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TITLE: Comprehensive Molecular Profiling of African-American Prostate Cancer to Inform on Prognosis and Disease Biology

PRINCIPAL INVESTIGATOR: Scott A. Tomlins, M.D., Ph.D.

CONTRACTING ORGANIZATION: Regents of the University of Michigan
Ann Arbor, MI 48109

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Scott A. Tomlins

E-Mail: tomlinss@umich.edu

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Regents of the University of
Michigan
3003 S. State Street
Ann Arbor, MI 48109

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14. ABSTRACT

Epidemiological studies consistently show worse prostate cancer (PCa) incidence and mortality rates in African American (AA) vs. white/Caucasian (CA) men. Although the etiology is likely multi-factorial, AA PCa may arise through distinct pathways and harbor unique molecular alterations. We hypothesized that comprehensive molecular analysis of a carefully annotated AA PCa cohort will inform on the applicability of PCa prognostic signatures and identify novel drivers of aggressive disease in AA patients, thereby impacting the clinical management of AA patients and improving our understanding of the molecular events that underlie racial disparities in PCa behavior. Herein, we generated integrative DNA and RNA profiles of over 200 PCa from AA men. Although we did not identify novel molecular alterations as mediators of aggressive disease, we found altered distribution of known PCa molecular subtypes as well as identified percent genome alteration and TP53 as indepdently predictors of metastasis after surgery.

15. SUBJECT TERMS

African American, prognostic signatures, anterior prostate cancer, molecular signatures, prostatectomy

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INTRODUCTION:

Epidemiological studies consistently show worse prostate cancer (PCa) incidence and mortality rates in African American (AA) vs. white/Caucasian (CA) men. Although the etiology is likely multi-factorial, increasing evidence supports biologic contributors. Our previous work and others show that that even after adjustment for socioeconomic factors, AA men show elevated risks of poor outcome. Likewise, we have shown that PCa in AA men has a unique zonal distribution within the prostate. Hence, AA PCa may arise through distinct pathways and harbor unique molecular alterations, however this possibility has not been well explored. High throughput technologies have enabled extraordinary insight into the PCa transcriptome/genome, including molecular subtypes driven by recurrent gene fusions; however such studies have been performed nearly exclusively in predominantly CA cohorts. Importantly, prognostic gene expression based tests for PCa have recently been developed, and are being aggressively marketed to patients, despite little validation in AA men. We hypothesized that comprehensive molecular analysis of a carefully annotated AA PCa cohort will inform on the applicability of PCa prognostic signatures and identify novel drivers of aggressive disease in AA patients, thereby impacting the clinical management of AA patients and improving our understanding of the molecular events that underlie racial disparities in PCa behavior. Using targeted multiplexed DNA and RNA PCR based next generation sequencing, we profiled over 200 PCa from AA men representing the entire PCa spectrum at radical prostatectomy. Although significantly limited in our ability to evaluate commercial gene expression profiles and identify novel gene fusions due to markedly reduced RNA quality, we were able to generate Decipher prognostic signatures for over 100 AA men. Importantly, we found that AA men show a unique distribution of known PCa molecular subtypes compared to CA men. Likewise, we found that the percent genome altered by copy number alterations (PGA) and TP53 mutations were independently prognostic of metastasis after radical prostatectomy, as they are in CA men. Hence, although we did not identify novel drivers of PCa in AA men, our results provide the largest collection of comprehensively profiled PCa in AA men.

KEYWORDS:

African American, prognostic signatures, anterior prostate cancer, molecular signatures, prostatectomy

ACCOMPLISHMENTS:

What were the major goals of the project?:

SPECIFIC AIMS

1) Perform comprehensive expression profiling of PCa in AA men to assess the performance of PCa prognostic gene expression signatures.
2) Characterize known and novel PCa gene fusions in AA men.
3) Characterize known and novel PCa mutations and CNAs in AA men to develop an integrated prognostic signature.

