Mutographs: Mutational signatures in colorectal cancer from varying-incidence countries reveal new insights in early-onset colorectal cancer

Wellington dos Santos[1], Marcos Diaz-Gay[2], Sarah Moody[3], **Sergey Senkin**[1], Mariya Kazachkova[2], Saamin Cheema[3], **Thomas Cattiaux**[1], Azhar Khandekar[2], Stephen Fitzgerald[3], **Behnoush Abedi-Ardekani**[1], Ammal Abbasi[2], Jingwei Wang[3], **Valerie Gaborieau**[1], Calli Latimer[3], **Christine Carreira**[1], **Priscilia Chopard**[1], Laura Humphreys[3], **Sandra Perdomo**[1], **Ana Carolina de Carvalho**[1], Mike Stratton[3], Ludmil Alexandrov[2], **Paul Brennan**[1]
Cancer Grand Challenges: Mutographs

1. International Agency for Research on Cancer (IARC), France
2. University of California San Diego, US
3. Wellcome Sanger Institute, UK

Email: oliveiraw@iarc.who.int

International Agency
for Research on Cancer

World Health
Organization
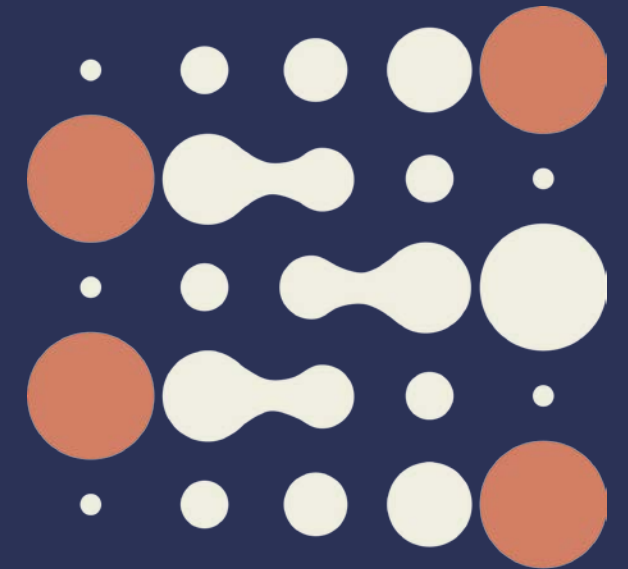
Mutographs: discovering the causes of cancer through mutational signatures

Understanding the causes of cancer by linking exposure and genomic data

Whole-genome sequencing and mutational signature analysis of 5000 cancers across 5 continents.

Mutational signatures: Patterns of mutations in DNA are often linked to mutational process

1

Colorectal cancer (CRC)

- CRC are the **4th most common** cancer worldwide and **3rd in mortality**.
- Overall CRC incidence is **stabilizing** or **declining** in **high-income countries**.
- An **alarming increasing** in CRC incidence **among younger individuals** (<50y).

USA ASR: **all ages**	USA ASR: **0-49y**

- **Known risk factors** for CRC do not seem to explain the increasing incidence in younger patients.

Risk factors with strong evidence

Processed meat

Alcohol

Tobacco

Excess body fatness

*Subnational data from USA
Rates are shown on a semi-log scale
Lines are smoothed by the LOESS regression algorithm (bandwidth: 0.25)
Cancer Over time | IARC - All Rights Reserved 2024 - Data version: 1.0

International Agency for Research on Cancer
World Health Organization

2

Mutographs Project: colorectal cancer series

Aims

- To investigate the **causes of CRC** through **mutational signatures.**
- To investigate the **differences in mutational signatures spectrum across different countries.**

| Whole-genome sequencing |
|---|
| • Mutational signature analysis |

Epidemiologic data
• Lifestyle and environmental exposure information

981 CRC samples from **11 varying-incidence countries**

Mutational signature profile

- When considering **only MSS cases**, **multiple signatures** associated with **known aetiology** were identified:

