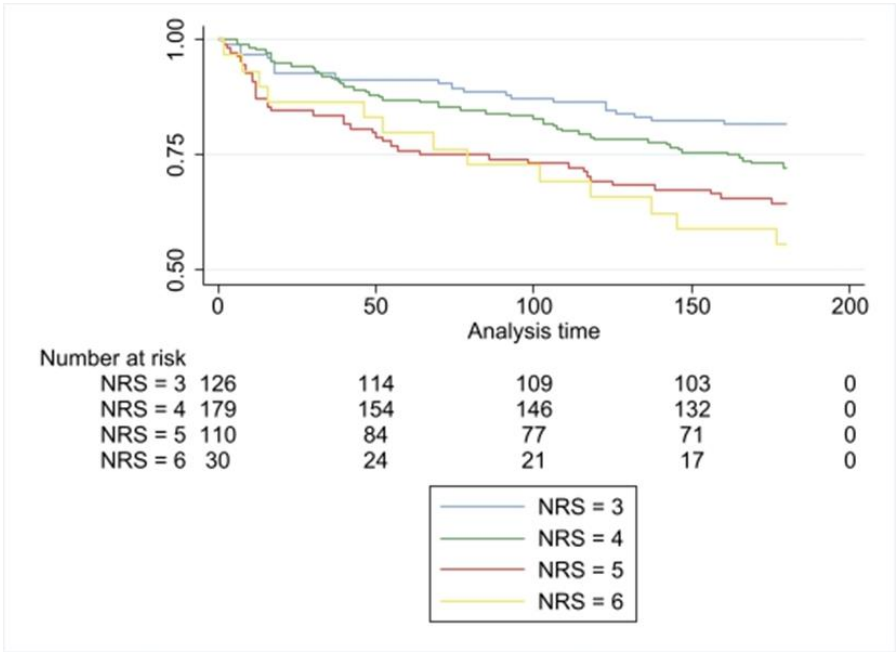
41 **Supplemental Figure 4: Mean rate of hyperglycemias in patients with diabetes**



42
43 *Figure 3: Bar graph illustrating the rates of hyperglycemia in patients with diabetes according to*
44 *randomization.*

45

46 **Supplemental Figure 5: 180-day Kaplan-Meier survival estimates for patients**
47 **with diabetes according to NRS total score**
48 *NRS, Nutritional Risk Screening 2002*



Supplemental Table 1: Baseline characteristics of the total EFFORT cohort compared to patients with diabetes stratified by randomization

Factor	Total cohort (n=2,028)	Patients with diabetes control group (n=223)	Patients with diabetes intervention group (n=222)	p-value
Sociodemographics				
Number	2,028	223	222	
Male	1064 (52%)	131 (59%)	139 (63%)	0.40
Age, mean (SD)	72. 6 (14.1)	75.3 (10.7)	75.5 (9.6)	0.80
Nutritional assessment				
Mean body-mass-index (kg/m²), mean (SD)	24.8 (5.3)	26.9 (5.9)	27.0 (5.5)	0.80
Weight (kg), mean (SD)	70.9 (16.7)	76.8 (17.2)	77.0 (17.6)	0.90
Height (cm), mean (SD)	168 (9.3)	168 (9.1)	168 (9.8)	0.99
NRS total score (%)				
3	624 (31%)	63 (28%)	63 (28%)	1.00
4	775 (38%)	88 (40%)	91 (41%)	
5	524 (26%)	56 (25%)	54 (24%)	
>5	105 (5%)	16 (7%)	14 (6%)	
Admission diagnosis				
Infection	613 (30%)	71 (32%)	55 (25%)	0.10
Cancer	374 (18%)	37 (17%)	35 (16%)	0.81
Cardiovascular disease	205 (10%)	30 (14%)	28 (13%)	0.79
Frailty	194 (10%)	16 (7%)	17 (8%)	0.85
Lung disease	125 (6%)	13 (6%)	6 (3%)	0.10
Gastrointestinal disease	164 (8%)	12 (5%)	29 (13%)	0.01
Neurological disease	95 (5%)	8 (4%)	7 (3%)	0.80
Renal disease	68 (3%)	11 (5%)	15 (7%)	0.41
Metabolic disease	62 (3%)	13 (6%)	11 (5%)	0.68
Other	55 (3%)	6 (3%)	10 (5%)	0.30
Comorbidity				
Hypertension	1109 (55%)	168 (75%)	161 (73%)	0.50
Malignant disease	667 (33%)	68 (31%)	64 (29%)	0.70
Chronic kidney disease	1347 (66%)	169 (76%)	172 (78%)	0.67
Coronary artery disease	566 (28%)	83 (37%)	77 (35%)	0.58
Congestive heart failure	353 (17%)	52 (23%)	42 (19%)	0.3
Chronic obstructive pulmonary disease	303 (15%)	32 (14%)	26 (12%)	0.41
Peripheral artery disease	186 (9%)	41 (18%)	33 (15%)	0.32
Stroke	162 (8%)	27 (12%)	19 (9%)	0.22
Dementia	75 (4%)	5 (2%)	11 (5%)	0.12