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What was accomplished under these goals?

To accomplish these aims, we developed a collaboration between Drs. Tomlins (PI; University of Michigan [UM]), Dr. Edward Schaffer (Qualifying Co-PI, Johns Hopkins Medical Institute [JHU]; moved to Northwestern University [NU] during the project period), Dr. Tamara Lotan (JHU) and Dr. Luigi Marchionni (JHU). Our proposed statement of work included work at both UM and JHU and progress is reported (in italics) according to the submitted statement of work

1. IRB Approval
    a. Local IRB/IACUC Approval (months 1-2)
    b. HRPO/ACURO Approval (months 2-3)

Both UM and JHU have received local IRB and HRPO approval. MTAs are in place between UM, JHU and GenomeDX for transferring material (no MTA with NU is needed).

Overall, these tasks are 100% complete.

1. Specific Aim 1: Assess the performance of prostate cancer (PCa) prognostic gene expression signatures in African American (AA) men
    a. Retrospectively identify prostatectomy cases from AA men (n=192) from institutional database. (months 2-9)
    b. Histopathological review of prostatectomy cases to identify tumor foci and evaluate anatomic location. (months 3-12)
    c. Histological processing of a representative formalin fixed paraffin embedded (FFPE) block from each case. (months 3-12)
    d. Macrodissection of FFPE sections to enrich for tumor content as needed (months 3-12).
    e. Transfer of FFPE tissue to UMMS for DNA/RNA isolation and next generation sequencing. (months 3-12)
    f. Isolate DNA/RNA from FFPE tissues. (months 3-12)
    g. Affymetrix profiling of RNA by GenomeDX to generate Decipher, Prolaris and Oncotype DX scores, identify known gene fusions through outlier analysis and nominate gene fusions (months 13-18)
    h. Evaluation of Decipher, Prolaris and Oncotype DX scores for predicting upgrading, high stage and margin status in AA men stratified by NCCN risk group. (months 18-20)

After local IRB and HRPO approval, a retrospective search was performed through the JMHI prostate cancer tissue bank. 192 AA PCa cases were identified, with a total of 220 AA PCa cases identified in an effort to replace poor quality samples . *Dr. Lotan reviewed all cases, identified tumor foci and noted anatomical locations, and punched tissue cores from the FFPE block for each case. All cases were transferred to UM and were subjected to co-isolation of DNA and RNA in the Tomlins laboratory. RNA was transferred to GenomeDX after significant delay due to finalization of workplan alignment and prioritization of clinical profiling at GenomeDX. Affymetrix profiling of RNA from 180 AA PCa cases (selected based on meeting QC parameters on UM targeted RNAseq) was completed, however only ~126 samples passed usual GenomeDX QC parameters for generation of Decipher, Prolaris and Oncotype DX scores . Evaluation of the*

performance of Decipher and other derived signatures is being performed as part of the final manuscript generation.

Overall, tasks a-g are 100% complete. Task h is approximately 75% complete.

2. Specific Aim 2: Characterize known and novel PCa gene fusions in AA men.
    a. Targeted capture RNA NGS of cases (n=96) with novel candidate gene fusions. (months 18-24)
    b. Exome capture RNA NGS of cases (n=36) without candidate gene fusions. (months 18-24)
    c. Targeted multiplexed PCR based next generation sequencing of RNA from AA cases (n=192) to confirm GenomeDX expression signatures and predicted gene fusions. (months 24-30)
    d. Compare known and novel gene fusion frequencies between AA and Caucasian (CA) men, NCCN risk groups of AA men, and anatomical tumor location. (months 30-36)