- **The clock-like (SBS1 and SBS5)** and the **ROS (SBS18)** associated signatures were the dominant contributors of mutational spectrum
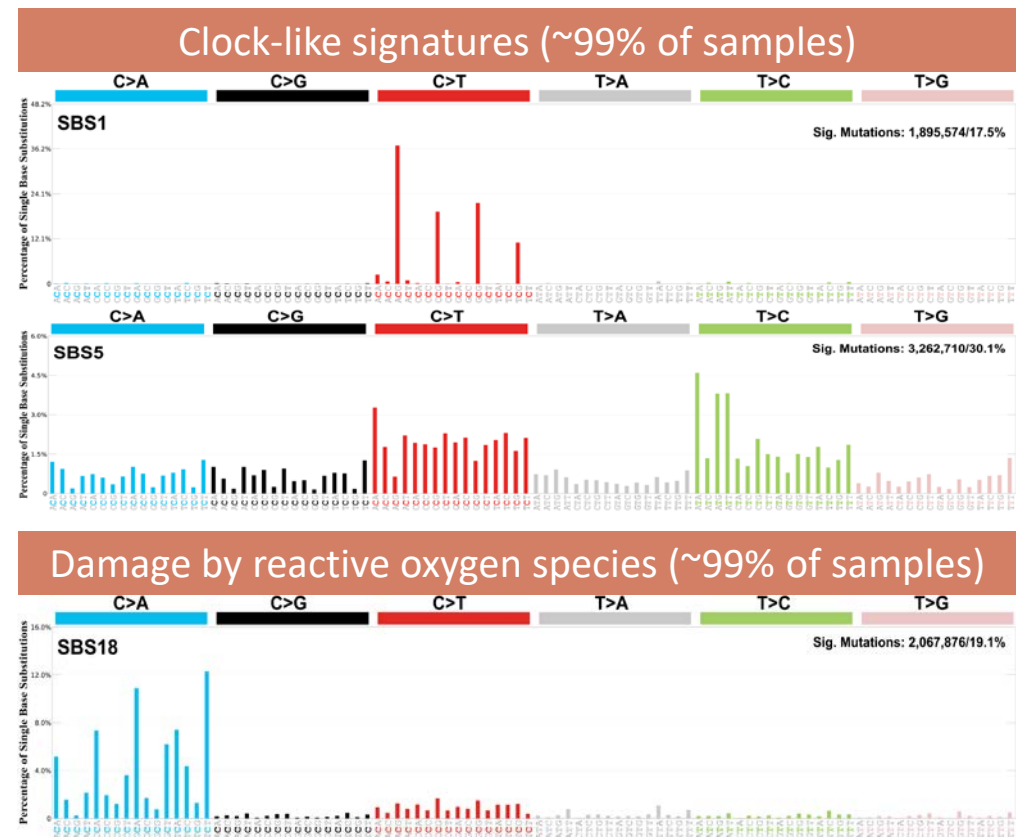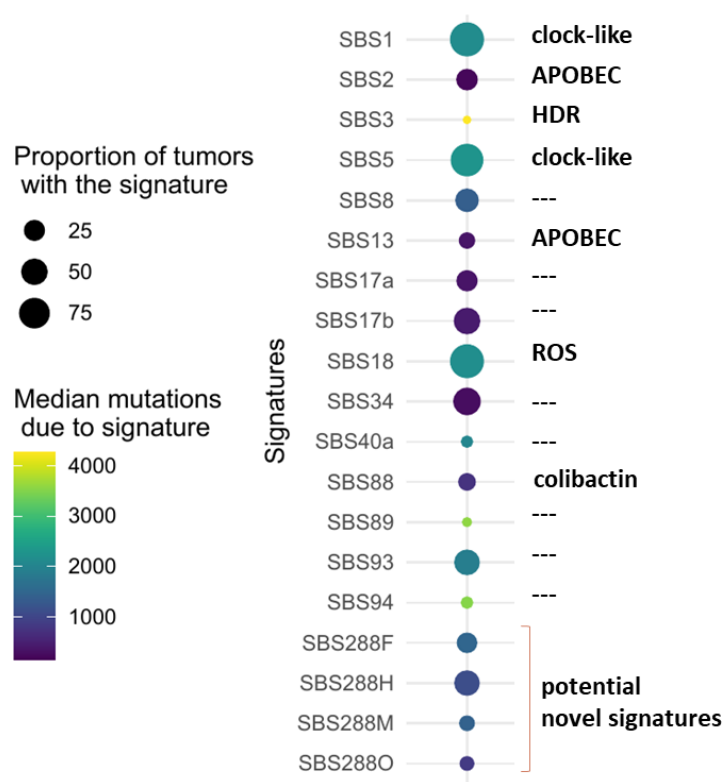
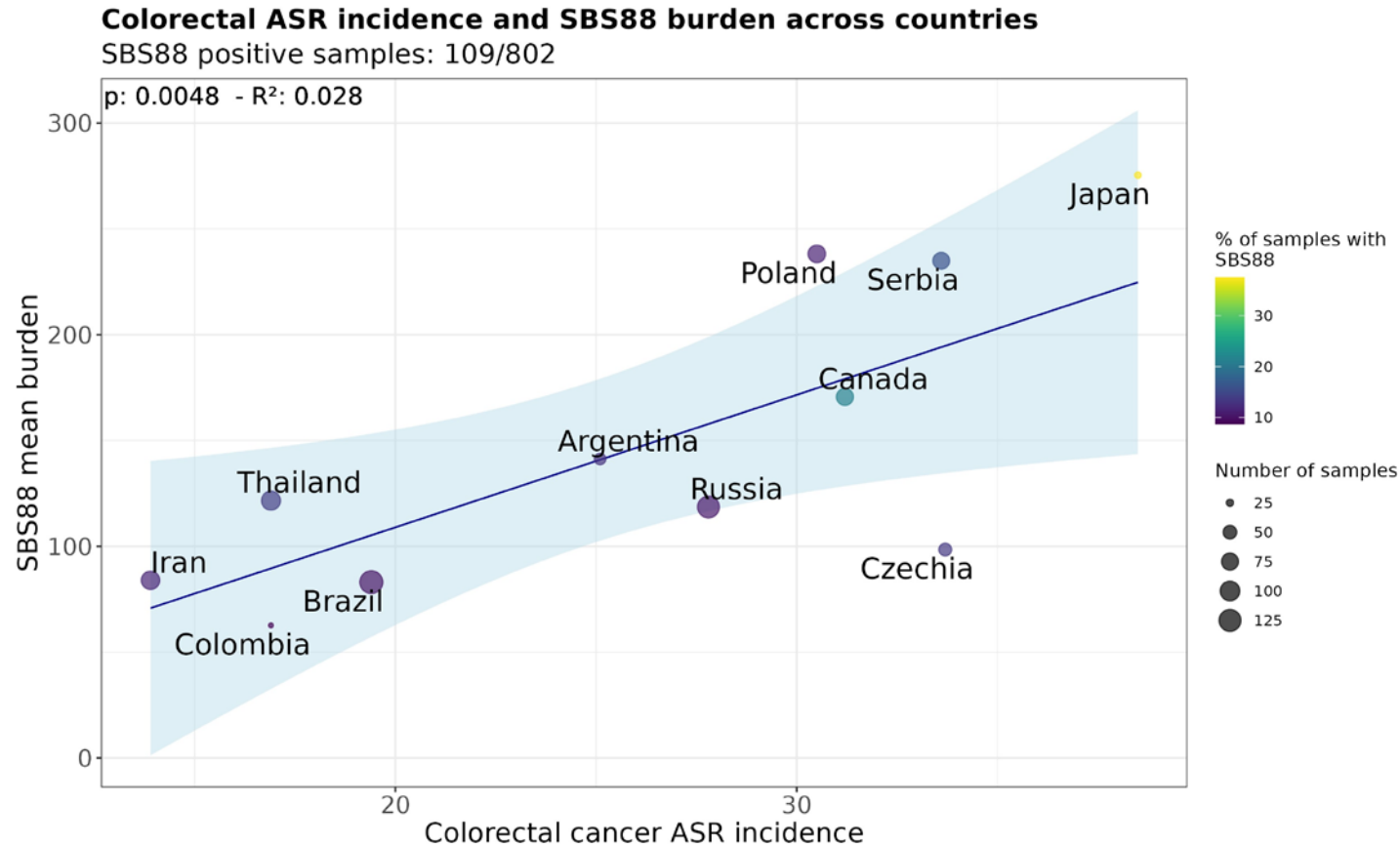# Mutational signature profile: colibactin signature

