Identification of a mutational signature of dietary acrylamide in renal cancer genomes

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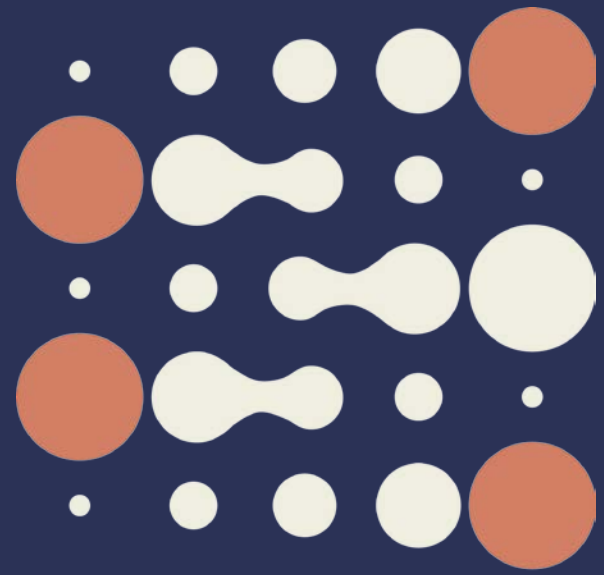
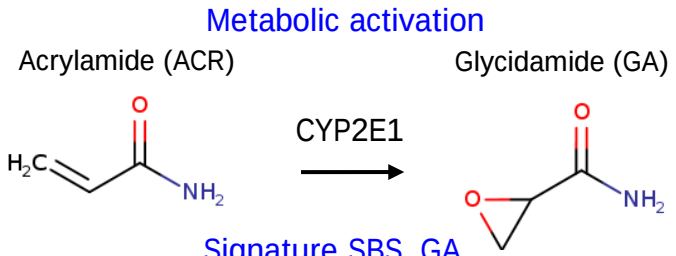
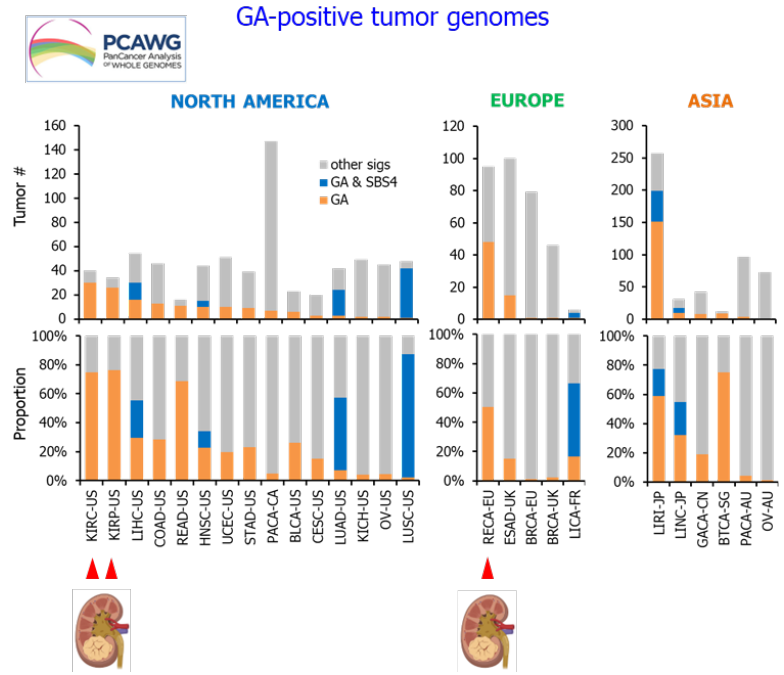


Introduction & Background

- Acrylamide (ACR) forms in heated starchy and other foods and in the tobacco smoke
- Probable human carcinogen (IARC Group 2A)
- ACR and its reactive metabolite glycidamide (GA) - high priority compounds for IARC Monograph evaluation
- EGM previously discovered mutational signature SBS_GA (Zhivagui M et al, 2019, PMID 30846532)
- SBS_GA was found operative in 30% of ~1,600 ICGC PCAWG tumour genomes (19 human tumour types, 14 organs)
- Clear-cell renal cell carcinomas (ccRCCs) were markedly enriched for SBS_GA (70% of 111 samples)