Unexpectedly, the quality of the isolated RNA was the lowest observed in the Tomlins laboratory at UM (>7,000 cases from numerous institutions) as well as at GenomeDX. Review of usual histology practices at JHU identified an accelerated fixation process for prostatectomy specimens to improve turnaround time as the likely cause. Importantly, targeted and exome capture of RNA for gene fusion discovery require higher quality RNA than the assays performed by UM and GenomeDX. Hence, characterization of novel candidate fusions and samples without candidate gene fusions could not be performed. Effort and funds were used re-running cases and assessing additional cases by targeted multiplexed PCR based RNA (and DNA) NGS to generate an informative cohort of at least 192 samples. Of a final cohort of 220 PCa from AA men, 180 had informative multiplexed PCR based RNA seq, which was only sufficient to characterize gene fusion status. Across these 180 samples, we achieved an average of 1,867,825 mapped end-to-end reads per sample. An integrative heatmap of the entire cohort is shown in ***Figure 1*** *(Appendix).*

Importantly, as shown in ***Table 1****, ERG and other ETS gene fusions were significantly less frequent in AA vs. Ca men (19% vs. 48% and 1% vs. 10%, respectively, two-sided Fisher's exact test p <0.0001 for both; n=180 AA men from our cohort and 233 Ca men from TCGA). Likewise, the rate of SPINK1$^+$ and ERG$^-$/ETS$^-$/SPINK1$^-$ status were higher in AA vs. Ca men (16% vs. 4% and 64% vs 38%, respectively; p<0.0001 for both).*

Table 1

	TCGA		This cohort	Fisher's exact *p*
Status	**CA**	**AA**	**AA**	**(This vs. TCGA CA)**
ERG+	48%	27%	19%	<0.0001
Other ETS+	10%	5%	1%	<0.0001
SPINK1+	4%	11%	16%	<0.0001
ETS-/SPINK1-	38%	57%	64%	<0.0001
Total *n*	233	37	180	

*As shown in **Tables 2** and **3**, across Grade Groups (GG) and pathologic tumor (T) stage (more informative for prostatectomy specimens than NCCN risk groups) in our cohort of AA men, ETS gene fusions were more common in men with GG1 PCa vs. higher grade disease.*

Table 2

Subtype	GG1	GG2	GG3	GG4	GG5
ERG+	50%	15%	15%	15%	15%
Other ETS+	0%	0%	2%	2%	0%
SPINK1+	10%	19%	13%	19%	15%
ETS-/SPINK1-	40%	67%	69%	65%	70%

Table 3

Subtype	T2	T3a	T3b
ERG+*	18%	19%	22%
Other ETS+	0%	3%	0%
SPINK1+	17%	11%	22%
ETS-/SPINK1-	65%	67%	56%

Incorporation of anatomical location with respect to fusion status is ongoing and will be included in the final manuscript.

Hence, tasks A and B could not be completed. Task c is 100% completed. Task d is 95% completed.

3. Specific Aim 3: Characterize known and novel somatic PCa mutations in AA men.
    a. Targeted multiplexed PCR based next generation sequencing of DNA from AA cases (n=192) to identify somatic copy number alterations, point mutations and indels. (months 13-18)

Task a is 100% completed. High quality DNA libraries were generated for a total of 205 samples (sufficient for copy number alteration calling), with 184 informative for both mutations and copy number alterations. We utilized a novel targeted DNA sequencing panel developed for this study. Of note, this panel, which includes 3,127 amplicons targeting 312,920 bases in 140 genes, enables assessment of both global copy number alterations (informed by assessment of LOH through targeting common SNPs) and oncogenic and tumor suppressive mutations.
Across the 184 samples informative for both mutations and copy number, we achieved an average of 3,886,093 mapped reads, >1,171x coverage and 94% uniformity.