Colibactin signature (SBS88):

- Results from *pks+ Escherichia coli* exposure.

  (Pleguezuelos-Manzano et al, **Nature**, 2020)

- Found in **normal colorectum** and **tumour tissues**.

  (Lee-Six et al, **Nature**, 2019)

- There is evidence that SBS88 reflects an **early-life exposure.**

  (Lee-Six et al, **Nature**, 2019)
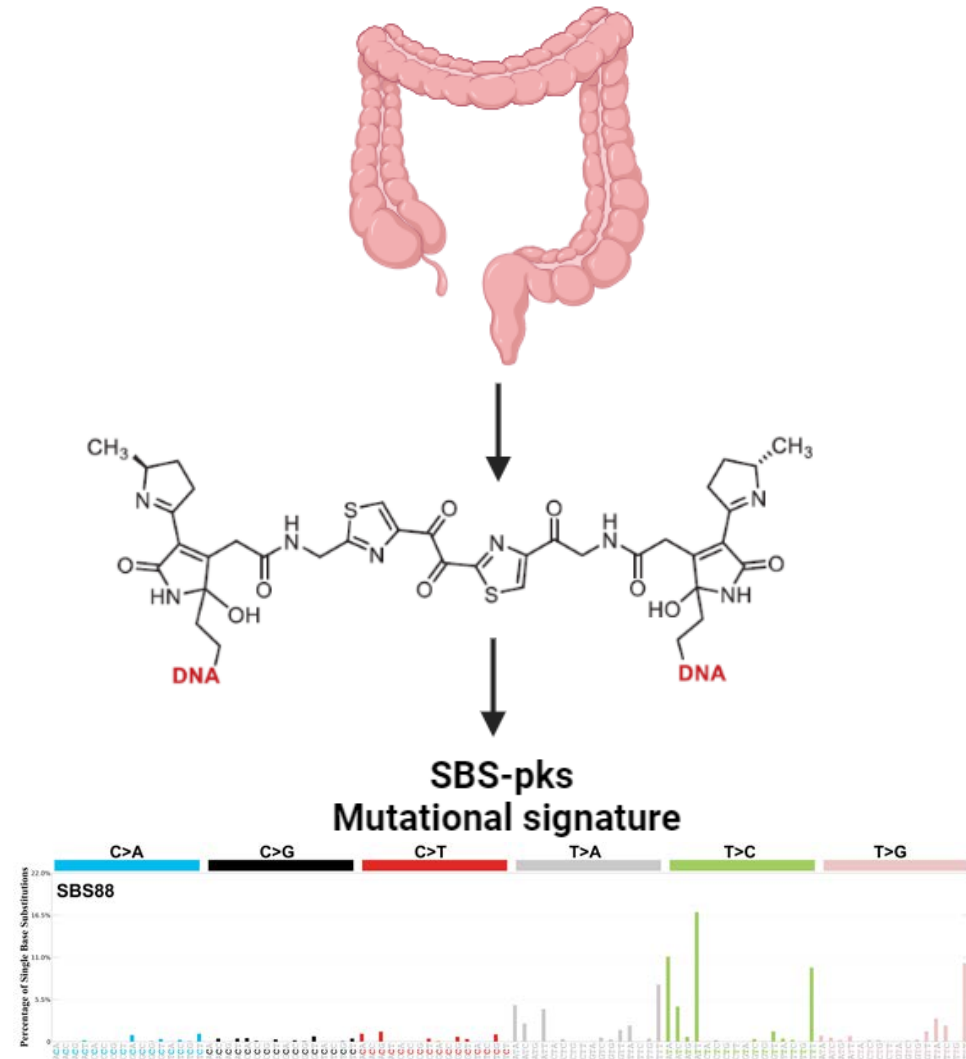
Colibactin signature: association with ASR

- Present in **13.6%** of samples **across all countries** evaluated.
- **Positively correlated** with **CRC age-standardized incidence rates**

Colorectal ASR incidence and SBS88 burden across countries
SBS88 positive samples: 109/802

