

## Supplementary appendix

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## **Supplemental Information**

**Title:** A probability score for preoperative prediction of type 2 diabetes remission following RYGB surgery.

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**Table S1. Characteristics of the Primary cohort (N=690) stratified by use of insulin (T2D: T2D patients not using insulin; T2D+I: T2D patients using insulin). INS: insulin sensitizing agent.**

|                                      |               | <b>T2D<br/>N=438</b> | <b>T2D+I<br/>N=252</b> |
|--------------------------------------|---------------|----------------------|------------------------|
| Gender                               | Male, % (n)   | 24% (n=104)          | 32% (n=80)             |
|                                      | Female, % (n) | 76% (n=334)          | 68% (n=172)            |
| Age (years)                          | Mean (SD)     | 48.8 (10.3)          | 53.6 (8.9)             |
|                                      | Range         | [19, 72]             | [26, 74]               |
| Ethnic group                         | White, % (n)  | 97% (n=423)          | 98% (n=246)            |
|                                      | Black, % (n)  | 3% (n=12)            | 2% (n=6)               |
|                                      | Other, % (n)  | <1% (n=3)            | 0% (n=0)               |
|                                      | Unknown (n)   | n=50                 | n=31                   |
| Weight at baseline (Kg)              | Mean (SD)     | 117 (27)             | 138 (29)               |
|                                      | Range         | [88, 241]            | [84, 265]              |
| BMI at baseline (Kg/m <sup>2</sup> ) | Mean (SD)     | 49.5 (8.0)           | 49.2 (8.8)             |
|                                      | Range         | [35.1, 82.2]         | [35.0, 81.6]           |
| Use of metformin                     | Yes, % (n)    | 88% (n=387)          | 60% (n=150)            |
|                                      | No, % (n)     | 12% (n=51)           | 40% (n=102)            |
| Use of sulfonylureas                 | Yes, % (n)    | 36% (n=159)          | 23% (n=58)             |
|                                      | No, % (n)     | 64% (n=279)          | 77% (n=194)            |
| Use of ISA other than metformin      | Yes, % (n)    | 29% (n=125)          | 38% (n=95)             |
|                                      | No, % (n)     | 71% (n=313)          | 62% (n=157)            |
| Pre-operative glucose (mg/dL)        | Mean (SD)     | 121.4 (46.8)         | 153.9 (80.6)           |
|                                      | Range         | [44, 351]            | [51, 607]              |
| Pre-operative HbA1c (%)              | Mean (SD)     | 6.8 (1.2)            | 8.2 (1.7)              |
|                                      | Range         | [4.5, 12.2]          | [4.9, 12.2]            |
| Pre-operative serum insulin (μU/mL)  | Mean (SD)     | 27.5 (26.9)          | 28.0 (42.2)            |
|                                      | Range         | [3.4, 234.0]         | [0.2, 510.2]           |

**Table S2. Kaplan-Meier survival estimates for percent (%) of patients with T2D [partial + complete] remission after RYGB surgery over five years, stratified by pre-operative use of insulin, in the Primary cohort.** (T2D: type 2 diabetes patients not using insulin; T2D+I: type 2 diabetes patients using insulin) (with reference to [Figure 2A](#)).

|   |                | 14-months*     | 2-year         | 3-year         | 5-year         |
|---|----------------|----------------|----------------|----------------|----------------|
| T2D<br>(N=438)  | % remission    | 70.6%          | 80.7%          | 87.8%          | 90.1%          |
|   | 95% CI         | [66.3%, 74.8%] | [76.9%, 84.5%] | [84.3%, 91.2%] | [86.6%, 93.6%] |
|   | N in follow-up | 129            | 61             | 25             | 12             |
| T2D+I<br>(N=252)  | % remission    | 10.3%          | 19.8%          | 26.6%          | 31.1%          |
|   | 95% CI         | [6.6%, 14.1%]  | [14.7%, 24.8%] | [20.5%, 32.6%] | [23.5%, 38.6%] |
|   | N in follow-up | 226            | 162            | 85             | 35             |
| Log-rank p-value < 0.0001   |                |                |                |                |                |
| *: The time point of 14-months was used to approximate the effect of surgery on diabetes remission (i.e. allow 2 months after surgery to reach diabetes free status then another 12-months required for remission). |                |                |                |                |                |