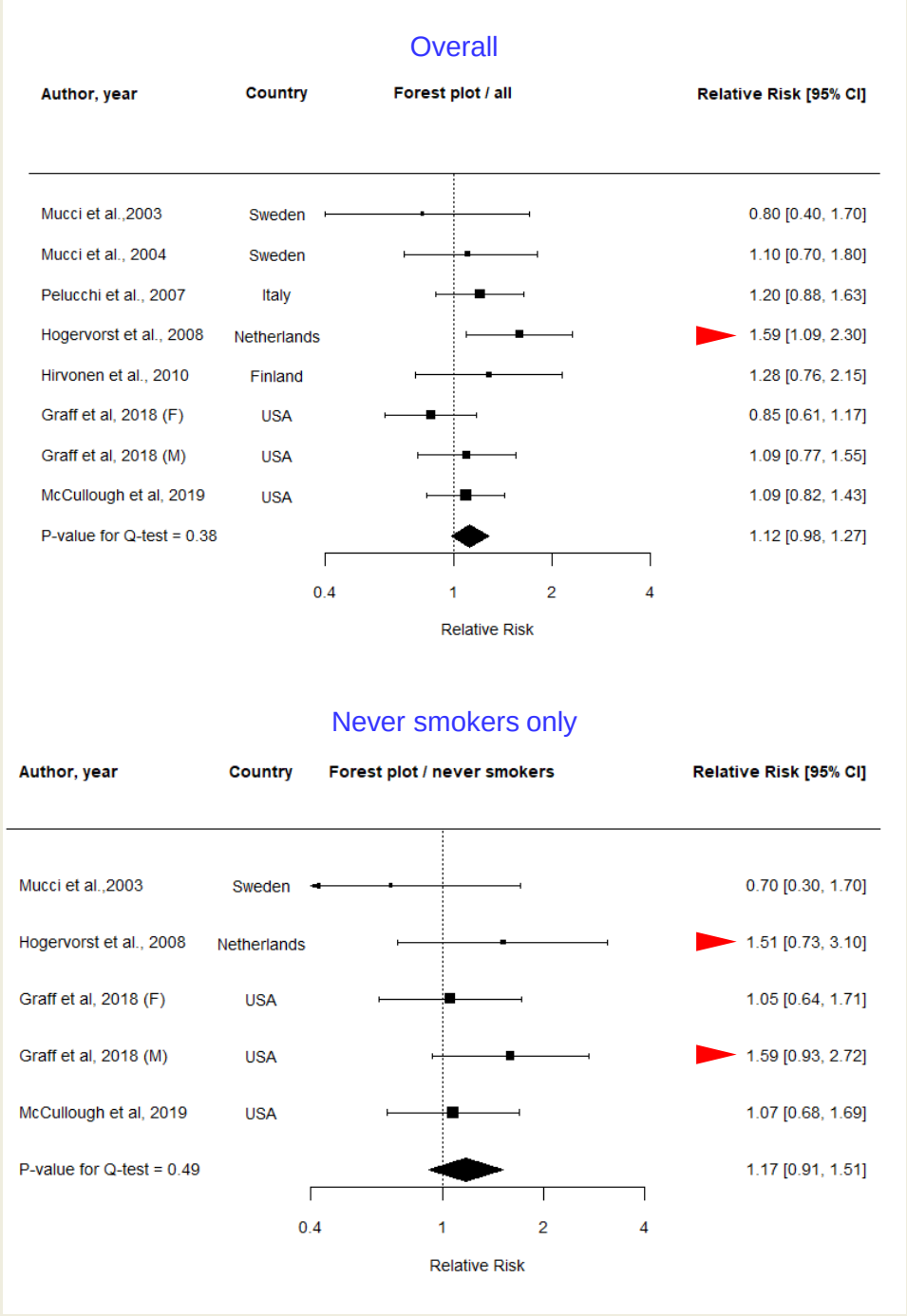


Introduction & Background

- The ccRCC findings were consistent with our re-analysis of epidemiological studies indicating elevated non-significant risk associated with dietary ACR in never smokers
- ACR/GA mutational signature has not yet been specifically linked to ACR exposure history

