

# Journal Pre-proof

Validation of the Decipher Genomic Classifier in Patients receiving Salvage Radiotherapy without Hormone Therapy after Radical Prostatectomy – An Ancillary Study of the SAKK 09/10 Randomized Clinical Trial

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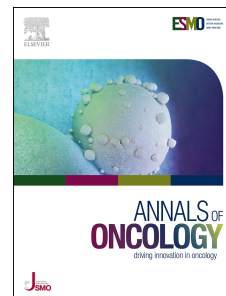
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4

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1 **Abstract**

2 **Background:** The Decipher genomic classifier (GC) has shown to independently prognosticate  
3 outcomes in prostate cancer. The objective of this study was to validate the GC in a randomized  
4 phase 3 trial of dose-escalated salvage radiotherapy (SRT) after radical prostatectomy.

5  
6 **Patients and Methods:** A clinical grade whole-transcriptome assay was performed on RP samples  
7 obtained from patients enrolled in SAKK 09/10, a phase 3 trial of 350 men with biochemical  
8 recurrence post-radical prostatectomy randomized to 64Gy vs. 70Gy without concurrent hormonal  
9 therapy or pelvic nodal radiotherapy (RT). A pre-specified statistical plan was developed to assess  
10 the impact of the GC on clinical outcomes. The primary endpoint was biochemical progression;  
11 secondary endpoints were clinical progression and time to hormone therapy. Multivariable  
12 analyses adjusted for age, T-category, Gleason score, post-radical prostatectomy persistent  
13 prostate-specific antigen (PSA), PSA at randomization, and randomization arm were conducted,  
14 accounting for competing risks.

15  
16 **Results:** The analytic cohort of 226 patients was representative of the overall trial, with median  
17 follow-up of 6.3 years (IQR 6.1-7.2). GC (high vs. low-intermediate) was independently  
18 associated with biochemical progression (subdistribution hazard ratio [sHR] 2.26 [95% CI 1.42-  
19 3.60],  $p < 0.001$ ), clinical progression (HR 2.29 [95% CI 1.32-3.98],  $p = 0.003$ ), and use of hormone  
20 therapy (sHR 2.99 [95% CI 1.55-5.76],  $p = 0.001$ ). GC high patients had 5-year freedom from  
21 biochemical progression of 45% vs. 71% for GC low-intermediate. Dose escalation did not benefit  
22 the overall cohort, nor patients with lower vs. higher GC scores.

23

1 **Conclusions:** This study represents the first contemporary randomized controlled trial in patients  
2 treated with early SRT without concurrent hormone therapy or pelvic nodal RT that has validated  
3 the prognostic utility of the GC. Independent of standard clinicopathologic variables and RT dose,  
4 high-GC patients were more than twice as likely than lower-GC patients to experience biochemical  
5 and clinical progression and receive of salvage hormone therapy. This data confirms the clinical  
6 value of Decipher GC to personalize the use of concurrent systemic therapy in the postoperative  
7 salvage setting.

8

### 9 **Keywords**

10 Biomarkers, Decipher, prognosis, prostate cancer, salvage radiotherapy, postoperative  
11 radiotherapy

12

### 13 **Highlights**

- 14 • Decipher identifies patients at highest risk of progression who may require treatment  
15 intensification
- 16 • Decipher defines subgroups associated with improved outcomes when treated with very  
17 early SRT compared to late SRT
- 18 • Transcriptomic profiling can guide personalized management of SRT timing and the  
19 addition of systemic therapy

## 1 **Introduction**

2 More than 40% of intermediate- or high-risk prostate cancers are estimated to recur after radical  
3 prostatectomy, which suggests more than 30,000 men every year in the USA are diagnosed with  
4 biochemically recurrent disease.<sup>1</sup> Salvage radiotherapy (SRT) is currently the only potentially  
5 curative treatment for this patient population. Outcomes after SRT are heterogenous. However,  
6 conventional clinicopathologic factors (i.e., Gleason score, T-category, and prostate-specific  
7 antigen [PSA]), and even multivariable models (e.g., Tendulkar nomogram) are >25% of the time  
8 inaccurate in estimation of patient prognosis.<sup>2</sup> Therefore, differences in clinical outcomes highlight  
9 an intrinsic biological heterogeneity that is commonly underappreciated in clinical decision-  
10 making.

11  
12 The Decipher genomic classifier (GC; Veracyte, Inc) is a commercial, tissue-based transcriptomic  
13 assay that was developed to aid in prostate cancer prognostication. It uses a machine-learning  
14 algorithm to summarize the expression of 22 genes into a risk score. A recent systematic review  
15 across 42 studies of the GC demonstrated that the GC improves prognostication and discrimination  
16 above and beyond clinicopathologic variables.<sup>3</sup> This includes the post-hoc analysis of the  
17 NRG/RTOG 9601 phase 3 clinical trial of SRT +/- hormonal therapy.<sup>4</sup>

18  
19 The analysis plan and GC score generation for this current translational study of the Swiss Group  
20 for Clinical Cancer Research (SAKK) phase 3 randomized trial, SAKK 09/10, were completed  
21 prior to data-lock for the trial's primary endpoint analysis, making this the first study to pre-specify  
22 validation of the GC in advance of the trial's primary analysis. SAKK 09/10 is a unique trial, as it  
23 represents one of the only contemporary trials worldwide that used SRT alone without hormone

1 therapy or pelvic nodal radiotherapy. It compared the use of standard vs. dose-escalated SRT to  
2 the prostate bed and found no difference in any oncologic endpoint to date.<sup>5</sup> Thus, it was primarily  
3 hypothesized that the GC would predict biochemical progression after SRT, independent of  
4 conventional clinicopathological factors. Furthermore, it was hypothesized that the GC would  
5 independently stratify the risk of clinical progression and the initiation of salvage hormone therapy  
6 after SRT.

## 7 **Methods**

### 8 ***SAKK 09/10 trial and Translational Research***

9 SAKK 09/10 (NCT01272050) is a prospective open-label, multicenter, randomized phase 3 trial  
10 testing whether dose-escalated SRT is superior to conventional dose SRT with respect to freedom  
11 from biochemical progression (FFBP). Three hundred and fifty patients with biochemical  
12 recurrence after radical prostatectomy were randomized to 64Gy (32 fractions, 2Gy/fraction) vs.  
13 70Gy (35 fractions, 2Gy/fraction) to the prostate bed. Patients did not receive concomitant  
14 hormone therapy or pelvic nodal radiotherapy. Patients with evidence of biochemical recurrence  
15 after radical prostatectomy (two consecutive rises in PSA with final PSA >0.1 ng/mL, or 3  
16 consecutive rises) and PSA at randomization  $\leq 2$  ng/mL were eligible. Further details on the  
17 inclusion and exclusion criteria can be found in **Supplementary Materials** or at ClinicalTrials.gov  
18 (NCT01272050).<sup>5</sup> The trial was sponsored by the SAKK with ethics committee approval at each  
19 of the 28 participating centers in Switzerland, Germany, and Belgium.

