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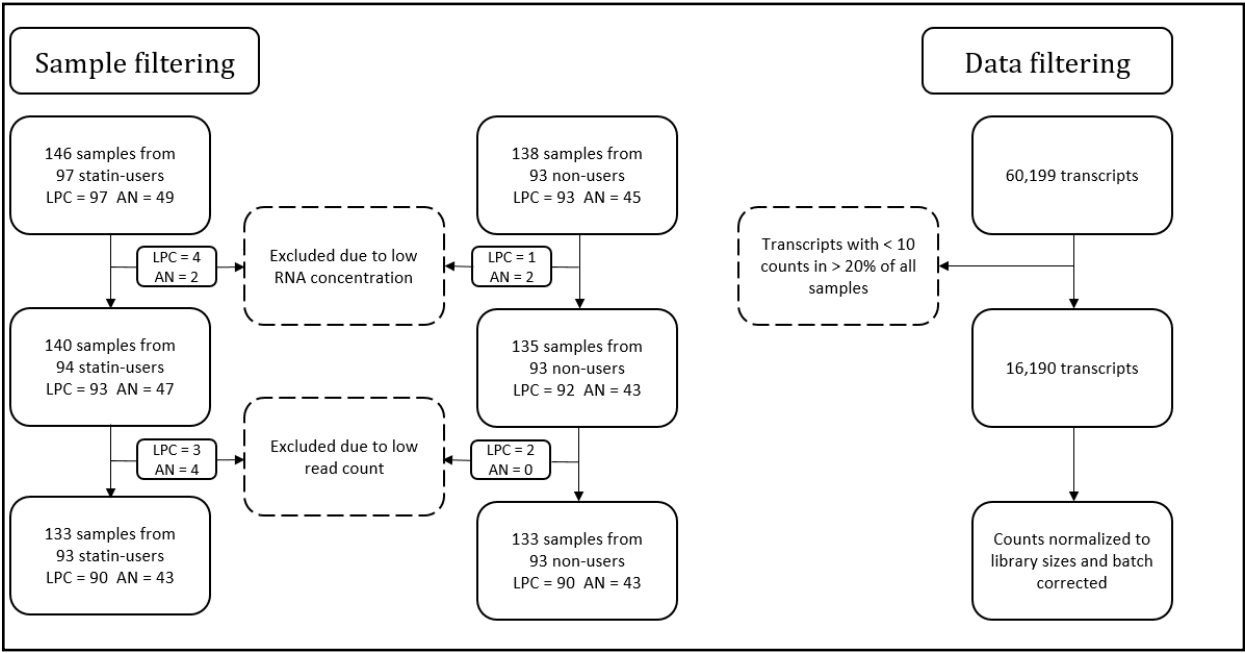
**Table S1: Patient clinical characteristics**

|                            | Non-user    | Statin-user | Atorvastatin-user | Simvastatin- user |
|----------------------------|-------------|-------------|-------------------|-------------------|
| <b>Patients</b>            |             |             |                   |                   |
| n                          | 93          | 93          | 45                | 48                |
| <b>Statin dose</b>         |             |             |                   |                   |
| Median, mg/day             | NA          | 30.3        | 32.6              | 28.5              |
| (IQR)                      |             | (20.4-38.0) | (19.4-41)         | (20.0-36)         |
| Unknown                    |             | 0 (0%)      | 0 (0%)            | 0 (0%)            |
| <b>Treatment length</b>    |             |             |                   |                   |
| Median, years              | NA          | 8.7         | 9.1               | 5.8               |
| (IQR)                      |             | (4.5- 11.9) | (5.0-11.7)        | (3.2-11.5)        |
| Unknown                    |             | 0 (0%)      | 0 (0%)            | 0 (0%)            |
| <b>P-cholesterol level</b> |             |             |                   |                   |
| < 5 mmol/L                 | 33 (35.5%)  | 70 (75.2%)  | 31 (68.9%)        | 39 (81.2 %)       |
| > 5 mmol/L                 | 49 (52.7 %) | 19 (20.4%)  | 10 (22.2%)        | 9 (18.8%)         |
| Unknown                    | 11 (11.8%)  | 4 (4.3%)    | 4 (8.8%)          | 0 (0%)            |
| <b>P-LDL level</b>         |             |             |                   |                   |
| < 3 mmol/L                 | 30 (32.2 %) | 68 (73.1%)  | 31(68.8%)         | 37 (77.1%)        |
| > 3 mmol/L                 | 49 (52.7 %) | 14 (15.1%)  | 7(15.6%)          | 7(14.6%)          |
| Unknown                    | 14 (18.3 %) | 11 (11.8%)  | 7(15.6%)          | 4(8.3%)           |

Data is n (%) or median (IQR).