Table 1: Baseline characteristics of the entire study cohort compared to the subgroup of patients with diabetes shown according to randomization: NRS, Nutritional Risk Screening 2002.

57 **Supplemental Table 2: Multivariate analysis of clinical outcomes and randomization for**
 58 **patients with diabetes (Extension)**

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Primary outcomes within 30 days	Events intervention group	Events control group	Adjusted OR or coefficient (95% CI)	p-value	p for interaction
Major complications					
Any major complications					
Patients with diabetes	13/222 (6%)	17/223 (8%)	0.71 (0.33 - 1.52)	0.37	0.46
Patients without diabetes	61/793 (8%)	59/790 (7%)	1.03 (0.70 - 1.51)	0.88	
Overall EFFORT cohort	74/1015 (7%)	76/1013 (8%)	0.95 (0.68 - 1.34)	0.79	
Respiratory failure					
Patients with diabetes	3/222 (1%)	3/223 (1%)	0.70 (0.11-4.27)	0.70	0.93
Patients without diabetes	11/793 (1%)	10/790 (1%)	1.24 (0.51 - 3.03)	0.64	
Overall EFFORT cohort	14/1015 (1%)	13/1013 (1%)	1.06 (0.49 - 2.28)	0.89	
Nosocomial infection					
Patients with diabetes	9/222 (4%)	8/223 (4%)	1.03 (0.38 - 2.81)	0.95	0.82
Patients without diabetes	31/793 (4%)	31/790 (4%)	0.93 (0.55 - 1.58)	0.80	
Overall EFFORT cohort	40 /1015 (4%)	39/1013 (4%)	1.01 (0.63 - 1.59)	0.98	
Major cardiovascular events					
Patients with diabetes	2/222 (1%)	2/223 (1%)	1.12 (0.15 - 8.49)	0.91	0.88
Patients without diabetes	6/793 (1%)	5/790 (1%)	1.53 (0.43 - 5.47)	0.51	
Overall EFFORT cohort	8 /1015 (1%)	7/1013 (1%)	1.11 (0.40 - 3.11)	0.84	
Acute kidney injury					
Patients with diabetes	7/222 (3%)	12/223 (5%)	0.47 (0.17 - 1.29)	0.14	0.15
Patients without diabetes	25/793 (3%)	19/790 (2%)	1.30 (0.70 - 2.40)	0.40	
Overall EFFORT cohort	32/1015 (3%)	31/1013 (3%)	1.01 (0.61 - 1.69)	0.96	
Gastrointestinal events					
Patients with diabetes	1/222 (<1%)	2/223 (1%)	0.46 (0.04 - 5.26)	0.54	0.88
Patients without diabetes	8/793 (1%)	13/790 (2%)	0.67 (0.27 - 1.65)	0.38	
Overall EFFORT cohort	9/1013 (1%)	15/1013 (1%)	0.57 (0.25 - 1.31)	0.19	
Side effects from nutritional therapy					
Gastrointestinal side-effects					
Patients with diabetes	8/222 (4%)	7/223(3%)	1.05 (0.35 - 3.19)	0.93	0.88
Patients without diabetes	35/793 (4%)	33/790 (4%)	1.15 (0.68 - 1.95)	0.60	
Overall EFFORT cohort	43/1015 (4%)	40/1013 (4%)	1.12 (0.68 - 1.83)	0.66	
Complications due to enteral feeding or parenteral nutrition					
Patients with diabetes	1/222 (<1%)	2/223 (1%)	0.48 (0.04 - 5.49)	0.55	0.21
Patients without diabetes	-	-	-	-	
Overall EFFORT cohort	5/1015 (<1%)	3/1013 (<1%)	1.63 (0.38 - 6.95)	0.51	
Liver or gallbladder dysfunction					
Patients with diabetes	2/222	4/223 (2%)	0.20 (0.02 - 1.97)	0.17	0.82