*The clinicopathological characteristics of the 205 copy number informative samples is shown in **Table 4.***

Table 4

Variable	AA (n=205)
Median PSA, ng/ml (IQR)	7.30 (5.24-13.00)
Median age, yr (IQR)	58 (53-63)
Clinical T stage, n (%) T1c T2a T2b/c	 154 (75.1) 34 (16.6) 17 (8.3)
Biopsy grade group, n (%) 1 (GS 6) 2 (GS 3+4) 3 (GS 4+3) 4 (GS 8) 5 (GS 9-10)	 72 (35.1) 49 (23.9) 48 (23.4) 26 (12.7) 10 (4.9)
RP grade group, n (%) 1 (GS 6) 2 (GS 3+4) 3 (GS 4+3) 4 (GS 8) 5 (GS 9-10)	 28 (13.7) 32 (15.6) 91 (44.4) 33 (16.1) 21 (10.2)
Pathologic T stage, n (%) T2N0 T3aN0 T3bN0 N1	 87 (43.1) 71 (35.2) 28 (13.9) 16 (7.9)
Median length of follow-up, yr (IQR)	5 (2-10)
Biochemical recurrence, n (%)	74 (39.2)
5-yr BCR-free survival (95% CI) 10-yr BCR-free survival (95% CI)	0.603 (0.518, 0.678) 0.468 (0.367, 0.562)
Metastasis, n(%)	20 (10.6)
5-yr metastasis-free survival (95% CI) 10-yr metastasis-free survival (95% CI)	0.918 (0.852, 0.956) 0.816 (0.711, 0.886)

b. Compare somatic alteration frequency between NCCN risk groups and anatomical tumor location.(months 18-20)

*Task b is 95% completed. The anatomic assessment is ongoing and part of the final manuscript preparation. Assessment of rates of prioritized recurrent somatic mutation alteration frequency across Grade Groups and pathologic stages are shown in **Tables 5** and **6**. Alterations known to be mutually exclusive and enriched with ETS gene fusions, respectively, are indicated in red and*

green in the tables. As shown, essentially no prioritized somatic alterations were identified in GG1 tumors. TP53 and BRCA2 alterations were more common in pT>2 tumors.

Table 5

Gene	GG1	GG2	GG3	GG4	GG5
SPOP	0%	15%	17%	13%	7%
CHD1	0%	9%	10%	19%	11%
FOXA1	6%	9%	10%	8%	15%
PTEN	0%	6%	6%	6%	11%
TP53	0%	0%	6%	6%	7%
BRAF	0%	0%	2%	4%	4%
BRCA2	0%	0%	4%	0%	7%
IDH1	0%	6%	2%	2%	0%
ZMYM3	0%	6%	2%	0%	4%
CDK12	0%	3%	0%	0%	7%
HRAS	0%	0%	2%	0%	4%
PIK3CA	0%	0%	2%	2%	0%
ATM	0%	0%	0%	0%	4%
MED12	0%	0%	0%	2%	0%
AKT1	0%	0%	0%	0%	0%
BRCA1	0%	0%	0%	0%	0%
CTNNB1	0%	0%	0%	0%	0%
RB1	0%	0%	0%	0%	0%

Table 6

Gene	T2	T3a	T3b
SPOP	15%	10%	10%
CHD1	2%	1%	0%
FOXA1	6%	13%	7%
PTEN	1%	0%	0%
TP53	0%	7%	10%
BRAF	2%	3%	0%
BRCA2	1%	1%	7%
IDH1	1%	3%	3%
ZMYM3	1%	3%	0%
CDK12	0%	3%	3%
HRAS	0%	3%	0%
PIK3CA	0%	3%	0%
ATM	0%	1%	0%
MED12	0%	1%	0%
AKT1	0%	0%	0%
BRCA1	0%	0%	0%
CTNNB1	0%	0%	0%
RB1	0%	0%	0%

c. Compare somatic alteration frequency between profiled AA cases and external CA cohorts. (months 18-20)

Task c is 100% completed. Assessment of rates of recurrent somatic mutation alteration frequency between this AA cohort and AA and CA men from the TCGA cohort are shown in ***Table 7****. Alterations known to be mutually exclusive with ETS gene were enriched in AA men in both our and the TCGA cohort vs. CA men from the TCGA cohort.*