Table text: IQR: interquartile range; NA: not applicable

**Figure S1: Sample and data filtration**



**Figure text:** LPC: Localized prostate cancer tissue; AN: Adjacent nonmalignant prostate tissue

**Table S2: Differential expression analysis**

| Top 30 differentially expressed genes       |          |       |        |                                                            |                                                                                                                                                                    |
|---------------------------------------------|----------|-------|--------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Downregulated in statin-users vs. non-users |          |       |        |                                                            |                                                                                                                                                                    |
| Gene                                        | P.val    | P.adj | LogFC  | Nomenclature                                               | Role                                                                                                                                                               |
| <b>ZNF853</b>                               | 5.93E-08 | 0.001 | -0.870 | Zinc Finger Protein 853                                    | Transcription factor (RNA binding), not previously associated with cancer (1).                                                                                     |
| <b>DCAF12L2</b>                             | 1.43E-06 | 0.006 | -1.123 | DDB1 And CUL4 Associated Factor 12 Like 2                  | Involved in a variety of cellular processes. High expression prolongs overall survival in breast cancer (2).                                                       |
| <b>ZNF800</b>                               | 1.48E-06 | 0.006 | -0.291 | Zinc Finger Protein 800                                    | DNA binding. A high expression is associated with lung cancer(3) and colorectal cancer (4).                                                                        |
| <b>NEURL1B</b>                              | 2.72E-06 | 0.009 | -0.545 | Neuralized E3 Ubiquitin Protein Ligase 1B                  | Protein degradation and endocytosis. Downregulated in colorectal cancer (5).                                                                                       |
| <b>RBPJ</b>                                 | 3.33E-06 | 0.009 | -0.191 | Recombination Signal Binding Protein For IG Kappa J Region | Transcriptional regulator in the Notch signaling pathway. Has tumor-promoting capacities (6).                                                                      |
| <b>FOXO1</b>                                | 4.72E-06 | 0.011 | -0.451 | Forkhead Box O1                                            | PI3K/AKT signaling. Described as a tumor suppressor in PC cancer (7, 8).                                                                                           |
| <b>TSC22D3</b>                              | 1.42E-05 | 0.023 | -0.493 | TSC22 Domain Family Member 3                               | Anti-inflammatory (9). Expression change with tumor grade/stage in PC (10).                                                                                        |
| <b>SNHG6</b>                                | 1.54E-05 | 0.023 | -0.336 | Small Nucleolar RNA Host Gene 6                            | Long non-coding RNA. Overexpressed in PC and associated with shorter disease-free survival.(11)                                                                    |
| <b>DOCK11</b>                               | 1.59E-05 | 0.023 | -0.740 | Dedicator Of Cytokinesis 11                                | B cell differentiation. Overexpression linked to testicular carcinoma. (12)                                                                                        |
| <b>PPP4R2</b>                               | 2.86E-05 | 0.027 | -0.223 | Protein Phosphatase 4 Regulatory Subunit 2                 | DNA double strand break repair. Low expression associated with leukemia. (13)                                                                                      |
| <b>CTDSPL</b>                               | 3.16E-05 | 0.027 | -0.251 | CTD Small Phosphatase Like                                 | Regulator of cell cycle. Described as tumor suppressor in lung cancer. (14)                                                                                        |
| <b>AL445426.1</b>                           | 4.18E-05 | 0.029 | -0.962 | -                                                          | -                                                                                                                                                                  |
| <b>DEK</b>                                  | 5.21E-05 | 0.030 | -0.199 | DEK Proto-Oncogene                                         | DNA modulation. Overexpression is associated with PC progression in neuroendocrine PC (15).                                                                        |
| <b>COL17A1</b>                              | 5.98E-05 | 0.030 | -1.282 | Collagen Type XVII Alpha 1 Chain                           | Transmembrane alpha chain collagen. Overexpression is seen in pancreas cancer(16), but in the contrary related to prolonged overall survival in breast cancer(17). |