	(1%)				
Patients without diabetes	2/793 (<1%)	3/790 (<1%)	0.69 (0.11 – 4.17)	0.69	
Overall EFFORT cohort	4/1015 (<1%)	7/1013 (1%)	1.63 (0.38 - 6.95)	0.51	
Mean length of stay (d)					
Patients with diabetes	10.4	9.8	0.49 (-0.67 - 1.66)	0.41	0.18
Patients without diabetes	9.2	9.6	-0.53 (-1.17 – 0.12)	0.11	
Overall EFFORT cohort	9.5	9.6	-0.21 (-0.76 - 0.35)	0.46	

Table 4: Multivariate analysis, adjusted for NRS, Center of admission and Barthel index, examining the association between nutritional support and clinical outcomes: NRS, Nutritional Risk Screening 2002

64 **Supplemental Table 3: Mean blood glucose values in patients with diabetes**

	Control group			Intervention group		
	Morning	Noon	Evening	Morning	Noon	Evening
Day 1	7.34	10.01	9.37	7.95	10.21	10.01
Day 2	7.36	9.57	9.42	7.61	10.22	10.38
Day 3	7.41	9.86	9.18	7.42	10.47	10.13
Day 4	7.41	10.08	9.11	7.71	9.80	9.67
Day 5	7.40	9.65	10.07	7.69	11.43	10.38
Day 6	7.45	9.71	9.45	7.58	10.24	10.66

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67 **Supplemental Table 4: Univariate analysis of the association of diabetes and outcomes**

Outcomes	Hazard ratio , coefficient or odds ratio	95% Confidence Interval	p-value
Survival analysis			
30-day mortality	1.10	0.78-1.56	0.59
180-day mortality	1.25	1.02-1.54	0.03
3-year mortality	1.14	0.98-1.33	0.08
Readmission rates			
30-day non-elective readmission	0.69	0.46-1.04	0.07
180-day non-elective readmission	0.92	0.73-1.17	0.51
5-year non-elective readmission	0.90	0.64-1.27	0.56
Major adverse outcomes within 30 days			
Major complications	0.88	0.58-1.33	0.55
Admission to intensive care unit	1.03	0.52-2.03	0.93
Nosocomial infection	0.97	0.56-1.68	0.93
Respiratory failure	1.02	0.41-2.53	0.97
Gastrointestinal events	0.50	0.15-1.70	0.27
Acute kidney injury	1.56	0.90-2.70	0.11
Major cardiovascular events	1.30	0.41-4.09	0.66
Functional decline $\geq 10\%^*$	1.03	0.75-1.42	0.87
Any adverse outcome	0.85	0.66-1.09	0.19
Side effects of nutritional support			
Any side-effects	2.15	1.65-2.80	<0.01
Gastrointestinal side effects	0.78	0.44-1.37	0.39
Severe hyperglycemia	6.76	4.39-10.42	<0.01
Liver or gallbladder dysfunction	4.31	1.31-14.20	0.02
Refeeding Syndrom	1.45	1.01-2.08	0.04
Feeding tube	1.42	0.28-7.37	0.67
Parenteral nutrition of feeding tube	2.14	0.51-9.00	0.30
Length of stay	0.71	0.02-1.40	0.04
180-day weight change	-0.94	-1.71--0.17	0.02
30-day weight change	-0.08	-0.75-0.58	0.81

68 *Table 1: Univariate regression; association of diabetes with different outcomes. Hazard ratios were*
69 *reported for survival analyses, odds ratios were reported for binary outcomes, coefficients were*
70 *reported for continuous outcomes.*

71 **Defined as decline in Barthel index of $\geq 10\%$*

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75 **Supplemental Table 5: Multivariate analysis of the association of diabetes and outcomes**