**Table S3. Kaplan-Meier survival estimates for percent (%) of patients with T2D complete remission after RYGB surgery over five years, stratified by pre-operative use of insulin, in the Primary cohort.** (T2D: type 2 diabetes patients not using insulin; T2D+I: type 2 diabetes patients using insulin) (with reference to [Figure 2B](#)).

|   |                | 14-months*     | 2-year         | 3-year         | 5-year         |
|---|----------------|----------------|----------------|----------------|----------------|
| T2D<br>(N=438)  | % remission    | 42.4%          | 60.3%          | 73.3%          | 77.7%          |
|   | 95% CI         | [37.6%, 46.9%] | [55.5%, 65.0%] | [68.6%, 78.0%] | [72.9%, 82.5%] |
|   | N in follow-up | 253            | 134            | 63             | 34             |
| T2D+I<br>(N=252)  | % remission    | 4.4%           | 8.5%           | 13.8%          | 15.4%          |
|   | 95% CI         | [1.8%, 6.9%]   | [5.0%, 12.0%]  | [9.3%, 18.3%]  | [10.5%, 20.3%] |
|   | N in follow-up | 241            | 208            | 154            | 63             |
| Log-rank p-value < 0.0001   |                |                |                |                |                |
| *: The time point of 14-months was used to approximate the effect of surgery on diabetes remission (i.e. allow 2 months after surgery to reach diabetes free status then another 12-months required for remission). |                |                |                |                |                |

**Table S4. Basic characteristics of T2D (non-insulin using) patients by remission [partial + complete] type, in the primary cohort** (with reference to Table 2) (ISA: insulin sensitizing agent). P-values were derived by ANOVA (comparisons of means) or Chi square tests (comparisons of percentages).

|                                      |               | <b>Early Remission<br/>N=309</b> | <b>Late Remission<br/>N=65</b> | <b>No Remission<br/>N=64</b> | <b>P-value</b> |
|--------------------------------------|---------------|----------------------------------|--------------------------------|------------------------------|----------------|
| Gender                               | Male, % (n)   | 23% (n=70)                       | 18% (n=12)                     | 34% (n=22)                   | 0.074          |
|                                      | Female, % (n) | 77% (n=239)                      | 82% (n=53)                     | 64% (n=42)                   |                |
| Age (years)                          | Mean (SD)     | 47.8 (10.5)                      | 49.3 (9.4)                     | 53.4 (9.1)                   | 0.0003         |
|                                      | Range         | [19, 72]                         | [29, 68]                       | [35, 70]                     |                |
| Ethnic group                         | White, % (n)  | 96% (n=296)                      | 100% (n=65)                    | 97% (n=62)                   | 0.0347         |
|                                      | Black, % (n)  | 4% (n=11)                        | 0% (n=0)                       | 2% (n=1)                     |                |
|                                      | Other, % (n)  | <1% (n=2)                        | 0% (n=0)                       | 2% (n=1)                     |                |
| Weight at baseline (Kg)              | Mean (SD)     | 139 (27)                         | 134 (26)                       | 136 (23)                     | 0.274          |
|                                      | Range         | [89, 241]                        | [98, 236]                      | [88, 198]                    |                |
| BMI at baseline (Kg/m <sup>2</sup> ) | Mean (SD)     | 49.8 (8.3)                       | 49.0 (7.6)                     | 48.6 (7.2)                   | 0.422          |
|                                      | Range         | [35.1, 82.2]                     | [35.2, 69.7]                   | [35.1, 76.2]                 |                |
| Use of metformin                     | Yes, % (n)    | 91% (n=281)                      | 83% (n=54)                     | 81% (n=52)                   | 0.032          |
|                                      | No, % (n)     | 9% (n=28)                        | 17% (n=11)                     | 19% (n=12)                   |                |
| Use of sulfonylureas                 | Yes, % (n)    | 28% (n=86)                       | 45% (n=29)                     | 69% (n=44)                   | 0.0001         |
|                                      | No, % (n)     | 72% (n=223)                      | 55% (n=36)                     | 31% (n=20)                   |                |
| Use of ISA other than metformin      | Yes, % (n)    | 21% (n=64)                       | 31% (n=20)                     | 64% (n=41)                   | 0.0001         |
|                                      | No, % (n)     | 79% (n=245)                      | 69% (n=45)                     | 36% (n=23)                   |                |
| Pre-operative glucose (mg/dL)        | Mean (SD)     | 113.8 (39.1)                     | 130.8 (49.8)                   | 149.0 (64.2)                 | <0.0001        |
|                                      | Range         | [44, 281]                        | [69, 313]                      | [72, 351]                    |                |
| Pre-operative HbA1c (%)              | Mean (SD)     | 6.5 (1.0)                        | 7.1 (1.4)                      | 7.7 (1.3)                    | <0.0001        |
|                                      | Range         | [4.5, 10.9]                      | [5.3, 11.4]                    | [5.5, 12.2]                  |                |
| Pre-operative serum insulin (μU/mL)  | Mean (SD)     | 29.6 (30.4)                      | 23.6 (13.0)                    | 20.8 (1.3)                   | 0.033          |
|                                      | Range         | [3.4, 234.0]                     | [6.2, 67.2]                    | [5.0, 77.3]                  |                |