| Upregulated in statin-users vs. non-users |          |       |       |                                                    |                                                                                                                                                             |
|-------------------------------------------|----------|-------|-------|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AC073225.1                                | 1.07E-06 | 0.006 | 0.787 | -                                                  | -                                                                                                                                                           |
| CCDC124                                   | 6.56E-06 | 0.013 | 0.401 | Coiled-Coil Domain Containing 124                  | RNA binding, is overexpressed in several cancers (18).                                                                                                      |
| PGBD4                                     | 1.9E-05  | 0.026 | 0.510 | PiggyBac Transposable Element Derived 4            | Transposase(1). Not previously associated with cancer                                                                                                       |
| GOLGA6L2                                  | 2.29E-05 | 0.027 | 1.343 | Golgin A6 Family Like 2                            | A part of the Protein receiving Cis-Golgi (1). Not previously associated with cancer.                                                                       |
| COA7                                      | 2.75E-05 | 0.027 | 0.467 | Cytochrome C Oxidase Assembly Factor 7             | Mitochondrial respiration (1). Not previously associated with cancer.                                                                                       |
| RNF223                                    | 2.85E-05 | 0.027 | 0.965 | Ring Finger Protein 223                            | Protein posttranslational modification. Downregulated is a unfavorable prognostic marker in Pancreas cancer(19)                                             |
| AL354919.1                                | 2.9E-05  | 0.027 | 0.590 | -                                                  | -                                                                                                                                                           |
| AP002748.6                                | 3.03E-05 | 0.027 | 0.973 | -                                                  | -                                                                                                                                                           |
| MIR3936HG                                 | 3.34E-05 | 0.027 | 0.594 | MIR3936 Host Gene                                  | lncRNA(1). Not previously associated with cancer.                                                                                                           |
| BCL2L14                                   | 3.69E-05 | 0.027 | 0.778 | BCL2 Like 14                                       | Apoptotic regulator. Overexpressed in breast cancer(20).                                                                                                    |
| MIEF2                                     | 3.7E-05  | 0.027 | 0.412 | Mitochondrial Elongation Factor 2                  | Regulates mitochondrial morphology. Overexpressed in ovarian cancer(21). Low expression observed in colon cancer and related to oxaliplatin resistance(22). |
| OR7E122P                                  | 4.47E-05 | 0.030 | 1.083 | Olfactory Receptor Family 7 Subfamily E Member 122 | G protein-mediated transduction (1). Not previously associated with cancer.                                                                                 |
| OTUB1                                     | 5.09E-05 | 0.030 | 0.242 | OTU Deubiquitinase, Ubiquitin Aldehyde Binding 1   | Protein turnover. Overexpressed in PC(23, 24).                                                                                                              |
| RN7SL440P                                 | 5.21E-05 | 0.030 | 0.886 | -                                                  | -                                                                                                                                                           |
| LDLR                                      | 5.37E-05 | 0.030 | 0.416 | Low Density Lipoprotein Receptor                   | LDL/cholesterol uptake. LDLR knock-down inhibits growth in PC cell lines (25). PC cells shown to lack normal feedback regulation of LDLR expression (26).   |
| GRHPR                                     | 6.02E-05 | 0.030 | 0.239 | Glyoxylate And Hydroxypyruvate Reductase           | Metabolism. High expression prolongs overall survival in breast cancer(27).                                                                                 |

**Table text:** P.val: p-value; P.adj: BH adjusted p-value; LogFC: log2 fold change  
Differential expression analysis with top DEGs between statin-users and non-users in PC samples based on P-value.

**Table S3: Androgen Receptor signaling and LDLR expression**

| Gene         | Median expression level (LogCPM)<br>All patients (n =180) |           |         | Correlation with LDLR expression<br>Non-users (n = 90) |         | Correlation with LDLR expression<br>Statin-users (n = 90) |         | Nomenclature                   |
|--------------|-----------------------------------------------------------|-----------|---------|--------------------------------------------------------|---------|-----------------------------------------------------------|---------|--------------------------------|
|              | Statin-users                                              | Non-users | P. val. | R                                                      | P. val. | R                                                         | P. val. |                                |
| <b>AR</b>    | 7.96                                                      | 8.11      | 0.1     | -0.2                                                   | 0.06    | -0.19                                                     | 0.07    | Androgen receptor              |
| <b>KLK3</b>  | 12.26                                                     | 12.16     | 1       | -0.19                                                  | 0.08    | -0.042                                                    | 0.69    | Prostate Specific Antigen      |
| <b>NCOA1</b> | 5.97                                                      | 5.96      | 1       | -0.074                                                 | 0.49    | -0.076                                                    | 0.47    | Nuclear receptor coactivator 1 |
| <b>NCOA2</b> | 4.86                                                      | 4.94      | 0.18    | -0.14                                                  | 0.2     | -0.062                                                    | 0.56    | Nuclear receptor coactivator 2 |
| <b>NCOA3</b> | 5.59                                                      | 5.6       | 0.88    | -0.21                                                  | 0.05    | -0.08                                                     | 0.46    | Nuclear receptor coactivator 3 |
| <b>NCOR1</b> | 8.1                                                       | 8.1       | 0.45    | -0.16                                                  | 0.13    | -0.3                                                      | 0.004   | Nuclear receptor corepressor 1 |
| <b>NCOR2</b> | 7.04                                                      | 7.13      | 0.026   | -0.3                                                   | 0.005   | -0.4                                                      | <0.0001 | Nuclear receptor corepressor 2 |