Outcomes	Hazard ratio, coefficient or Odds ratio	95% Confidence Interval	p-value
Mortality analysis			
30-day mortality	1.05	0.73-1.53	0.76
180-day mortality	1.21	0.98-1.49	0.07
3-year mortality	1.10	0.94-1.28	0.22
Hospital readmissions			
30-day non-elective readmission	0.70	0.46-1.05	0.08
180-day non-elective readmission	0.95	0.75-1.21	0.69
5-year non-elective readmission	0.95	0.67-1.35	0.77
Major complications within 30 days			
Admission to intensive care unit	1.01	0.50-2.06	0.98
Nosocomial Infection	0.95	0.54-1.68	0.87
Acute kidney injury	1.44	0.81-2.54	0.21
Respiratory failure	0.85	0.31-2.29	0.74
Gastrointestinal events	0.52	0.15-1.75	0.29
Adverse outcomes	0.83	0.64-1.07	0.16
Major complications	0.84	0.55-1.29	0.43
Major cardiovascular event	1.27	0.39-4.09	0.69
Functional decline $\geq 10\%^*$	0.99	0.72-1.37	0.97
Side effects from nutritional therapy			
Any side effects	2.24	1.70-2.95	<0.01
Gastrointestinal side effects	0.76	0.41-1.42	0.38
Severe hyperglycemia	6.82	4.39-10.59	<0.01
Liver or gallbladder dysfunction	3.49	0.97-12.58	0.06
Refeeding syndrome	1.43	0.98-2.07	0.06
Feeding tube	1.72	0.31-9.51	0.53
Parenteral feeding or feeding tube	2.66	0.59-12.01	0.20
Length of stay	0.46	-0.22-1.14	0.18
180-day weight change	-0.94	-1.71--0.16	0.02
30-day weight change	-0.09	-0.76-0.58	0.80

76 Table 2: Multivariate regression adjusted for Nutritional Risk Screening 2002, Barthel Index and center
77 of admission, association of diabetes with different outcomes. *Hazard ratios were reported for survival*
78 *analyses, odds ratios were reported for binary outcomes, coefficients were reported for continuous*
79 *outcomes.*

80 **Defined as decline in Barthel index of $\geq 10\%$*

81

82 **Full list of investigators involved in the EFFORT trial:**

- 83 • Kantonsspital Aarau: Thomas Baumgartner; Valerie Bächli; Luca Bernasconi; Lisa Bonoure;
84 Manuela Deiss; Andreas Eckart; Rebecca Fehr, Susan Felder; Natalie Friedli; Martina Geiser,
85 Filomena Gomes, Lena Grädel; Andreas Huber; Daniel Koch; Alexander Kutz; Svenja
86 Laukemann; Olivia Neeser; Manuela Nickler; Marc Meier; Marc Meili; Beat Mueller; Jonas
87 Odermatt; Manuel Ottiger; Isabel Pulvermüller; Anna Christina Rast; Katharina Regez; Ramon
88 Sager; Diana Sbiti; Ursula Schild; Philipp Schuetz; Deborah Steiner; Alaadin Vögeli; Yannick
89 Wirz; Esther Wyrtsch; Giedre Zurauskaite; Seline Zurfluh;
- 90 • Inselspital Bern: Evelyne Abgottsporn; Drahomir Aujesky; Adrian Baumann; Kathrin Blaser;
91 Jacques Donzé, Tanja Flückiger; Cindy Groen; Daniela Häfeli; Corinne Hänni; Katrin
92 Lengacher; Melisa Merdanovic; Sarah Pfaffen; Nicolas Rodondi; Nathalie Schwab; Zeno
93 Stanga; Monica von Brevern; Sophie von Lerber;
- 94 • Spital Lachen: Thomas Bregenzer; Bruno Schiesser; Pascal Tribolet; Anita Wild;
- 95 • Luzerner Kantonsspital: Daniela Buhl, Christoph Henzen; Silvia Mattmann; Melina Nigg; Sara
96 Ramseier; Michael Trummler
- 97 • Kantonsspital Münsterlingen: Nina Braun; Claus Hoess, Cornelia Ebner; Dominique
98 Mannhart; Vojtech Pavlicek, Sarah Schmid
- 99 • Bürgerspital Solothurn: Cornelia Albrecht; Claudia Brand; Katharina Ilic; Lisa Tanner; Robert,
100 Thomann; Rahel von Felten;
- 101 • Kantonsspital St.Gallen: Carmen Benz; Michael Brändle, Stefan Bilz; Madlaina Höhener;
102 Sarah Sigrist; Rahel Stadler; Alexandra Wick
- 103 • Kantonsspital Baselland, Bruderholz: Jonas Rutishauser; Marianne Waldmeier

104

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