p: 0.0048 - R²: 0.028

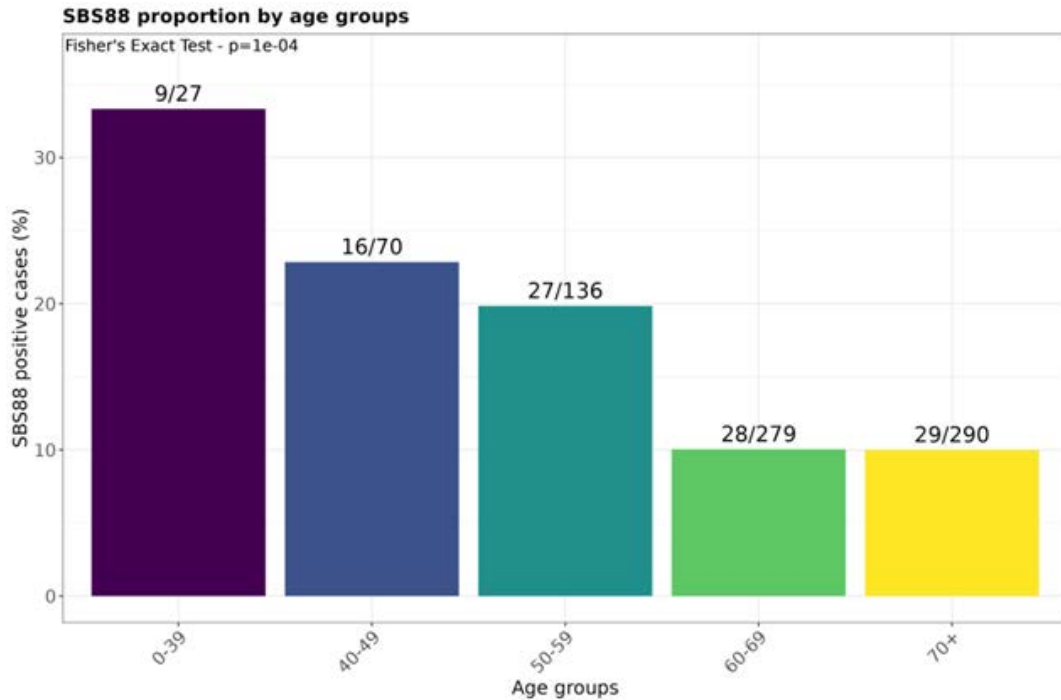# Colibactin signature: association with tumour site