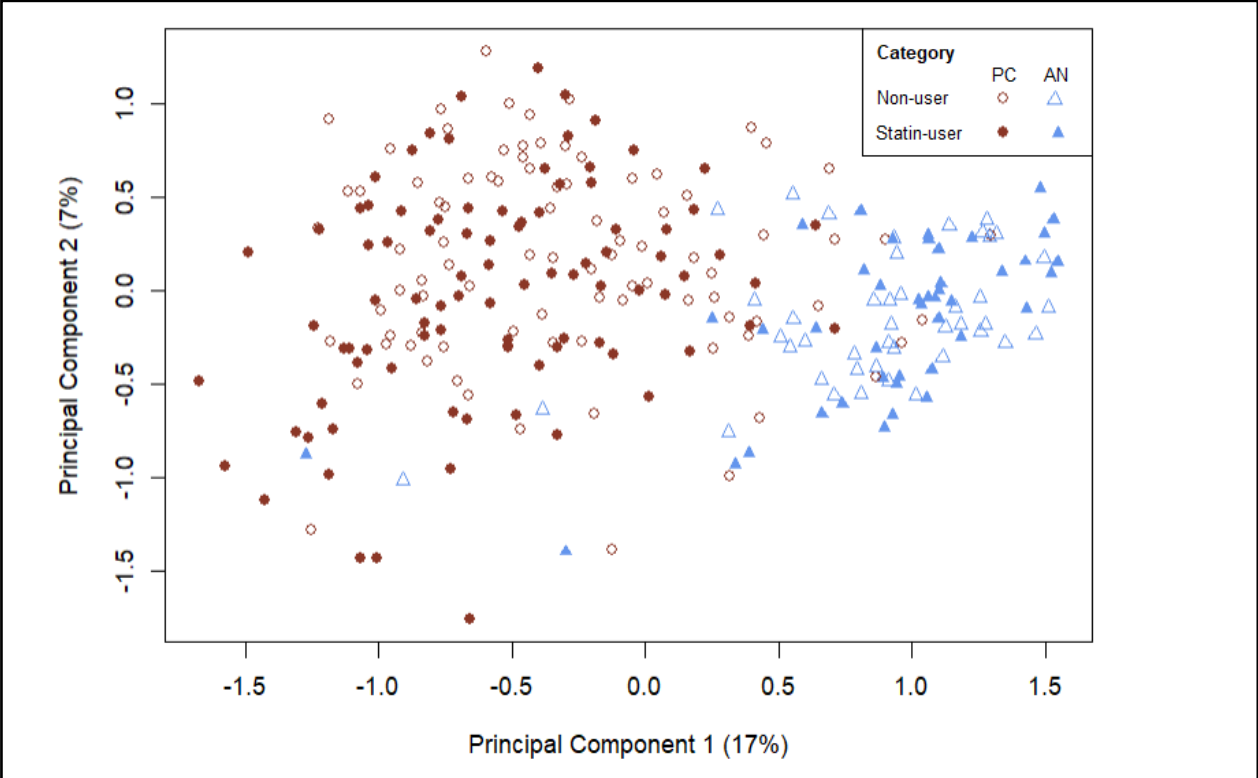
**Table text:** LogCPM: Log counts pr. Million; P.val: p value; R: Spearman correlation coefficient  
Expression level of genes described in androgen receptor signaling statin-users vs. non-users compared using Wilcoxon signed-rank. The correlation between gene expression and LDLR expression was assessed using Spearman correlation.