Hypothesis

- Exposure to dietary ACR/GA leads to dose-dependent genome-wide mutagenesis underlying ccRCC development



Specific Aims

- Determine SBS_GA in ccRCC and its correlation with documented dietary ACR intake

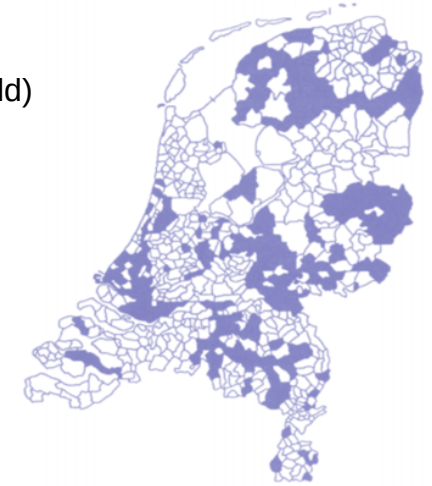
Strategy & Design

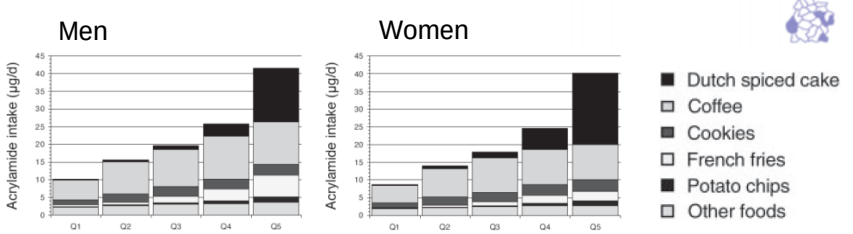
- ccRCCs of never-smokers from the Netherlands Cohort Study on Diet and Cancer (NLCS)
- Compare low vs. high dietary ACR intake groups
- Whole-genome sequencing of macro-dissected FFPE material
- Innovative mutational signature analysis (extraction coupled with per-sample attribution)

Netherlands Cohort Study on Diet and Cancer

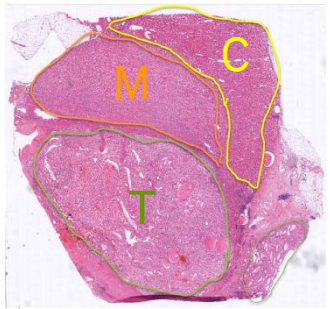
120,852 subjects
(birth years 1961-1931, 55-69 yrs old)
204 municipalities
Food frequency questionnaire:
- dietary habits (150 items)
- other risk factors

Cancer follow up >20 years
480 cases of renal cancer
235 available in tumor blocks