Table 7

Gene	TCGA		This cohort
	CA	AA	AA
SPOP	8.9%	20.9%	12.5%
CHD1	5.9%	14.0%	11.4%
FOXA1	3.7%	7.0%	9.2%
PTEN	18.1%	7.0%	6.0%
TP53	8.9%	0.0%	4.3%
BRAF	1.9%	7.0%	2.2%
BRCA2	3.3%	4.7%	2.2%
IDH1	0.7%	2.3%	2.2%
ZMYM3	1.9%	0.0%	2.2%
CDK12	2.6%	2.3%	1.6%
HRAS	1.5%	0.0%	1.1%
PIK3CA	1.9%	2.3%	1.1%
ATM	4.1%	4.7%	0.5%
MED12	1.9%	2.3%	0.5%
AKT1	1.1%	0.0%	0.0%
BRCA1	1.1%	0.0%	0.0%
CTNNB1	2.6%	2.3%	0.0%
RB1	0.7%	2.3%	0.0%
Total *n*	270	43	184

d. Determine whether the inclusion of gene fusions or somatic events improves the performance of the gene expression classifiers from Aim 1. (months 20-34)

Task d is 50% completed and is being performed as part of the manuscript writing. Importantly, we have observed that percent genome alteration (PGA, the percentage of the assessed genome with copy number alterations) increases with GG and tumor stage as shown in ***Table 8****. Additionally, PGA was also an independent prognostic factor predicting metastasis after radical prostatectomy by multivariate Cox proportional hazard modeling as shown in* ***Table 9****. Lastly, in the 184 patients evaluable for mutations,* TP53 *mutation status was independently associated with the development of metastasis by multivariate Cox proportional hazard modeling as shown in* ***Table 10****.*

Table 8

Pathologic characteristic	PGA (continuous), median (IQR)	p-value*
RP grade group		**<0.001**
1 (GS 6)	0.935 (0-4.205)	
2 (GS 3+4)	1.869 (0-3.271)	
3 (GS 4+3)	3.738 (0.935-10.280)	
4 (GS 8)	8.411 (2.804-11.215)	
5 (GS 9-10)	4.673 (0.935-9.346)	
Pathologic T stage		**0.0194**
T2N0	2.804 (0.935-6.542)	
T3aN0	5.607 (0.935-11.215)	
T3bN0	3.271 (1.869-9.813)	
N1	2.336 (0.467-10.748)	

** Kruskal-Wallis test*

Table 9

Variable	HR (95% CI)	p-value
Univariate analysis		
PGA (continuous) ‡	1.11 (1.06, 1.17)	<0.001
Age	1.05 (0.98, 1.12)	0.212
PSA	0.99 (0.99, 1.01)	0.735
RP grade group ≥4*	4.73 (2.03, 11.01)	<0.001
Pathologic T stage		
T2N0	1.00 (reference)	
T3aN0	2.10 (0.47, 9.40)	0.332
T3bN0	10.69 (2.89, 39.53)	<0.001
N1	9.51 (2.27, 39.82)	0.002
Multivariate analysis		
PGA (continuous) ‡	1.15 (1.07, 1.23)	<0.001
Age	1.06 (0.97, 1.16)	0.217
PSA	0.96 (0.90, 1.03)	0.258
RP grade group ≥4*	5.77 (1.91, 17.43)	0.002
Pathologic T stage		
T2N0	1.00 (Reference)	
T3aN0	1.41 (0.22, 9.06)	0.715
T3bN0	20.04 (4.15, 96.85)	<0.001
N1	17.58 (2.44, 126.45)	0.004

**RP grade group analyzed as dichotomous variable given low number of metastatic events per grade group and especially low events in lower grade groups*