**Table S4: Genes contributing with the highest rank in EMT downregulation**

| Gene         | RankMetric | Median expression level (LogCPM) |           |         | Role                                                                                                                                                                |
|--------------|------------|----------------------------------|-----------|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|              |            | Statin-users                     | Non-users | P. val. |                                                                                                                                                                     |
| <b>GAS1</b>  | -0.66      | 2.4                              | 2.98      | 0.008   | Acts as a tumor suppressor in colorectal cancer. Is expression increases E-cadherin and decreases Snail and N-cadherin in cancer cells.                             |
| <b>ACTA2</b> | -0.63      | 9.17                             | 9.68      | 0.005   | Encodes alpha-smooth muscle actin, a hallmark of the mesenchymal/myofibroblast phenotype; upregulated during EMT and involved in prostate cancer stroma remodeling. |
| <b>FLNA</b>  | -0.52      | 9.58                             | 10.03     | 0.001   | Actin-binding cytoskeletal protein that supports cell motility and structural reorganization; plays a role in EMT and metastasis.                                   |
| <b>MYLK</b>  | -0.48      | 8.52                             | 8.9       | 0.004   | Regulates actomyosin contraction and cell migration; contributes to cytoskeletal changes required for EMT.                                                          |

Table text: LogCPM: Log counts pr. Million; P.val: p value  
Expression level of Leading-Edge genes (RankMetric) for the Hallmark EMT pathway analysis.  
Statin-users vs. non-users are compared using the Wilcoxon signed-rank.

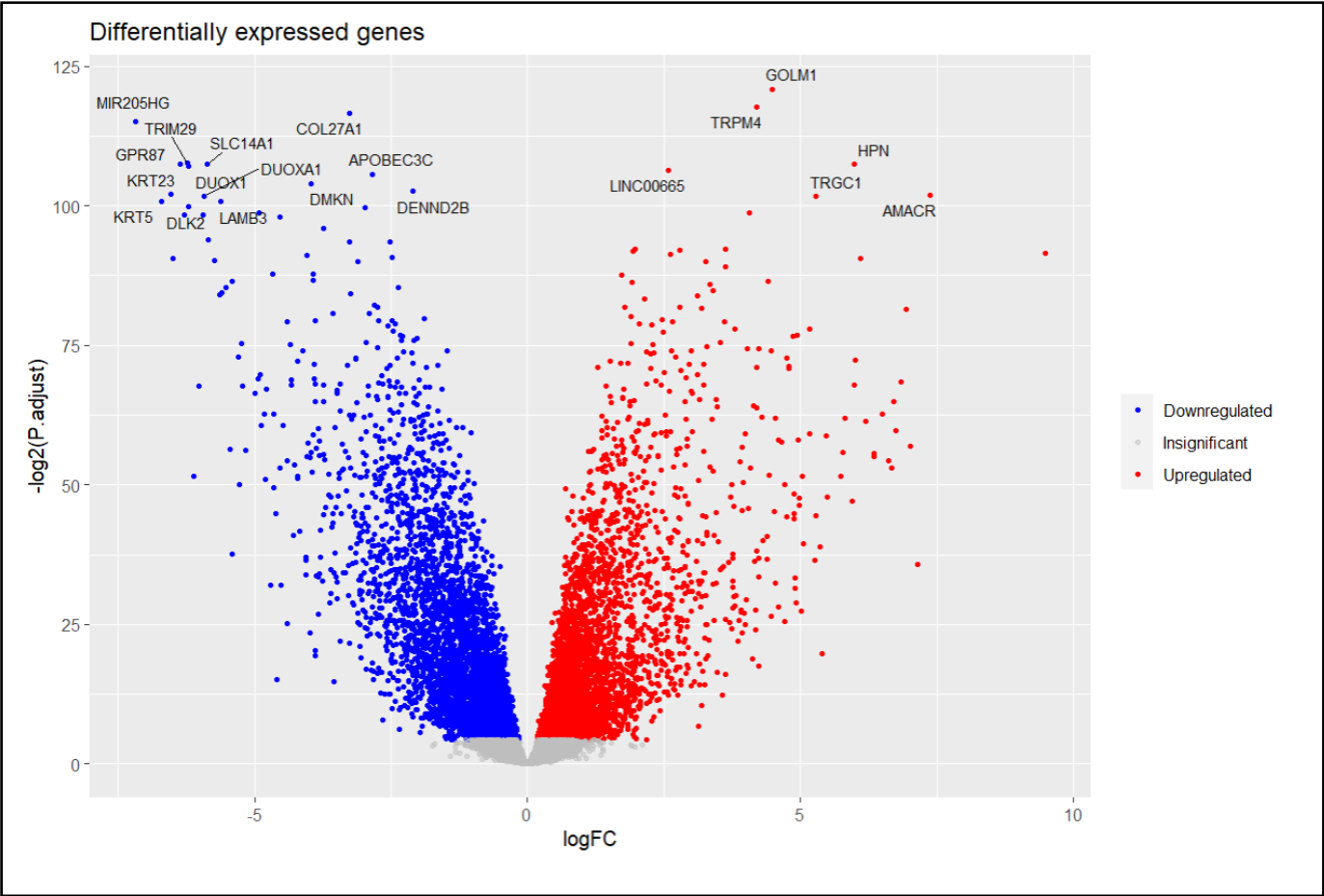
**Figure S2: Principal Component Analysis**