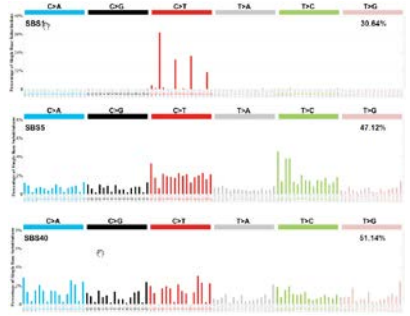


FFPE ccRCC



WGS Illumina
NovaSeq 6000
150 PE
30-50x

Mutational signature analysis

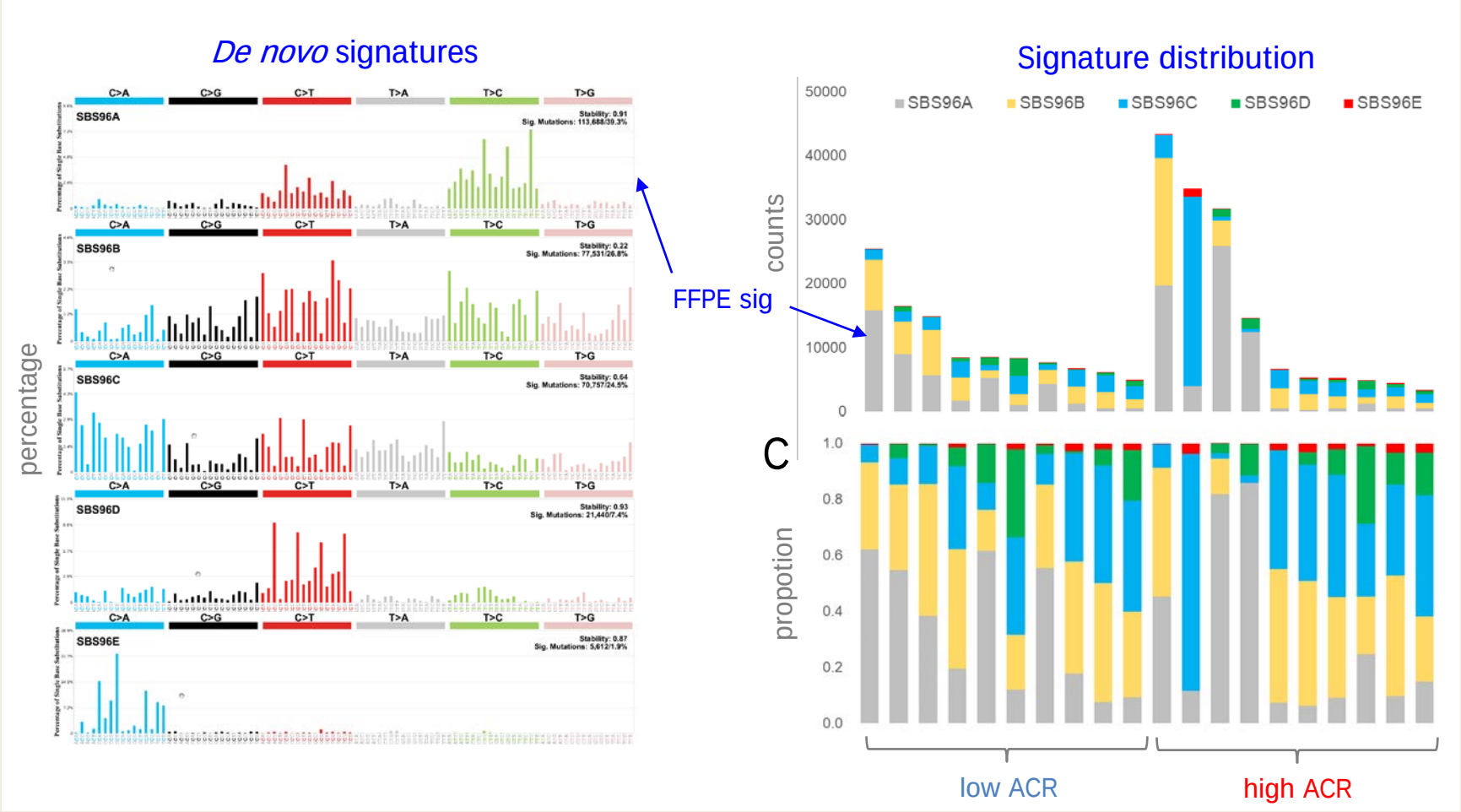


SigProfiler Extractor

MSA

Results

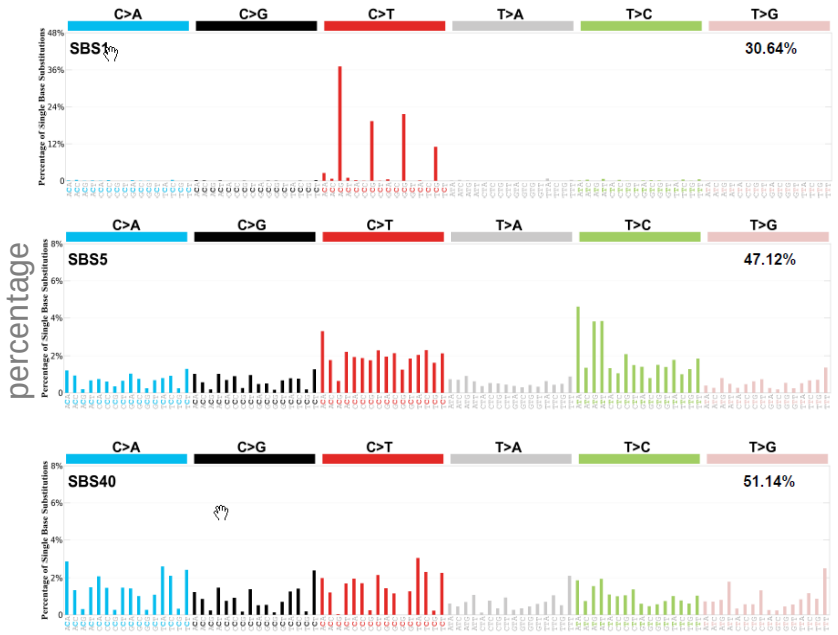