**Table S5. Basic characteristics of T2D+I (insulin using) patients by T2D remission [partial + complete] type in the primary cohort** (with reference to Table 3) (ISA: insulin sensitizing agent). P-values were derived by ANOVA (comparisons of means) or Chi square tests (comparisons of percentages).

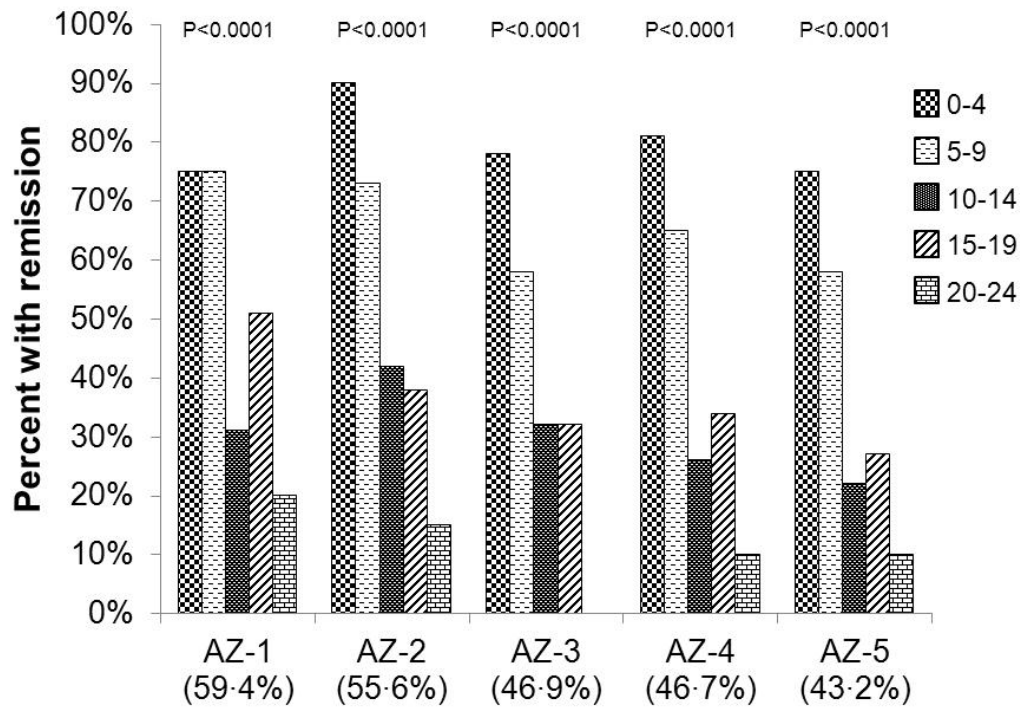
|                                      |               | <b>Early Remission<br/>N=26</b> | <b>Late Remission<br/>N=36</b> | <b>No Remission<br/>N=190</b> | <b>P-value</b> |
|--------------------------------------|---------------|---------------------------------|--------------------------------|-------------------------------|----------------|
| Gender                               | Male, % (n)   | 15% (n=4)                       | 42% (n=15)                     | 32% (n=61)                    | 0.088          |
|                                      | Female, % (n) | 85% (n=22)                      | 58% (n=21)                     | 68% (n=129)                   |                |
| Age (years)                          | Mean (SD)     | 48.4 (10.7)                     | 50.5 (7.0)                     | 54.9 (8.6)                    | 0.0001         |
|                                      | Range         | [26, 64]                        | [37, 65]                       | [23, 74]                      |                |
| Ethnic group                         | White, % (n)  | 100% (n=26)                     | 100% (n=36)                    | 97% (n=184)                   | 0.790          |
|                                      | Black, % (n)  | 0% (n=0)                        | 0% (n=0)                       | 3% (n=6)                      |                |
|                                      | Other, % (n)  | 0% (n=0)                        | 0% (n=0)                       | 0% (n=0)                      |                |
| Weight at baseline (Kg)              | Mean (SD)     | 137 (29)                        | 146 (30)                       | 137 (29)                      | 0.232          |
|                                      | Range         | [100, 234]                      | [93, 203]                      | [84, 565]                     |                |
| BMI at baseline (Kg/m <sup>2</sup> ) | Mean (SD)     | 49.4 (9.8)                      | 50.2 (8.8)                     | 49.0 (8.7)                    | 0.757          |
|                                      | Range         | [35.7, 72.1]                    | [35.2, 66.8]                   | [35.0, 81.6]                  |                |