20  
21  
22 A translational research project was proposed primarily to study the prognostic performance of a  
23 biomarker on the patient samples in the SAKK 09/10 trial. Samples used for the GC analysis were

1 retrieved from the SAKK biobank and analyzed prior to the completion of the trial. A separate  
2 informed consent was signed by all patients who agreed on biobanking their tissue samples.  
3 Approval for this ancillary study was granted by the SAKK Board and Ethics Committee  
4 (Kantonale Ethikkommission Bern, KEK). Funding to support the costs of pathology review and  
5 for the genomic classifier testing was provided by Decipher Biosciences. The study followed  
6 PRoBE and REMARK criteria for prospective-blinded evaluation and analysis of a prognostic  
7 biomarker.<sup>6,7</sup>

8

### 9 *Gene Expression Profiling and Decipher Genomic Classifier Scores*

10 Tumor specimens were centrally reviewed and selected from the radical prostatectomy block with  
11 the index lesion (defined as the lesion with the highest-grade group and tumor volume) and were  
12 sampled using a 1.0 mm diameter punch tool. GC scores were generated using the clinical-grade,  
13 whole-transcriptome Decipher assay (San Diego, CA) as previously described on the punch  
14 sample.<sup>4</sup> GC scores were calculated based on the locked GC model and scores were generated on  
15 a scale of 0 to 1 (**Appendix**). The continuous GC scores were generated and then linked to the  
16 clinical trial database at the SAKK Statistics and Data Management Center. Locked categorical  
17 analyses used the validated low- (<0.45), intermediate- (0.45-0.60), and high- (>0.60) risk groups.<sup>8</sup>  
18 Due to the low number of samples in the study when analyzed by two arms and three GC risk  
19 groups, low- and intermediate-risk GC scores ( $\leq 0.60$ ), which reported similar risks, were  
20 combined (as previously described).<sup>9</sup>

21

### 22 *Study Objectives and Endpoints*



1 The primary objective of this ancillary project was to study the independent association of the  
2 GC with the trial's original primary endpoint: time to FFBP. Similarly, the secondary objectives  
3 were to analyze the association of GC with secondary endpoints including time to clinical  
4 progression-free survival (PFS) and time to hormone therapy. All primary and secondary  
5 endpoints were defined per the trial protocol.

6  
7 Events for FFBP were characterized by biochemical progression, defined as time from  
8 randomization to first occurrence of PSA rise ( $\geq 0.4\text{ng/mL}$  and greater than the previous PSA  
9 value), clinical recurrence (local, regional, and/or distant recurrence detected by imaging), or death  
10 due to clinical recurrence. Secondary endpoints included time to hormone therapy (from  
11 randomization) and clinical progression-free survival (events were characterized by clinical  
12 progression, defined as time from randomization to first record of clinical recurrence, start of  
13 hormone therapy, or death due to any cause).

14  
15 Exploratory endpoints included rapid biochemical failure (rapid-BF; a binary event defined by  
16 PSA progression [ $\geq 0.4\text{ng/mL}$ ] within 18 months), time to metastasis (defined as time from  
17 randomization to the first record of regional and/or distant recurrence), and metastasis-free survival  
18 (MFS; defined as time from randomization to the first record of regional and/or distant recurrence,  
19 or death of any cause). All analyses on exploratory endpoints were deemed to be exploratory and  
20 hypothesis-generating.

21

22 **Statistical Analysis**

1 A statistical analysis plan was pre-specified and approved by the SAKK Coordinating Center  
2 prior to data-lock for the SAKK 09/10 trial primary endpoint analysis; specifically, before  
3 clinical outcome data and trial results were available for analyses in this translational study. All  
4 patients with available samples were analyzed as randomized. A sample size justification was  
5 performed for the prognostic evaluation of GC for the primary endpoint, FFBP. Out of 350  
6 patients enrolled in the trial, 272 patients had radical prostatectomy tissues available for  
7 transcriptomic profiling. A conservative failure rate of 20% sample-loss and a 40% estimated  
8 event rate, as per the original trial's assumptions, were assumed, resulting in an expected 217  
9 samples yielding Decipher scores and 87 events. These assumptions provided 90% power to  
10 detect a hazard ratio of 1.2 per 0.1-unit increase in a univariable Cox regression model, using a  
11 two-sided alpha of 0.05. Therefore, the study was powered to validate GC as a prognostic  
12 classifier for FFBP. The power calculation was performed with an assumed Decipher standard  
13 deviation of 0.2.

14  
15 All endpoints, except rapid-BF, were analyzed as time-to-event endpoints. FFBP was analyzed  
16 with death due to any cause without events or receipt of hormonal therapy as competing risks.  
17 Both time to metastasis and MFS were analyzed with local recurrence, receipt of hormone therapy,  
18 or death due to any cause without events (time to metastasis only) as competing risks, limited by  
19 how the data were collected in the trial. Details can be found in **Supplementary Table 1**. The  
20 event-free rates at given times within arms or GC risk groups were estimated by the cumulative  
21 incidence method and compared using Gray's test, when accounting for competing risks, or the  
22 log-rank test, otherwise.<sup>10,11</sup> To properly assess the association of GC with the time-to-event  
23 endpoints, univariable (UVA) and multivariable (MVA) survival analysis models were

1 constructed: Fine and Gray for FFBP, time to hormone therapy, time to metastasis, and MFS and  
2 Cox proportional hazards for clinical PFS.<sup>12</sup> Logistic regression models were constructed for rapid-  
3 BF. MVAs were adjusted for randomization arm, age, and most of the trial's stratification  
4 variables: Gleason score, pathological stage, post-radical prostatectomy PSA persistent status  
5 (defined as PSA between [0.1-0.4 ng/mL]), and PSA at randomization.

6  
7 Subgroup analyses were performed with GC in addition to standard pre-SRT PSA cut points (0.2  
8 ng/mL and 0.5 ng/mL) for all endpoints. Due to the low number of samples and events in the study  
9 when analyzed by two GC risk groups and three pre-SRT PSA groups, model-based estimates  
10 adjusting for GC risk group and pre-SRT PSA group were predicted from the appropriate models  
11 and 95% confidence intervals were constructed via bootstrapping.

12  
13 Statistical analyses were performed using R (version 3.6.1) and SAS 9.4. All statistical tests were  
14 2-sided and considered statistically significant at the 0.05 level. No adjustment for multiple testing  
15 was applied.

## 17 **Results**

18 Out of 350 patients enrolled in the trial, 233 patients had tissue available for genomic analysis  
19 (**Figure 1**). Samples from 226 patients (97%) passed quality control and were included for final  
20 analysis (median age, 66 years [interquartile range (IQR) 62-70]). Median time from radical  
21 prostatectomy to randomization was 2.1 years (IQR 1.1-3.6) and median follow-up time for  
22 censored patients was 6.3 years (IQR 6.08-7.23). Median PSA at randomization was 0.3 ng/mL  
23 (IQR 0.2-0.53). The 64Gy ( $n=111$ ) and 70Gy ( $n=115$ ) arms were well balanced (**Table 1**) and

1 representative of the overall cohort (**Supplementary Table 2**). Similar treatment effects were  
2 observed for the full SAKK 09/10 cohort ( $n=344$ ) and the GC analytic cohort ( $n=226$ )  
3 (**Supplementary Figure 1**). The distribution of GC scores between arms is shown in **Figure 2A**,  
4 with no significant differences in GC distribution between the 2 study arms. The median GC scores  
5 of each arm in the final cohort were similar: 0.36 (IQR 0.23-0.63) vs. 0.36 (IQR 0.2-0.59) for the  
6 64Gy and 70Gy arms, respectively (Wilcoxon  $p=0.56$ ). However, there were significant  
7 relationships between GC and other clinicopathologic variables, as expected. The GC score  
8 distribution by pathological T-stage, Gleason score, PSA persistence after radical prostatectomy,  
9 PSA at randomization, and EAU risk are shown in **Figures 2B-F**, respectively.