Table 10

Outcome	Mutation	HR (95% CI)	p-value
Metastasis: multivariate	TP53	9.45 (2.20, 40.55)	**0.002**
	Age	1.07 (0.98, 1.18)	0.145
	PSA	0.99 (0.98, 1.02)	0.826
	RP GG ≥4*	6.93 (2.29, 20.02)	0.001
	Pathologic T stage		
	T2N0	1.00 (reference)	--
	T3aN0	1.69 (0.27, 10.72)	0.578
	T3bN0	20.93 (4.27, 102.75)	<0.001
	N1	10.23 (1.72, 61.05)	0.011

*RP grade group analyzed as dichotomous variable given low number of metastatic events per grade group and especially low events in lower grade groups

e. Prepare manuscript on study. (months) 34-36

Task e is 50% completed. The above described data is being integrated and prepared for submission, which is expected in the next few months.

What opportunities for training and professional development has the project provided?
Nothing to Report

How were the results disseminated to communities of interest?
Nothing to Report. The manuscript describing the findings is in preparation.

What do you plan to do during the next reporting period to accomplish the goals?
N/A. We have completed all planned experiments and are completing all required analyses to enable submission of the planned manuscript. Both UM and JHU have ongoing local IRB approval to continue working with the data until project completion.

IMPACT:
What was the impact on the development of the principal discipline(s) of the project?
Our study is notable in several aspects. First, to our knowledge, it is the largest cohort of comprehensively profiled PCa from AA men and detailed clinicopathologic information is available. Additionally, our results did not identify novel drivers of PCa in AA men, but rather different frequencies of known subtype defining alterations between AA and CA men. We also identified PGA and TP53 mutations as independent prognostic factors in AA men, as has been reported for CA men, despite the differences in molecular subtypes.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?
Nothing to Report

What was the impact on society beyond science and technology?
Nothing to Report

CHANGES/PROBLEMS:
Changes in approach and reasons for change
Targeted capture and exome capture could not be performed due to unexpected RNA quality issues (despite sufficient quantity). Hence, additional multiplex DNA/RNAseq was performed both to repeat samples and profile additional samples to ensure the overall cohort size was

Actual or anticipated problems or delays and actions or plans to resolve them
RNA microarray profiling with our commercial partner was delayed however it was completed during year 3 of the award.

Changes that had a significant impact on expenditures
Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to Report

PRODUCTS:
Publications, conference papers, and presentations
Nothing to Report

Website(s) or other Internet site(s)
Nothing to Report

Technologies or techniques
Nothing to Report

Inventions, patent applications, and/or licenses
Nothing to Report

Other Products
Nothing to Report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Scott Tomlins
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Tomlins has led all aspects of the study as the PI, including coordinating the project with JHU (and NU) investigators.
Funding Support:	

Name:	Edward Schaeffer
Project Role:	Qualifying Co-PI
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Schaeffer led the identification of cases from JHU and interaction with GenomeDX to advance the microarray profiling.
Funding Support:	

Name:	Tamara Lotan
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Lotan led the histologic review and anatomic localization assessment.
Funding Support:	
Name:	Luigi Marchionni

Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Marchionni has led the integration of clinicopathologic information from reviewed samples into a study specific database.
Funding Support:	

Name:	Albert Liu
Project Role:	Technician
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	12
Contribution to Project:	Mr. Liu led the RNA and DNA profiling in the Tomlins lab.
Funding Support:	

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  N/A with ending of awardEggbert5!

- **What other organizations were involved as partners?**

Johns Hopkins University
353 Garland Hall
3400 North Charles Street
Baltimore, MD 21218-2688
Partnering PI and Co-Investigators (Drs. Schaeffer, Lotan and Marchionni)

Northwestern University
Tarry Building Room 16-703
300 E. Superior
Chicago, IL 60611-3010
Partnering PI (Dr. Schaeffer moved institutions during the year 1 project period)