- 5 *de novo* signatures identified, including at least one specific for FFPE-related artefacts
- No exposure-group signature enrichment was observed



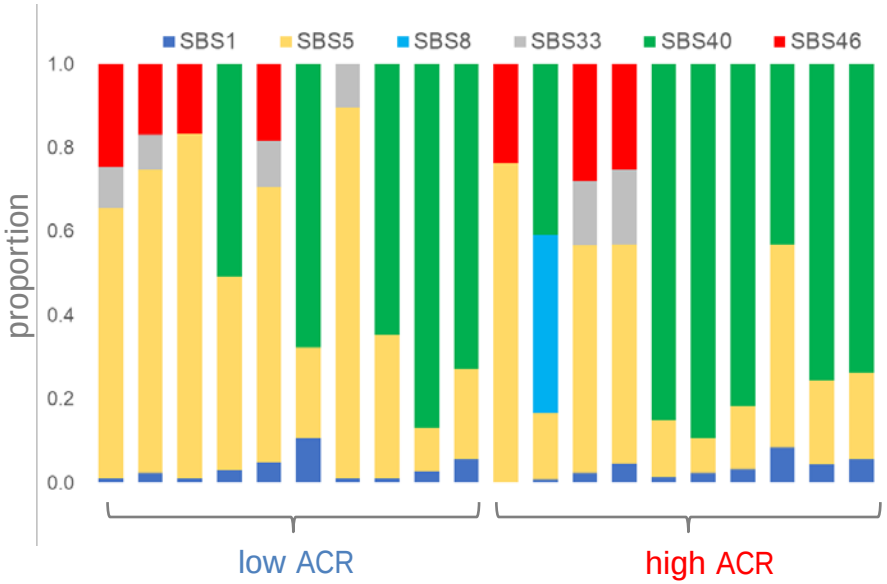
Results

- 3 expected endogenous COSMIC signatures identified: SBS1, SBS5, SBS40
- No exposure-group signature enrichment was observed