**Figure text:** PC: Prostate Cancer tissue; AN: Adjacent nonmalignant tissue; LogFC: log2 fold-change.

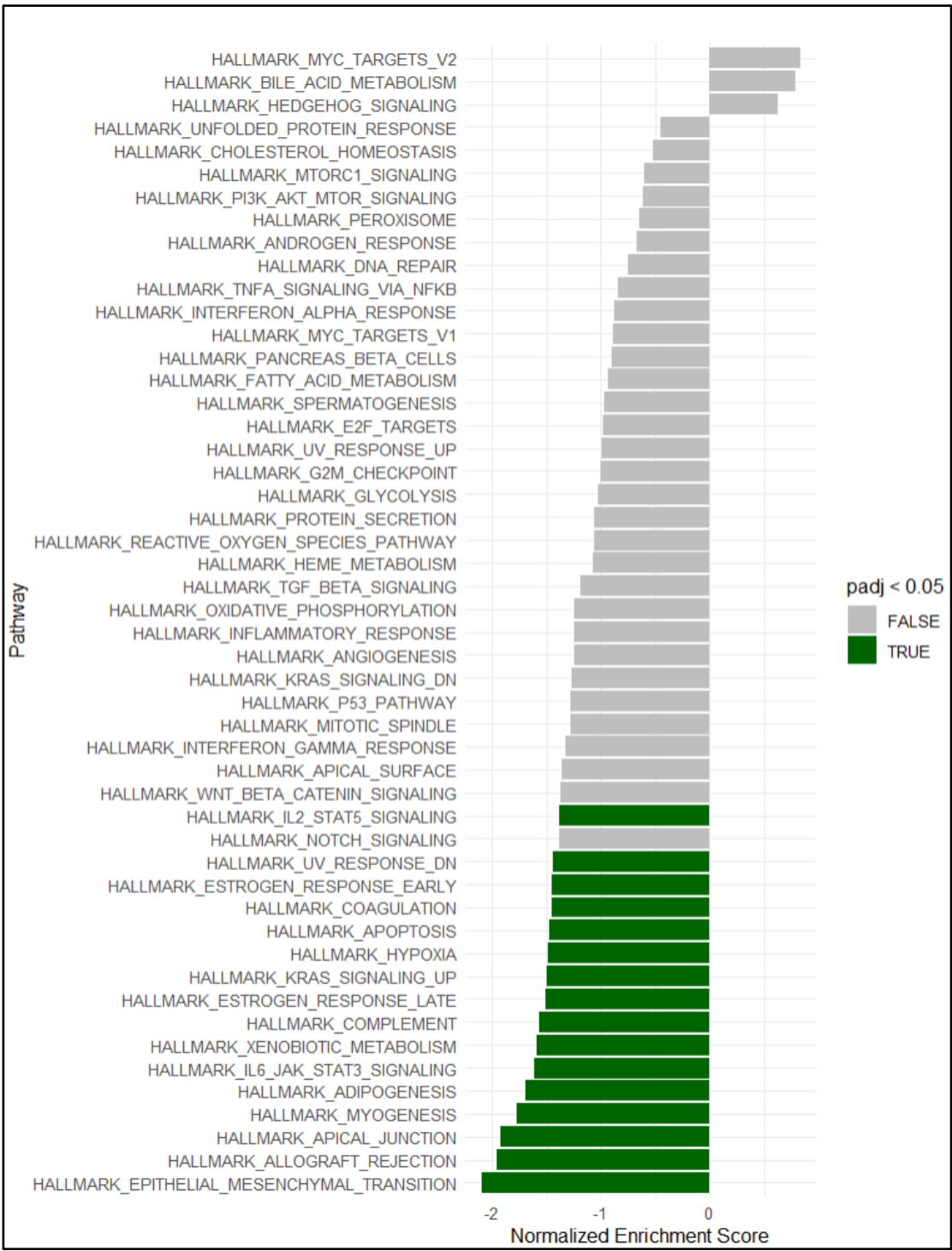
Unsupervised analysis illustrating the greatest variance among all 16,190 genes.