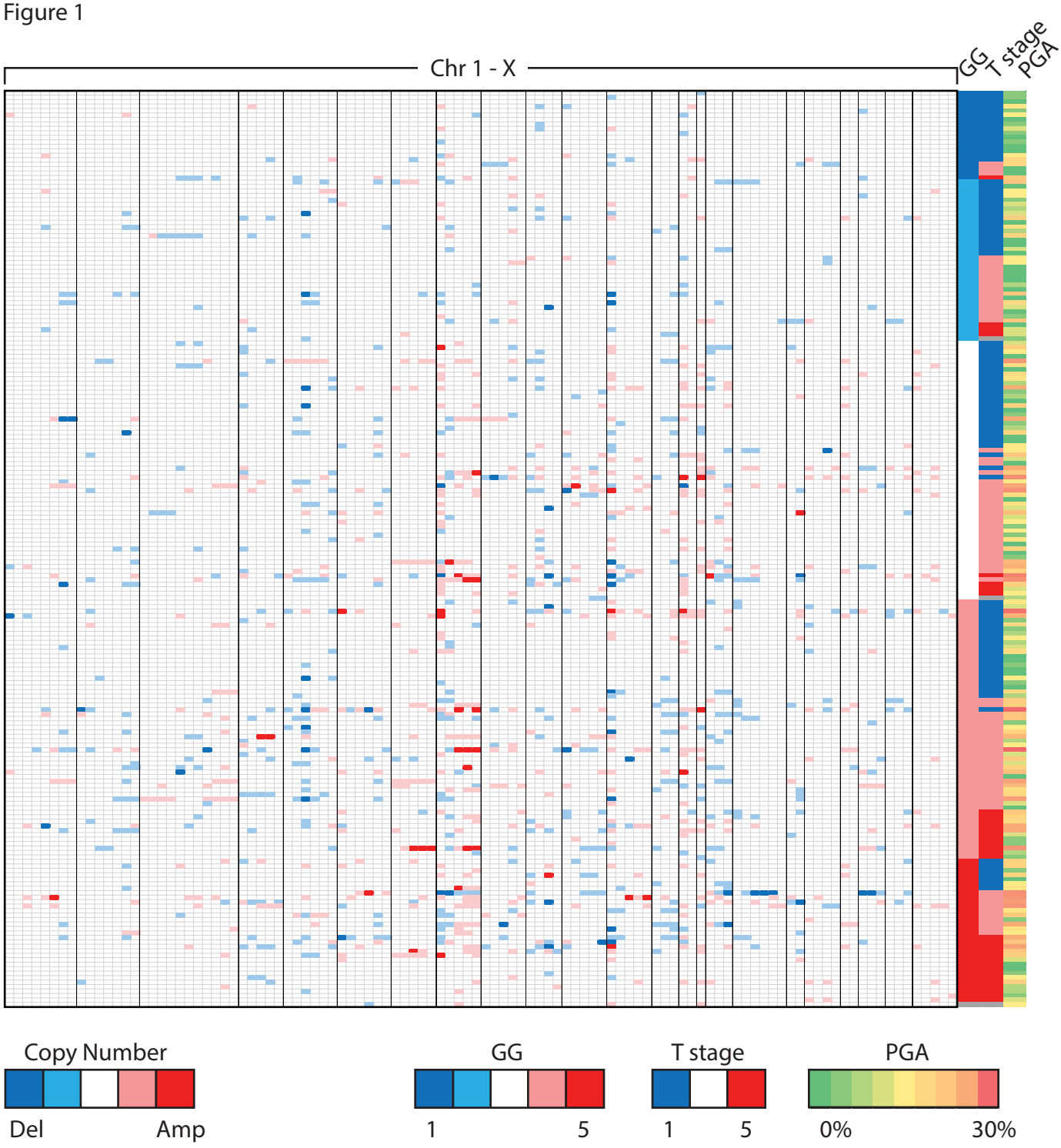
SPECIAL REPORTING REQUIREMENTS

Collaborative Awards:
N/A

Quad Charts:
N/A

APPENDICES (see next page):
Figure 1

Figure 1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