10

### 11 *Decipher is Associated with Biochemical Progression*

12 Higher GC was associated with a higher risk of biochemical progression. The GC was analyzed  
13 as both a continuous (scale, 0-1) and a categorical (binary) variable. As a continuous variable, the  
14 GC was significantly associated with biochemical progression, in both univariable (sHR 1.13 [95%  
15 CI 1.03-1.23],  $p=0.009$ ) and multivariable analyses (sHR 1.14 [95% CI 1.04-1.25],  $p=0.006$ )  
16 (**Table 2**). Similar results were seen for categorical GC (high- vs. low-intermediate) in both  
17 univariable (sHR 2.21 [95% CI 1.41-3.47],  $p<0.001$ ) and multivariable analyses (sHR 2.26 [95%  
18 CI 1.42-3.60],  $p<0.001$ ) (**Table 2**). Patients with GC high had 5-year FFBP of 45% [95% CI 32-  
19 59] vs. 71% [95% CI 64-78] in GC low-intermediate (**Figure 3a**). Similar estimates were observed  
20 in the 64Gy vs. 70Gy arms within GC high (5-year FFBP of 51% [95% CI 32-70] vs. 39% [95%  
21 CI 20-59]) and within GC low-intermediate (75% [95% CI 65-84] vs. 69% [95% CI 59-78])  
22 (**Supplementary Figure 2b-c; Supplementary Figure 5**).

23

1 ***Decipher is Associated with Clinical Progression, Use of Hormonal Treatment, and Other***  
2 ***Relevant Oncological Endpoints***

3 Higher GC scores were independently associated with time to clinical progression-free survival  
4 (CPFS) and time to hormone therapy. In multivariable analyses, GC high vs. low-intermediate had  
5 an HR of 2.29 ([95% CI 1.32-3.98],  $p=0.003$ ) for clinical progression and an sHR of 2.99 ([95%  
6 CI 1.55-5.76],  $p=0.001$ ) for time to hormone therapy (**Supplementary Table 3**). Specifically, GC  
7 high had a 5-year freedom from hormonal treatment of 74% ([95% CI 61-86]) compared to 89%  
8 ([95% CI 84-94]) for GC low-intermediate (**Figure 3c**). The estimated probabilities of FFBP,  
9 CPFS, and freedom from hormone therapy according to low, intermediate, and high GC are shown  
10 in **Supplementary Figure 3**.

11  
12 GC was prognostic for all endpoints, including exploratory endpoints, when evaluated both  
13 categorically and continuously (**Figure 4 and Supplementary Figure 4**). GC remained prognostic  
14 for biochemical progression in established clinical subgroups (**Supplementary Figure 5**). For  
15 example, GC (high vs. low-intermediate) was prognostic within Gleason score  $\leq 7$  tumors (sHR  
16 2.16 [95% CI 1.30-3.58],  $p=0.003$ ), pathological stage pT2-3a (sHR 1.97 [95% CI 1.18-3.29],  
17  $p=0.009$ ), undetectable and persistently elevated PSA post- radical prostatectomy (sHR 1.95 [95%  
18 CI 1.15-3.31],  $p=0.01$  and sHR 5.31 [95% CI 1.76-16.01],  $p=0.003$ , respectively), and PSA at  
19 randomization  $>0.5$  ng/mL (sHR 3.75 [95% CI 1.84-7.64],  $p<0.001$ ). There were no significant  
20 interactions between GC score, clinical subgroup, and clinical endpoints.

21  
22 ***Pre-SRT Subgroups***

1 Pre-salvage RT PSA and the GC have been shown in NRG/RTOG 9601 to be valuable tools to  
2 personalize the use of hormone therapy with SRT, with those having higher pre-SRT PSAs and  
3 higher GCs deriving the most benefit from hormone therapy.<sup>4</sup> Given in SAKK 09/10 patients  
4 received SRT alone, outcomes by GC score in patients receiving late SRT (pre-SRT PSA >0.5  
5 ng/mL, a stratification variable at randomization) were assessed. Late SRT was administered in  
6 27% of patients (61/226), and the 5-year FFBP was 64% [95% CI 49-79] for GC low-intermediate  
7 compared to only 13% [95% CI 0-32] for GC high.

8  
9 Similarly, for the time to hormone therapy endpoint, among the patients who received very early  
10 SRT with PSA <0.2 ng/mL, the 5-year hormonal treatment-free survival was 98% [95% CI 93-  
11 100] for GC low-intermediate and 88% [95% CI 63-100] for GC high. In contrast, for patients who  
12 received SRT with PSA >0.5 ng/mL, the 5-year hormonal treatment-free survival was 83% [95%  
13 CI 72-95] for GC low-intermediate compared to only 54% [95% CI 27-80] for GC high. In  
14 sensitivity analysis, categorical model-based estimates showed similar results to the empirical  
15 estimates for all endpoints (**Supplementary Table 4**).

16

## 17 **Discussion**

18 Herein, we confirm in a phase 3 randomized trial that there are heterogenous outcomes post-SRT,  
19 and that the GC adds independent prognostic performance to better identify men who are more or  
20 less likely to recur after SRT alone. Our results add to data from multiple other clinical trials of  
21 the Decipher GC demonstrating this tool can change clinical decision making (e.g., PRO-IMACT  
22 and G-MINOR) and identify those who will derive greater or lesser benefit from treatment  
23 intensification with hormone therapy.<sup>13-16</sup> In addition, there are ongoing phase 3 studies that

1 incorporate GC in different clinical scenarios and will shed further light on GC's role for better  
2 patient selection (E.g. NCT04513717, NCT05050084, NCT04484818). Our study represents level  
3 1 data by the Simon et al. criteria for prognostic biomarkers, and to our knowledge, the Decipher  
4 GC is the only post-radical prostatectomy test to have this level of evidence.<sup>17</sup>

5  
6 Through a pre-specified analysis of the SAKK 09/10 trial, it was hypothesized that the Decipher  
7 GC would be able to stratify patients with a significantly higher likelihood of PSA progression,  
8 clinical progression, and use of hormone therapy. Indeed, patients with high GC score tumors were  
9 more than twice as likely than patients with lower GC scores to experience PSA and clinical  
10 progression and receive salvage hormone therapy. In this contemporary trial, we observed a sample  
11 pass rate of 97% (similar to commercial testing pass rates), which reflects the overall better quality  
12 in the biological material obtained from SAKK 09/10 patients with an increased reliability in the  
13 genomic assessment.