| Use of metformin                     | Yes, % (n)    | 81% (n=21)                      | 67% (n=24)                     | 55% (n=105)                   | 0.029          |
|                                      | No, % (n)     | 19% (n=5)                       | 33% (n=12)                     | 45% (n=85)                    |                |
| Use of sulfonylureas                 | Yes, % (n)    | 38% (n=10)                      | 22% (n=8)                      | 21% (n=40)                    | 0.140          |
|                                      | No, % (n)     | 62% (n=16)                      | 78% (n=28)                     | 79% (n=150)                   |                |
| Use of ISA other than metformin      | Yes, % (n)    | 31% (n=8)                       | 39% (n=14)                     | 38% (n=73)                    | 0.743          |
|                                      | No, % (n)     | 69% (n=18)                      | 61% (n=22)                     | 62% (n=117)                   |                |
| Pre-operative glucose (mg/dL)        | Mean (SD)     | 143.4 (69.7)                    | 167.2 (86.5)                   | 152.7 (80.9)                  | 0.485          |
|                                      | Range         | [55, 368]                       | [58, 490]                      | [51, 607]                     |                |
| Pre-operative HbA1c (%)              | Mean (SD)     | 7.4 (1.6)                       | 7.8 (1.5)                      | 8.4 (1.7)                     | 0.011          |
|                                      | Range         | [5.2, 10.3]                     | [5.0, 11.2]                    | [4.9, 14.1]                   |                |
| Pre-operative serum insulin (μU/mL)  | Mean (SD)     | 25.5 (12.1)                     | 26.8 (19.5)                    | 28.5 (47.6)                   | 0.935          |
|                                      | Range         | [10.3, 49.3]                    | [0.9, 80.1]                    | [0.2, 510.2]                  |                |

**Table S6. Kaplan-Meier survival estimates and 95% confidence intervals for the percent (%) of T2D patients with [partial + complete] remission after RYGB surgery, over five years, by using four variables (age, HbA1c, insulin levels, and type of preoperative medication).** The *DiaRem* score of this model ranges from 0-22 and was stratified into 5 groups corresponding to 5 ranges of probabilities of diabetes remission: 0-2 (88%-99%), 3-7 (64%-88%), 8-12 (23%-49%), 13-17 (11%-33%), 18-22 (2%-16%) (with reference to Figure 3A).