**Figure S3: Volcano plot illustrating all DEGs between PC and AN tissue**



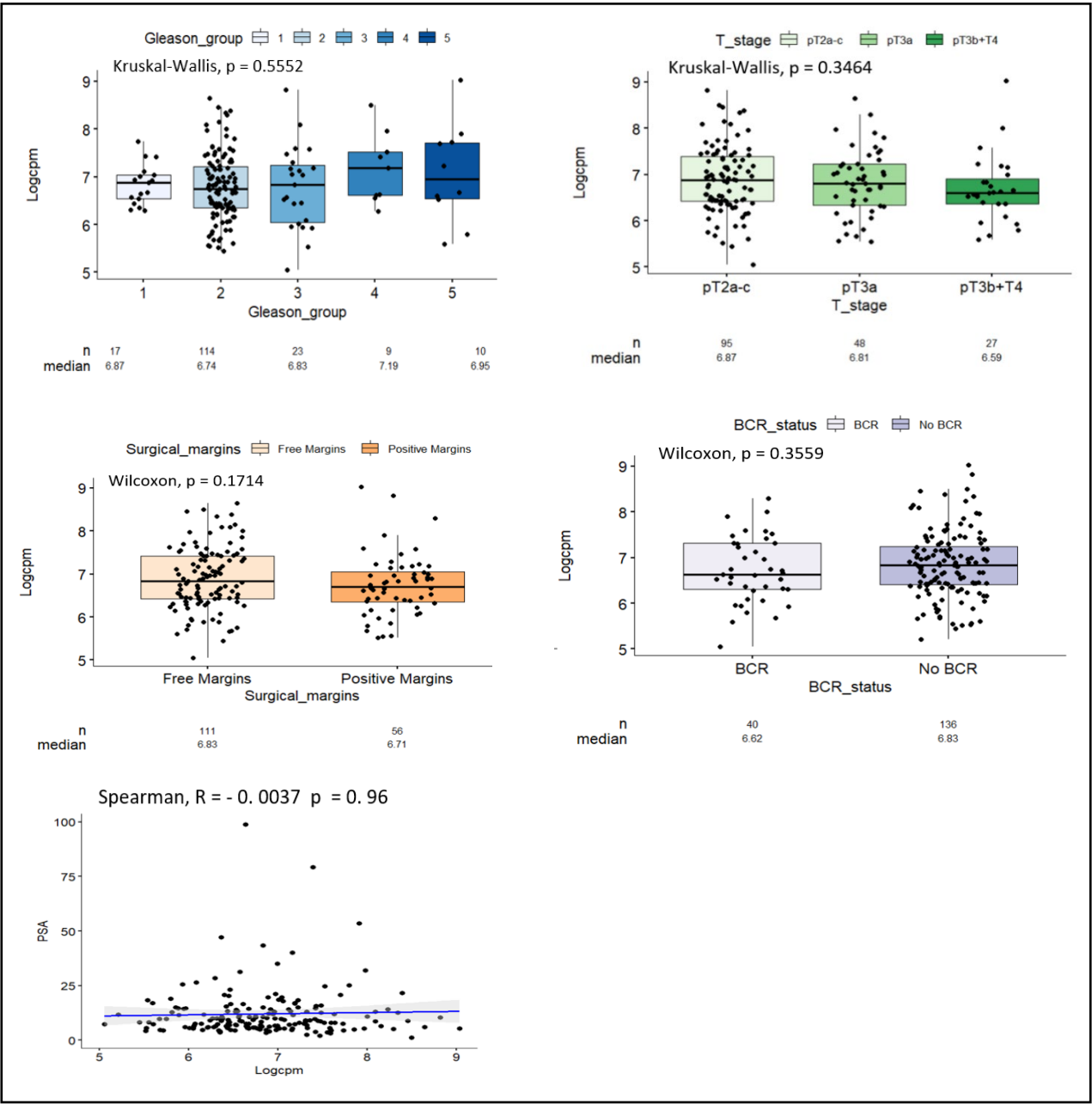
**Figure text:** DEGs: Differentially expressed genes; PC: Prostate Cancer tissue; AN: Adjacent nonmalignant tissue; LogFC: log<sub>2</sub> foldchange p.adjust: Adjusted p-values  
Label on top 20 DEGs based on p-value.