14  
15 Currently, clinicopathologic multivariable models (e.g., Tendulkar nomogram) have only modest  
16 performance to discriminate outcomes for men that receive SRT.<sup>2</sup> This makes it difficult to  
17 clinically decide which patients should or should not receive treatment intensification with  
18 hormone therapy or pelvic nodal radiotherapy. For this reason, in part, current AUA/ASTRO  
19 guidelines recommend all patients be offered treatment intensification with hormone therapy to  
20 SRT based on the overall survival benefit identified in NRG/RTOG 9601.<sup>4,18</sup> However, in this  
21 current study, only 65 patients experienced a clinical progression event during the study follow-  
22 up. Thus, the SOC recommendations to treat everyone with concurrent hormone therapy would,  
23 in theory, overtreat 71% of patients. In contrast, if treatment recommendations were guided solely

1 by Decipher (and not a more complex clinic-genomic model), only 33% of patients would  
2 potentially be over- or under-treated. Taking results from this study as an example, application of  
3 GC testing could decrease the absolute reduction in concurrent use of hormone therapy by 38%.  
4 In other words, 2.6 patients would need to be tested with GC (and provided care with GC-based  
5 treatment) to prevent 1 incorrect treatment decision: either withholding beneficial treatment or  
6 administering unnecessary hormonal treatment with SRT.

7  
8 Routine treatment decisions made for men post-radical prostatectomy include the use of very early  
9 SRT (<0.2 ng/mL), early SRT (0.2-0.5 ng/mL), or late SRT (>0.5 ng/mL). This was confirmed in  
10 the current study as well; the 5-year FFBP was 80% [95% CI 69-91] for patients with pre-SRT  
11 PSA <0.2 ng/mL, compared to 65% [95% CI 57-74] for patients with pre-SRT PSA 0.2-0.5 ng/mL  
12 and 50% [95% CI 37-63] for patients with pre-SRT PSA >0.5 ng/mL. The use of GC can  
13 complement pre-SRT PSA and provide further risk stratification, allowing patients to make better  
14 informed treatment decisions around the timing of salvage treatment and/or adding hormone  
15 therapy. More specifically, for patients with lower GC scores, waiting to administer SRT until  
16 PSA rose to 0.2-0.5 ng/mL resulted in a decrease in 5-year FFBP rates of 11% (from 81% for very  
17 early to 70%), which for some patients, may not be considered a sufficient risk reduction to initiate  
18 salvage RT. Conversely, for patients with high GC, waiting too long to administer SRT resulted  
19 in a decrease in 5-year FFBP rates of 62% (from 75% for very early to 13% for late SRT). These  
20 results suggest that for GC high patients, intervening when the PSA burden is lowest results in  
21 improved outcomes. Furthermore, results from this study showed that patients with GC high and  
22 pre-salvage RT PSA >0.5 ng/mL have a nearly 90% risk of progression by 5 years, suggesting that  
23 knowledge of GC risk at radical prostatectomy and early referral for radiation oncology upon



1 initial PSA rise (especially for GC high) is critically important to delivering optimal care in this  
2 setting.

3  
4 This study was based on a pre-specified analysis plan prior to data-lock of the parent randomized  
5 trial, but limitations are present. The sample size of the parent trial, and patients with available  
6 tissue, precluded additional subgroup analyses. Use of salvage hormone therapy was at the  
7 discretion of the treating physician, as in most trials, and was not based on strict pre-defined  
8 criteria. All interaction tests were non-significant, indicating that the GC had similar prognostic  
9 performance across all tested subgroups. However, the sample size and event rates preclude  
10 sufficient power to robustly rule out potential treatment effect differences.

11

## 12 ***Conclusion***

13 This study represents the first contemporary randomized controlled trial in patients with recurrent  
14 prostate cancer treated with early SRT without concurrent hormone therapy or pelvic nodal  
15 radiotherapy that has validated the prognostic utility of the GC. Independent of standard  
16 clinicopathologic variables, patients with a high-GC were more than twice as likely than patients  
17 with a lower-GC to experience biochemical and clinical progression and receive salvage hormone  
18 therapy. Patients with high-GC have markedly improved outcomes when treated with very early  
19 SRT as compared to late SRT, and this data can help personalize the timing of SRT and use of  
20 concurrent hormone therapy in this patient population.

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5  
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10

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20 V. Y. T. L., E.D, H-C.H, Y.L., and X.Z. are employees of Decipher Biosciences (Veracyte Inc.).

21 D. J. S. T. is a contractor to Decipher Biosciences. All remaining authors have declared no conflicts  
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1 **Main Table Titles and Legends**

2 **Table 1** Demographic and clinical characteristics among the GC analytic cohort, Arm A patients,  
3 and Arm B patients.

4 *Abbreviations: GC = genomic classifier; Gy = Gray; Q1, Q3 = the first and third quartile;*  
5 *WHO = World Health Organization; Op = operative; PSA = prostate-specific antigen; GG =*  
6 *grade group; RP = radical prostatectomy; EAU = European Association of Urology; GETUG =*  
7 *Genitourinary Group; RT = radiation therapy; 3D-CRT = 3-dimensional conformal radiation*  
8 *therapy; IMRT = intensity-modulated radiation therapy.*

9  
10 *P-values were calculated using Wilcoxon rank sum test for continuous variables and Fisher's*  
11 *exact test or chi-squared test for categorical variables, as appropriate.*  
12

13 **Table 2** GC performance for the prediction of biochemical progression in Fine and Gray models.

14 *Abbreviations: Subdist. = Subdistribution; CI = confidence interval; GC = genomic classifier;*  
15 *Gy = Gray; PSA = prostate-specific antigen; Path. = Pathological.*

16  
17 *Subdistribution Hazard Ratios of GC score were per 0.1-unit increase. Randomization arm was*  
18 *treated as a main effect in the models labelled univariable analyses, where applicable (arm*  
19 *effect not reported). Two patients with missing clinical data were dropped from the relevant*  
20 *models: one patient was missing pathological stage and one patient was missing pathological*  
21 *stage and Gleason score. Two patients with follow-up time = 0 were still included in analysis as*  
22 *per the trial's intent-to-treat principle.*

23  
24 *\* indicates p-values < 0.05*  
25

26 **Main Figure Titles and Legends**

27 **Figure 1** CONSORT diagram of the patient sample availability and sample quality from the  
28 SAKK 09/10–Decipher ancillary project

29 *Abbreviations: Gy = Gray; QC = quality control; GC = genomic classifier.*

30

31 **Figure 2** GC distributions within clinical subgroups (A) for the GC analytic cohort and by  
32 treatment arm, (B) by pathological stage, (C) by Gleason score, (D) by persistent PSA after RP,  
33 (E) by PSA at randomization, and (F) by EAU risk.