| DiaRem score             |                | 14-months* | 2-year     | 3-year      | 5-year     |
|--------------------------|----------------|------------|------------|-------------|------------|
| 0-2<br>(n=188)           | % remission    | 88%        | 96%        | 99%         | 100%       |
|                          | 95% CI         | [83%, 92%] | [93%, 99%] | [98%, 100%] | NA         |
|                          | N in follow-up | 23         | 5          | 1           | 0          |
| 3-7<br>(n=209)           | % remission    | 64%        | 76%        | 85%         | 88%        |
|                          | 95% CI         | [58%, 71%] | [70%, 82%] | [80%, 90%]  | [83%, 93%] |
|                          | N in follow-up | 75         | 38         | 14          | 8          |
| 8-12<br>(n=70)           | % remission    | 23%        | 37%        | 49%         | 49%        |
|                          | 95% CI         | [13%, 33%] | [25%, 49%] | [36%, 63%]  | [36%, 63%] |
|                          | N in follow-up | 54         | 32         | 16          | 7          |
| 13-17<br>(n=169)         | % remission    | 11%        | 21%        | 29%         | 33%        |
|                          | 95% CI         | [6%, 16%]  | [15%, 28%] | [22%, 37%]  | [24%, 41%] |
|                          | N in follow-up | 150        | 107        | 61          | 25         |
| 18-22<br>(n=54)          | % remission    | 2%         | 4%         | 4%          | 16%        |
|                          | 95% CI         | [0%, 5%]   | [0%, 9%]   | [0%, 9%]    | [0%, 38%]  |
|                          | N in follow-up | 53         | 41         | 18          | 7          |
| Log-rank p-value <0.0001 |                |            |            |             |            |

**Table S7. Kaplan-Meier survival estimates and 95% confidence intervals for the percent (%) of T2D patients with complete remission after RYGB surgery, over five years, by using four variables (age, HbA1c, insulin levels, and type of preoperative medication).** The diabetes remission score (*DiaRem* score) of this model has a range of 0-22 and was stratified into 5 groups: *DiaRem* 0-2 (61%-94%), 3-7 (32%-72%), 8-12 (10%-34%), 13-17 (5%-16%), 18-22 (0%) (with reference to Figure 3B).

| <i>DiaRem</i> score      |                | 14-months* | 2-year     | 3-year     | 5-year     |
|--------------------------|----------------|------------|------------|------------|------------|
| 0-2<br>(n=188)           | % remission    | 61%        | 82%        | 94%        | 94%        |
|                          | 95% CI         | [54%, 68%] | [76%, 88%] | [89%, 98%] | [89%, 98%] |
|                          | N in follow-up | 74         | 27         | 5          | 1          |
| 3-7<br>(n=209)           | % remission    | 32%        | 49%        | 65%        | 72%        |
|                          | 95% CI         | [25%, 38%] | [42%, 56%] | [57%, 72%] | 64%, 80%]  |
|                          | N in follow-up | 143        | 82         | 42         | 23         |
| 8-12<br>(n=70)           | % remission    | 10%        | 21%        | 31%        | 34%        |
|                          | 95% CI         | [3%, 17%]  | [11%, 30%] | [19%, 42%] | [21%, 48%] |
|                          | N in follow-up | 63         | 47         | 28         | 16         |
| 13-17<br>(n=169)         | % remission    | 5%         | 9%         | 14%        | 16%        |
|                          | 95% CI         | [2%, 9%]   | [5%, 13%]  | [9%, 20%]  | [10%, 22%] |
|                          | N in follow-up | 160        | 136        | 107        | 43         |
| 18-22<br>(n=54)          | % remission    | 0%         | 0%         | 0%         | 0%         |
|                          | 95% CI         | NA         | NA         | NA         | NA         |
|                          | N in follow-up | 54         | 50         | 35         | 14         |
| Log-rank p-value <0.0001 |                |            |            |            |            |



**Figure S1. *DiaRem* scores predicting percent T2D remission rates, according to five different definition of diabetes remission at 14 months after RYGB surgery using the replication cohort from Arizona (AZ).** The five definitions of diabetes remission (percent) were according to fasting glucose (FG) levels, and/or antidiabetic medication use, and/or HbA1c levels, as follows: AZ-1 (59.4%): FG <100 mg/dL, no medication, AZ-2 (55.6%): HbA1c <6.0%, no medication, AZ-3 (46.9%): HbA1c <5.7%, no medication, AZ-4 (46.7%): FG <100 mg/dL, HbA1c <6.0%, AZ-5: FG <100 mg/dL, HbA1c <5.7% (REF # 5). Cochran-Armitage trend tests were used to confirm that lower *DiaRem* scores were associated with higher chance of remission within each cohort ( $P < 0.0001$ ).