**Figure S4: Gene set enrichment analysis (GSEA) between statin-users and non-users**



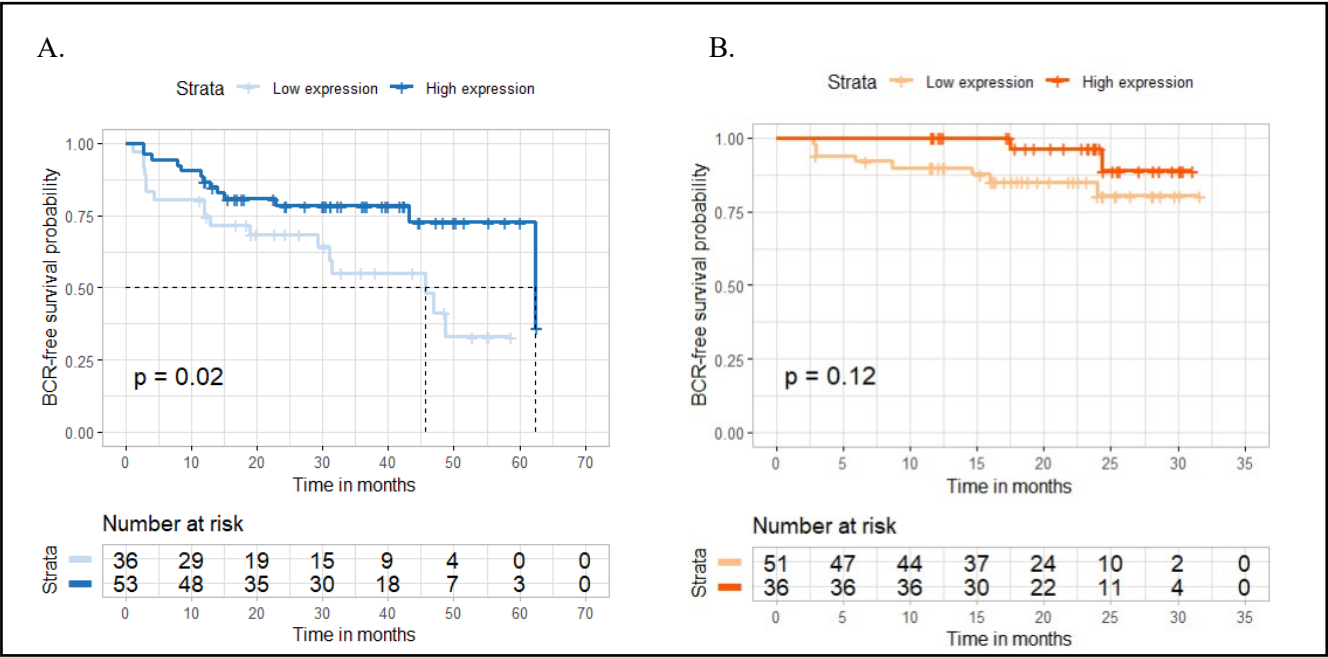
**Figure text:** P.adj: adjusted p-value  
Hallmark gene sets enrichment analysis based on all 16,190 genes in statin-users versus non-users in PC samples. Green bars are significantly downregulated pathways in statin-users versus non-users. No pathways were significantly upregulated. Significance threshold = p-value < 0.05, adjusted by the Benjamin-Hochberg Procedure.

**Figure S5: LDLR expression association with patient clinical characteristics**



**Figure text:** P: p-value; BCR: Biochemical recurrence; R: Correlation coefficient; IQR: Interquartile range.  
Association of LDLR expression to GG, pT-stage, surgical margin status, BCR status and PSA level before RP.

**Figure S6: Kaplan-Meier analysis of BCR time in statin-users and non-users**



**Figure text:** P: p-value; BCR: Biochemical recurrence.

Kaplan-Meier analysis of BCR-free survival with low and high LDLR expression in statin-users (A) and non-users (B). Patients with missing information regarding BCR, time to BCR, or total follow-up time were excluded from this analysis.

## Supplementary References

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