1 *Abbreviations: GC = genomic classifier; Gy = Gray; PSA = prostate-specific antigen; RP =*  
 2 *radical prostatectomy; EAU = European Association of Urology.*

3

4 **Figure 3** Cumulative incidence estimates (1 – cumulative incidence) of GC Low-Intermediate-  
 5 ( $\leq 0.60$ ) and High- ( $> 0.60$ ) risk for (A) biochemical progression, (B) clinical progression, and (C)  
 6 hormonal treatment.

7 *Abbreviations: GC = Genomic Classifier; yrs = years; CI = confidence interval.*

8

9 *Cumulative incidence estimates (1 – cumulative incidence) were compared using Gray's test for*  
 10 *biochemical progression and hormonal treatment and the log-rank test for clinical progression;*  
 11 *estimates with 95% confidence intervals at 1, 3, and 5 years explicitly reported.*

12

13 *\* indicates p-values < 0.05.*

14

15 **Figure 4** Prognostic performance of GC risk group for all endpoints.

16 *Abbreviations: Est. = estimate; GC = genomic classifier; Low-Int = Low-Intermediate; CI =*  
 17 *confidence interval; mo = months; MFS = metastasis-free survival.*

18

19 *Number of patients, number of events, and 5-year event-free estimates are reported by GC risk*  
 20 *group. Randomization arm was treated as a main effect in the Fine and Gray and Logistic*  
 21 *models and as strata in the Cox proportional hazards model. Five-year event-free estimates and*  
 22 *95% confidence intervals were estimated by the cumulative incidence method, with the exception*  
 23 *of rapid biochemical failure, which reports the event-free proportion. Effect sizes of GC are*  
 24 *reported for each endpoint from the appropriate model (Fine and Gray for biochemical*  
 25 *progression, hormonal treatment, metastasis, and metastasis or death (i.e., metastasis-free*  
 26 *survival); Cox proportional hazards for clinical progression; and logistic for rapid biochemical*  
 27 *failure). Two patients with follow-up time = 0 were still included in analysis as per the trial's*  
 28 *intent-to-treat principle: one patient had follow-up time = 0 for all time-to-event endpoints and*  
 29 *one patient had follow-up time = 0 for FFBP only.*

30

31 *\* indicates p-values < 0.05; † indicates event-free proportion.*

32

### 33 **Supplementary Table Titles and Legends**

34 **Supplementary Table 1** Definitions of events and competing risks for all study endpoints.

35 *Abbreviations: w/in = within; mo = months; PSA = prostate-specific antigen; HT = hormonal*  
 36 *therapy.*

37

1 *Events are marked as “x” and competing risks are marked as “o”. Metastasis and metastasis-*  
 2 *free survival are defined by regional and/or distant recurrence via imaging, as defined by the*  
 3 *trial variable “clinical progression type”. Thus, local recurrence (denoted by +) and receipt of*  
 4 *HT prior to the presence of recurrence (denoted by \*) are treated as competing risks for the*  
 5 *metastasis-related variables.*  
 6

7 **Supplementary Table 2** Demographic and clinical characteristics in the full SAKK 09/10 trial  
 8 cohort, the non-analytic cohort, and the GC cohort.

9 *Abbreviations: GC = genomic classifier; Q1, Q3 = the first and third quartile; WHO = World*  
 10 *Health Organization; Op = operative; PSA = prostate-specific antigen; GG = grade group; RP*  
 11 *= radical prostatectomy; EAU = European Association of Urology; GETUG = Genitourinary*  
 12 *Group; RT = radiation therapy; 3D-CRT = 3-dimensional conformal radiation therapy; IMRT =*  
 13 *intensity-modulated radiation therapy.*  
 14

15 *P-values were calculated using Wilcoxon rank sum test for continuous variables and Fisher’s*  
 16 *exact test for categorical variables.*  
 17

18 **Supplementary Table 3** GC performance for the prediction of (A) Clinical Progression in Cox  
 19 Proportional Hazards models and (B) receipt of Hormonal Treatment in Fine and Gray models.

20 *Abbreviations: Subdist. = Subdistribution; CI = confidence interval; GC = genomic classifier;*  
 21 *PSA = prostate-specific antigen; Path. = pathological.*  
 22

23 *(Subdistribution) Hazard Ratios of GC score were per 0.1-unit increase. Randomization arm was*  
 24 *treated as a main effect in the Fine and Gray models (including the models labelled univariable*  
 25 *analyses; arm effect not reported) and as strata in the Cox proportional hazards models. Two*  
 26 *patients with missing clinical data were dropped from relevant models: one patient was missing*  
 27 *pathological stage and one patient was missing pathological stage and Gleason score. One*  
 28 *patient with follow-up time = 0 for clinical progression was still included in analysis as per the*  
 29 *trial’s intent-to-treat principle.*  
 30

31 *\* indicates p-values < 0.05.*  
 32

33 **Supplementary Table 4** Five-year event-free estimates with bootstrapped 95% confidence  
 34 intervals within pre-salvage RT PSA subgroups (<0.2, 0.2-0.5, and >0.5 ng/mL) by GC risk  
 35 group for all endpoints.

1 *Abbreviations: PSA = prostate-specific antigen; GC = genomic classifier.*

2  
3 *Empirical estimates and 95% confidence intervals were estimated by the cumulative incidence*  
4 *method, with the exception of rapid biochemical failure, which reports the event-free proportion.*  
5 *Model-based estimates were predicted from the appropriate model (Fine and Gray for FFBP,*  
6 *freedom from HT, freedom from metastasis, and MFS; Cox Proportional Hazards for clinical*  
7 *PFS; and logistic for rapid biochemical failure), adjusting for categorical Decipher and pre-SRT*  
8 *PSA group. The 95% confidence intervals were constructed via bootstrapping (B=1000).*  
9

## 10 **Supplementary Figure Titles and Legends**

11 **Supplementary Figure 1** Cumulative incidence estimates (1 – cumulative incidence) for Arm A  
12 (64Gy) and Arm B (70Gy) for (A) biochemical progression, (B) clinical progression, and (C)  
13 hormonal treatment in the full SAKK 09/10 trial cohort and the GC analytic cohort.

14 *Abbreviations: GC = genomic classifier.*

15  
16 *Cumulative incidence estimates (1 – cumulative incidence) with 95% CI at 1, 3, and 5 years*  
17 *explicitly reported.*

18  
19 *\* indicates p-values < 0.05.*

20

21 **Supplementary Figure 2** Cumulative incidence estimates (1 – cumulative incidence) of GC  
22 Low-Intermediate- ( $\leq 0.60$ ) and High- ( $> 0.60$ ) risk in (A) the GC analytic cohort, (B) Arm A  
23 (64Gy), and (C) Arm B (70Gy) for biochemical progression.

24 *Abbreviations: GC = genomic classifier; Gy = Gray; yrs = years; CI = confidence interval.*

25  
26 *Cumulative incidence estimates (1 – cumulative incidence) were compared using Gray's test;*  
27 *estimates with 95% CI at 1, 3, and 5 years explicitly reported.*

28  
29 *\* indicates p-values < 0.05.*

30



1 **Supplementary Figure 3** Cumulative incidence estimates (1 – cumulative incidence) of GC  
 2 Low- (<0.45), Intermediate- (0.45-0.60), and High- (>0.60) risk for (A) biochemical progression,  
 3 (B) clinical progression, and (C) hormonal treatment.