COSMIC signatures



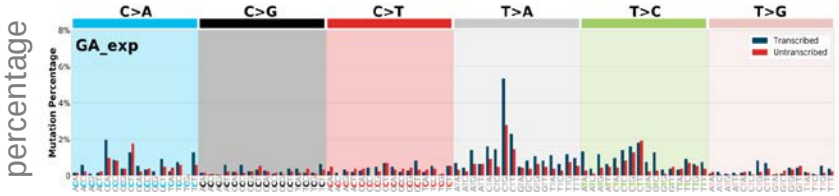
Signature distribution



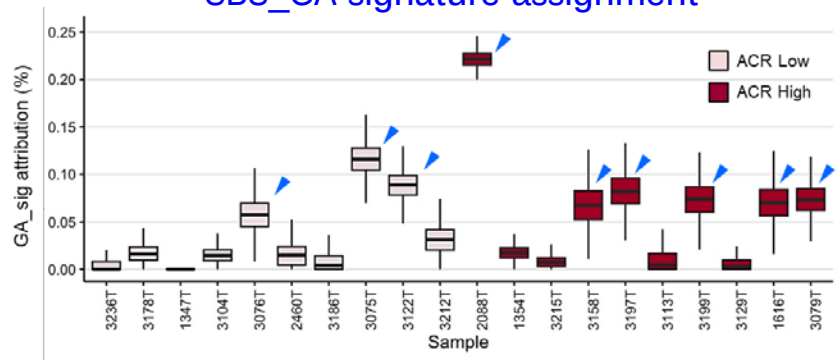
Results

- Signature SBS_GA is found enriched in the high ACR exposure group (2-fold)
- SBS_GA levels can discriminate the exposure groups
- No correlation with sex, age, alcohol or BMI has been observed

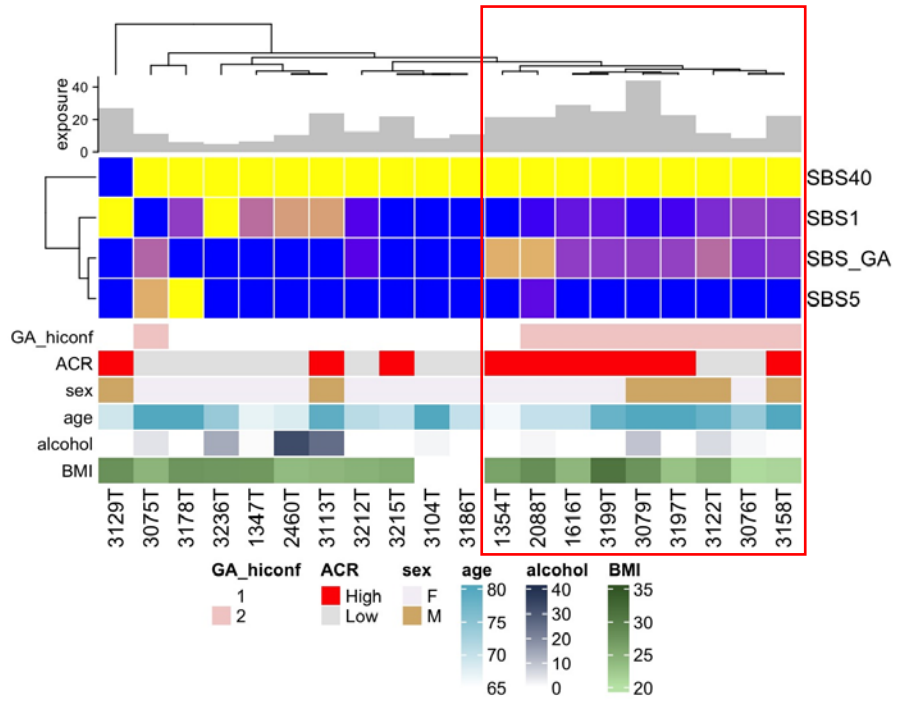
SBS_GA signature (TSB)



SBS_GA signature assignment



Patient-signature clusters



Conclusions

- Our study reveals that the SBS_GA signature enrichment in renal tumors of patients with documented ACR intake history, suggesting contributing effects of dietary ACR
- The findings may have important implications for the planned IARC Monographs evaluation of ACR and GA, and for cancer prevention aimed at the reduction of human exposure to ACR
- The study should be extended to a larger sample set and to other cancers sites

References

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Acknowledgements

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Key take-home message

- Dietary acrylamide generates a specific mutational signature in human kidneys, via the mutagenic effects of glycidamide, its reactive metabolite. This signature contributes to the mutational landscapes of renal tumors and it reflects the past acrylamide intake levels.