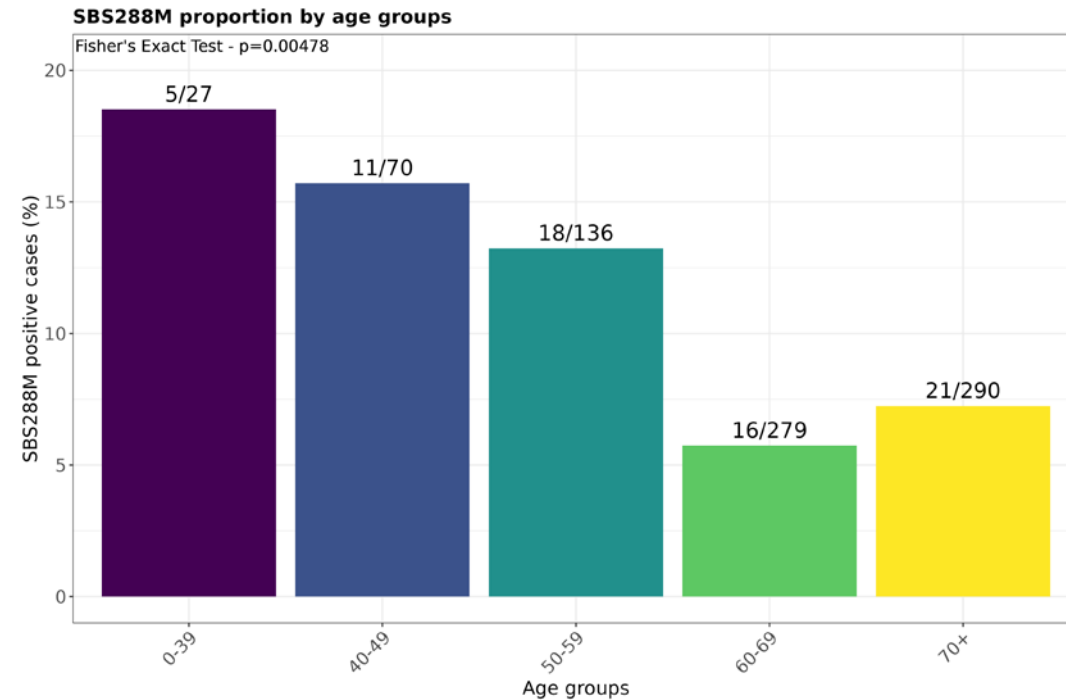**SBS88** was more prevalent in **distal** and **rectum tumours**
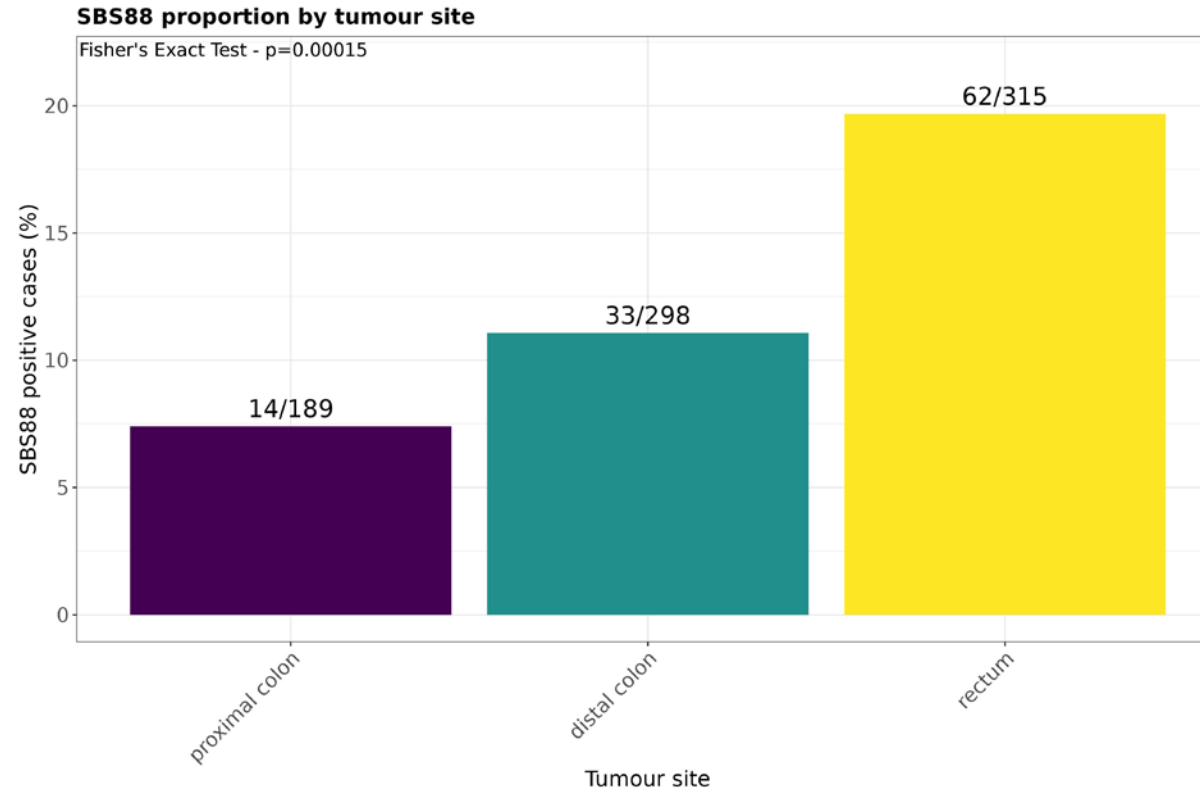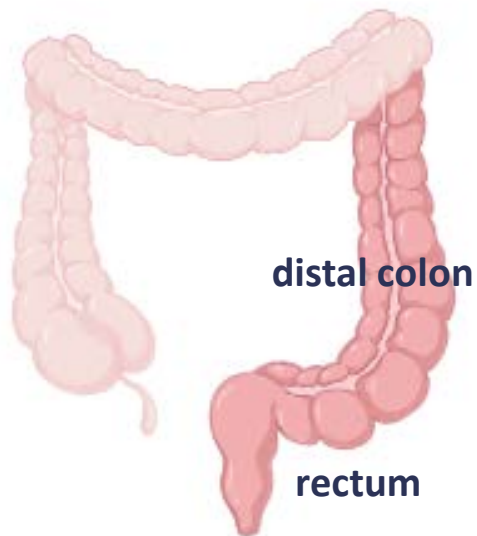
Early onset associated signatures

Colibactin signature **(SBS88)** was significantly **enriched in younger patients**

A potential new signature **(SBS288M)** with unknown aetiology was significantly **enriched in younger patients**

SBS88 proportion by age groups

Fisher's Exact Test - p=1e-04

SBS288M proportion by age groups

Fisher's Exact Test - p=0.00478

Conclusion

❑ *pks+ E.coli* **associated signature** is enriched in **distal and rectum tumours** and correlates with **age-standardized incidence rates**

❑ Two signatures, the *pks+ E.coli* associated signature and a signature with **unknown aetiology**, were **highly enriched** in tumours from **early-onset colorectal patients**

Key take-home message

Mutational signature analysis suggest a potential contribution of *early-age infection with **pks+ E.coli*** and the **increasing incidence** of colorectal cancer in **younger individuals**

Acknowledgements