4 *Abbreviations: GC = genomic classifier; yrs = years; CI = confidence interval.*

5  
 6 *Cumulative incidence estimates (1 – cumulative incidence) were compared using Gray's test for*  
 7 *biochemical progression and hormonal treatment and the log-rank test for clinical progression;*  
 8 *estimates with 95% CI at 1, 3, and 5 years explicitly reported.*

9  
 10 *\* indicates p-values < 0.05.*

11

12 **Supplementary Figure 4** Prognostic performance of GC score for all endpoints.

13 *Abbreviations: GC = genomic classifier; CI = confidence interval; mo = months; MFS =*  
 14 *metastasis-free survival.*

15

16 *Randomization arm was treated as a main effect in the Fine and Gray model and logistic model*  
 17 *and as strata in the Cox proportional hazards model. Effect sizes of GC score were per 0.1-unit*  
 18 *increased and are reported for each endpoint from the appropriate model (Fine and Gray for*  
 19 *biochemical progression, hormonal treatment, metastasis, and metastasis or death (i.e.,*  
 20 *metastasis-free survival); Cox proportional hazards for clinical progression; and logistic for*  
 21 *rapid biochemical failure). Two patients with follow-up time = 0 were still included in analysis*  
 22 *as per the trial's intent-to-treat principle: one patient had follow-up time = 0 for all time-to-*  
 23 *event endpoints and one patient had follow-up time = 0 for FFBP only.*

24

25 *\* indicates p-values < 0.05.*

26

27 **Supplementary Figure 5** Prognostic performance of GC risk groups within clinical subgroups

28 for biochemical progression.

29 *Abbreviations: Est. = estimate; GC = genomic classifier; Subdist. = Subdistribution; HR =*  
 30 *Hazard Ratio; Low-Int = Low-Intermediate; CI = confidence interval; Gy = Gray; PSA =*  
 31 *prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.*

32

33 *Number of patients, number of events, and 5-year event-free estimates are reported by GC risk*  
 34 *group. Five-year event-free estimates and 95% confidence intervals were estimated by the*  
 35 *cumulative incidence method. GC effect sizes are reported from the Fine and Gray model, where*  
 36 *applicable. Two patients with missing clinical data were dropped from relevant models: one*  
 37 *patient was missing pathological stage and one patient was missing pathological stage and*

1 *Gleason score. Two patients with follow-up time were still included in analysis as per the trial's*  
2 *intent-to-treat principle.*

3

4 *\* indicates p-values < 0.05; ‡ indicates Cox proportional hazards model was used, due to no*  
5 *competing risks in the clinical subgroup.*

6

7 **Supplementary Materials** SAKK 09/10 Inclusion/Exclusion Criteria

**Appendix** Decipher algorithm

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Table 1

Variables	GC Analytic Cohort	Arm A (64 Gy)	Arm B (70 Gy)	<i>p-value</i>
<b>Total</b>	226 (100.0)	111 (49.1)	115 (50.9)	
<b>Age</b>				
Median (Q1, Q3)	66 (62, 70)	66 (63, 71)	66 (62, 70)	0.515
<b>WHO performance status</b>				
0	213 (94.2)	107 (96.4)	106 (92.2)	0.254
1	13 (5.8)	4 (3.6)	9 (7.8)	
<b>Pre-Op PSA</b>				
Median (Q1, Q3)	8.05 (5.55, 12.1)	8.11 (5.47, 10.7)	7.83 (5.56, 13.3)	0.356
<b>Positive surgical margins (%)</b>				
Yes	113 (50.0)	57 (51.4)	56 (48.7)	0.734
Unavailable	3 (1.3)	2 (1.8)	1 (0.9)	
<b>Extra-prostatic extension (%)</b>				
Yes	105 (46.5)	49 (44.1)	56 (48.7)	0.624
Unavailable	1 (0.4)	1 (0.9)		
<b>Seminal vesical invasion (%)</b>				
Yes	28 (12.4)	13 (11.7)	15 (13.0)	0.920
Unavailable	2 (0.9)	1 (0.9)	1 (0.9)	
<b>Lymphovascular invasion (%)</b>				
Yes	29 (12.8)	12 (10.8)	17 (14.8)	0.504
Unavailable	1 (0.4)	1 (0.9)		
<b>Lymphadenectomy type (%)</b>				
Limited lymph node dissection	145 (64.2)	74 (66.7)	71 (61.7)	0.622
Extended lymph node dissection	51 (22.6)	22 (19.8)	29 (25.2)	
None	27 (11.9)	13 (11.7)	14 (12.2)	
Unavailable	3 (1.3)	2 (1.8)	1 (0.9)	
<b>Pathological stage (%)</b>				
pT2	120 (53.1)	61 (55.0)	59 (51.3)	0.854
pT3a	76 (33.6)	36 (32.4)	40 (34.8)	
pT3b	28 (12.4)	13 (11.7)	15 (13.0)	
Unavailable	2 (0.9)	1 (0.9)	1 (0.9)	
<b>Pathological Gleason group (%)</b>				
6 [GG1]	28 (12.4)	14 (12.6)	14 (12.2)	0.806

7 (3+4) [GG2]	94 (41.6)	46 (41.4)	48 (41.7)	
7 (4+3) [GG3]	71 (31.4)	36 (32.4)	35 (30.4)	
8 [GG4]	15 (6.6)	5 (4.5)	10 (8.7)	
9-10 [GG5]	17 (7.5)	9 (8.1)	8 (7.0)	
Unavailable	1 (0.4)	1 (0.9)		
<b>Post-Op PSA</b>				
Median (Q1, Q3)	0.04 (0.0142, 0.09)	0.04 (0.02, 0.09)	0.047 (0.01, 0.09)	0.941
<b>Persistent PSA after RP (%)</b>				
Undetectable (< 0.1 ng/mL)	175 (77.4)	85 (76.6)	90 (78.3)	0.886
Detectable ( $\geq$ 0.1 ng/mL)	51 (22.6)	26 (23.4)	25 (21.7)	
<b>EAU High-risk (%)</b>				
Yes	171 (75.7)	91 (82.0)	80 (69.6)	0.043
<b>GETUG High-risk (%)</b>				
Yes	179 (79.2)	90 (81.1)	89 (77.4)	0.604
<b>PSA at randomization</b>				
Median (Q1, Q3)	0.3 (0.2, 0.53)	0.3 (0.196, 0.53)	0.33 (0.2, 0.565)	0.362
<b>PSA at randomization (%)</b>				
$\leq$ 0.5 ng/mL	165 (73.0)	82 (73.9)	83 (72.2)	0.890
> 0.5 ng/mL	61 (27.0)	29 (26.1)	32 (27.8)	
<b>RT technique (%)</b>				
3D-CRT	106 (46.9)	53 (47.7)	53 (46.1)	0.907
IMRT/Rotational	120 (53.1)	58 (52.3)	62 (53.9)	

**Table 2**

Model	Variable	Univariable		Multivariable	
		Subdist. Hazard Ratio (95% CI)	<i>P</i> -value	Subdist. Hazard Ratio (95% CI)	<i>P</i> -value
GC score	GC Score	1.13 (1.03 - 1.23)	0.009*	1.14 (1.04 - 1.25)	0.006*
	Arm B (70 Gy) vs Arm A (64 Gy)	1.38 (0.91 - 2.10)	0.13	1.29 (0.85 - 1.96)	0.24
	Age	0.94 (0.91 - 0.97)	<0.001*	0.93 (0.89 - 0.96)	<0.001*
	PSA at Randomization > 0.5 ng/mL vs ≤ 0.5 ng/mL	1.86 (1.19 - 2.91)	0.006*	2.60 (1.66 - 4.08)	<0.001*
	Path. Stage pT3b vs pT2-3a	1.75 (1.00 - 3.07)	0.05	1.12 (0.59 - 2.10)	0.73
	Gleason Score 8-10 vs ≤ 7	1.90 (1.14 - 3.19)	0.01*	1.55 (0.88 - 2.71)	0.13
	Persistent PSA Detectable vs Undetectable	0.64 (0.36 - 1.14)	0.13	0.53 (0.31 - 0.92)	0.02*
GC risk group	GC High vs Low-Intermediate	2.21 (1.41 - 3.47)	<0.001*	2.26 (1.42 - 3.60)	<0.001*
	Arm B (70 Gy) vs Arm A (64 Gy)	-	-	1.28 (0.84 - 1.94)	0.25
	Age	-	-	0.93 (0.90 - 0.97)	<0.001*
	PSA at Randomization > 0.5 ng/mL vs ≤ 0.5 ng/mL	-	-	2.54 (1.63 - 3.98)	<0.001*
	Path. Stage pT3b vs pT2-3a	-	-	1.30 (0.72 - 2.33)	0.39
	Gleason Score 8-10 vs ≤ 7	-	-	1.49 (0.83 - 2.67)	0.18
Persistent PSA Detectable vs Undetectable	-	-	0.53 (0.30 - 0.92)	0.02*	

Figure 1

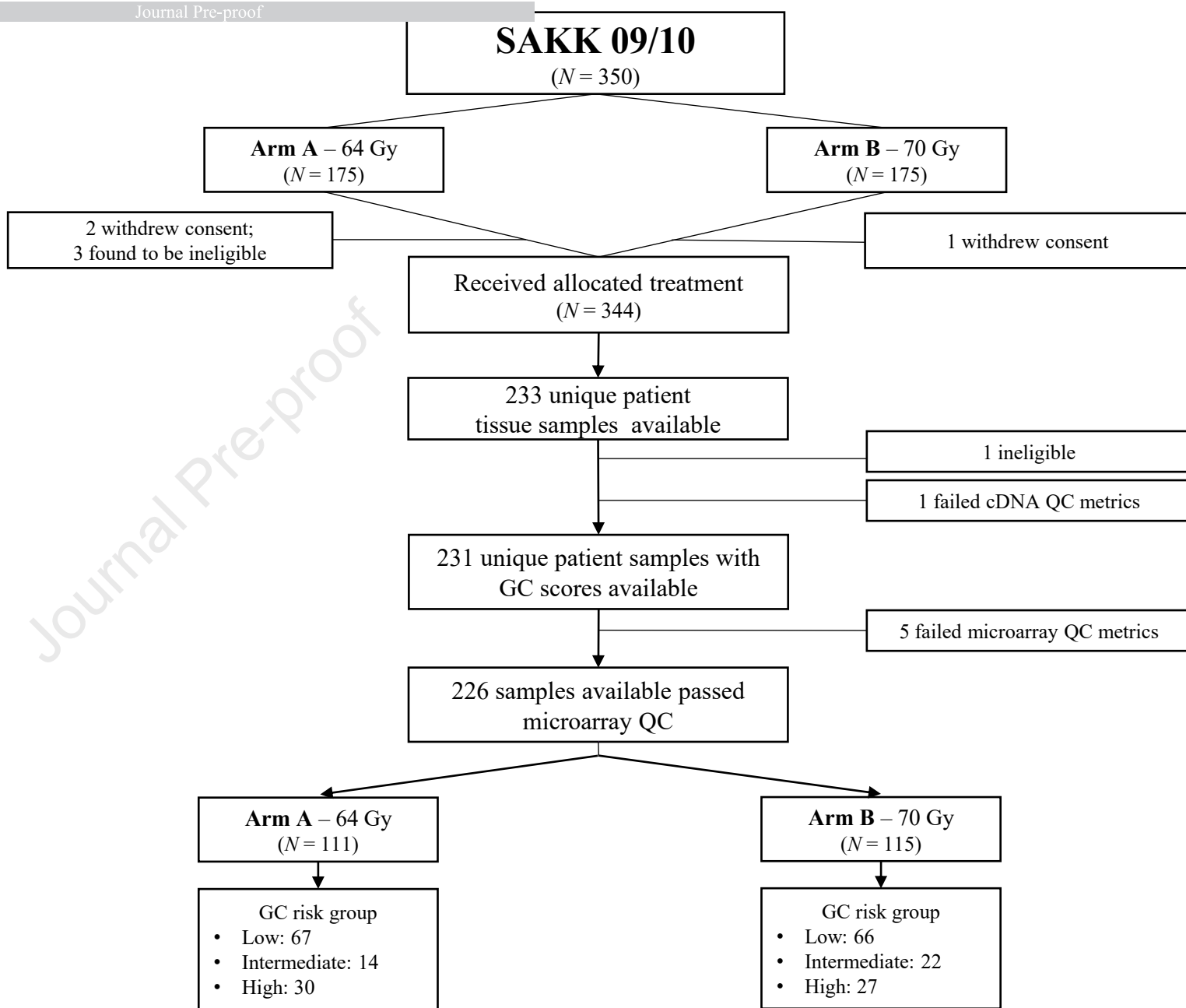


Figure 2

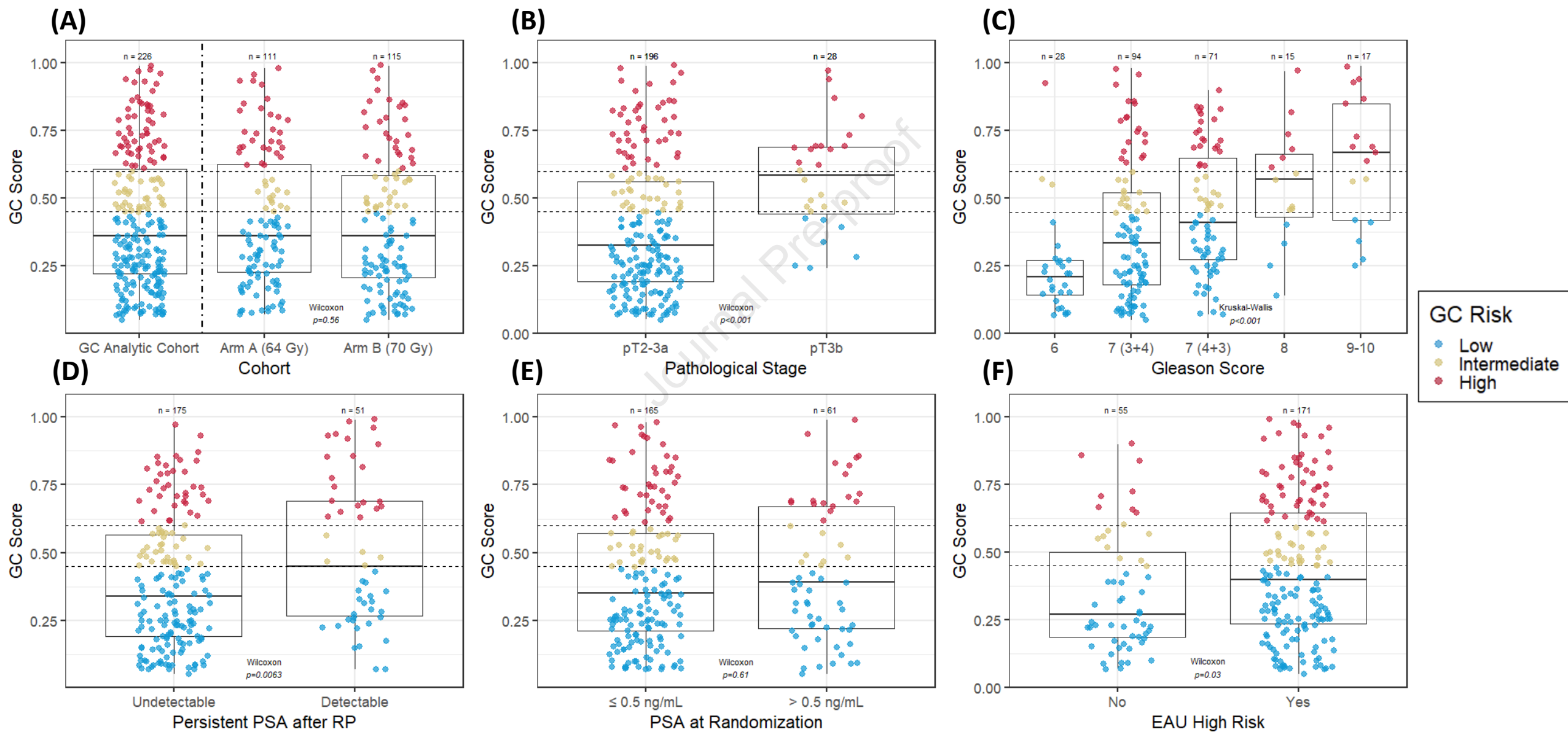
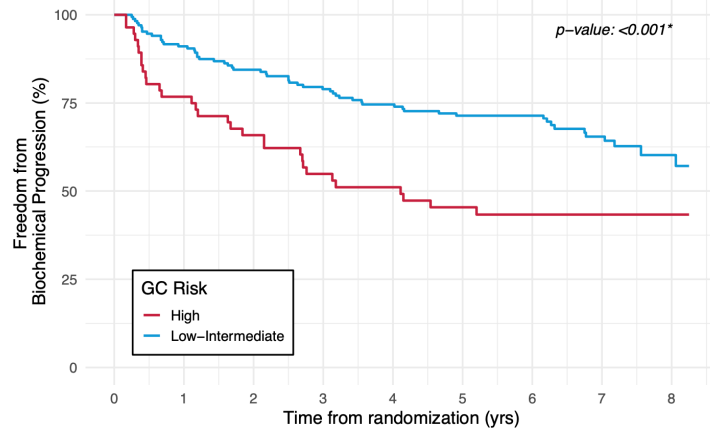


Figure 3

(A)



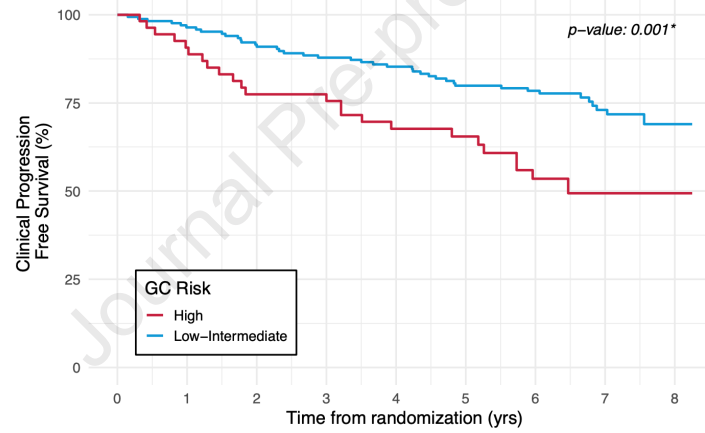
<b>High</b>	56	(2)	36	(2)	27	(3)	19	(18)	2
<b>Low-Intermediate</b>	168	(3)	138	(7)	116	(17)	100	(63)	18

Patients at risk (censored)

<b>High</b>	77% (66%–88%)	55% (42%–68%)	45% (32%–59%)
<b>Low-Intermediate</b>	91% (87%–95%)	79% (73%–85%)	71% (64%–78%)

Event-free rate (95% CI)

(B)



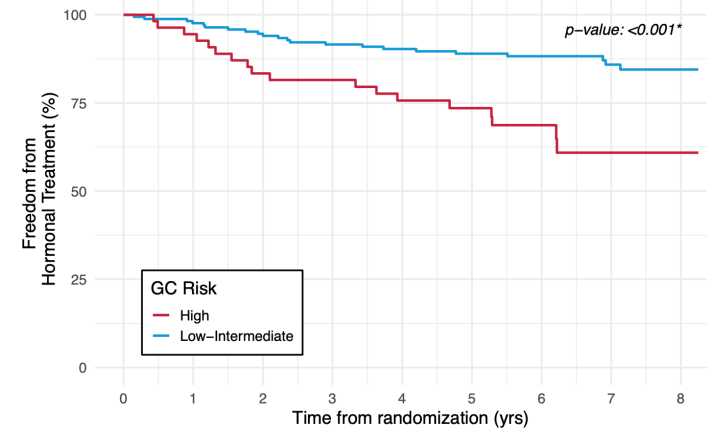
<b>High</b>	57	(4)	41	(4)	34	(9)	22	(25)	2
<b>Low-Intermediate</b>	168	(2)	149	(7)	132	(20)	107	(70)	19

Patients at risk (censored)

<b>High</b>	91% (83%–99%)	76% (64%–87%)	65% (52%–79%)
<b>Low-Intermediate</b>	96% (94%–99%)	88% (83%–93%)	80% (74%–86%)

Event-free rate (95% CI)

(C)



<b>High</b>	57	(3)	45	(3)	39	(10)	27	(31)	2
<b>Low-Intermediate</b>	169	(2)	155	(6)	138	(25)	115	(81)	20

Patients at risk (censored)

<b>High</b>	95% (88%–100%)	82% (71%–92%)	74% (61%–86%)
<b>Low-Intermediate</b>	98% (95%–100%)	92% (87%–96%)	89% (84%–94%)

Event-free rate (95% CI)



Figure 4

