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1. Laboratorio di Genomica, Fondazione Edo ed Elvo Tempia, Biella (Italy) (https://www.fondazionetempia.org/genomics-lab/)

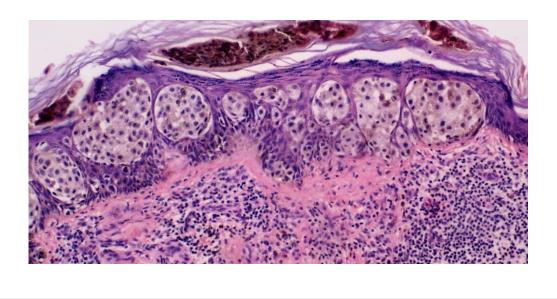2. Department of Clinical and Biological Sciences, Università di Torino (Italy) (https://dott-scsv.campusnet.unito.it/do/home.pl)

Analysis of sex-related biomarkers for early detection of primary melanoma recurrence

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1. Introduction
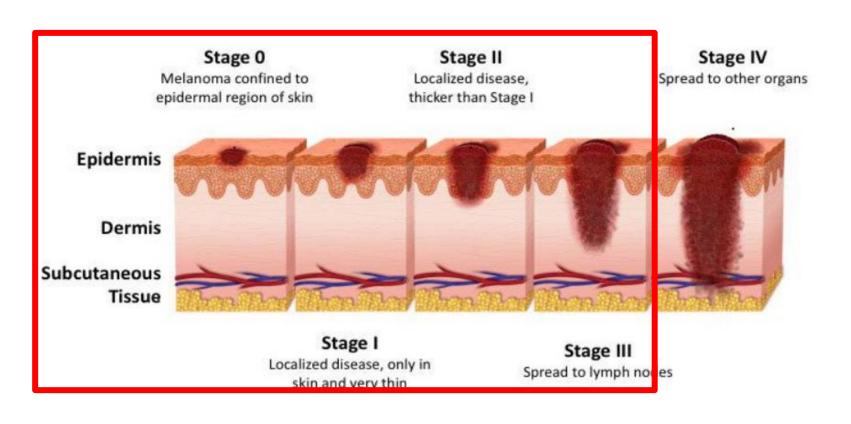
Cutaneous malignant melanoma (CMM)

- It is the most aggressive type of skin cancer
- It is the most metastatic tumor overall
- Men have a higher risk of developing melanoma than females
- There is 1.5x higher risk of mortality in men than in women
- CMM incidence rate increases dramatically with age and becomes 3x more common in males than in females by the age of 70 years old
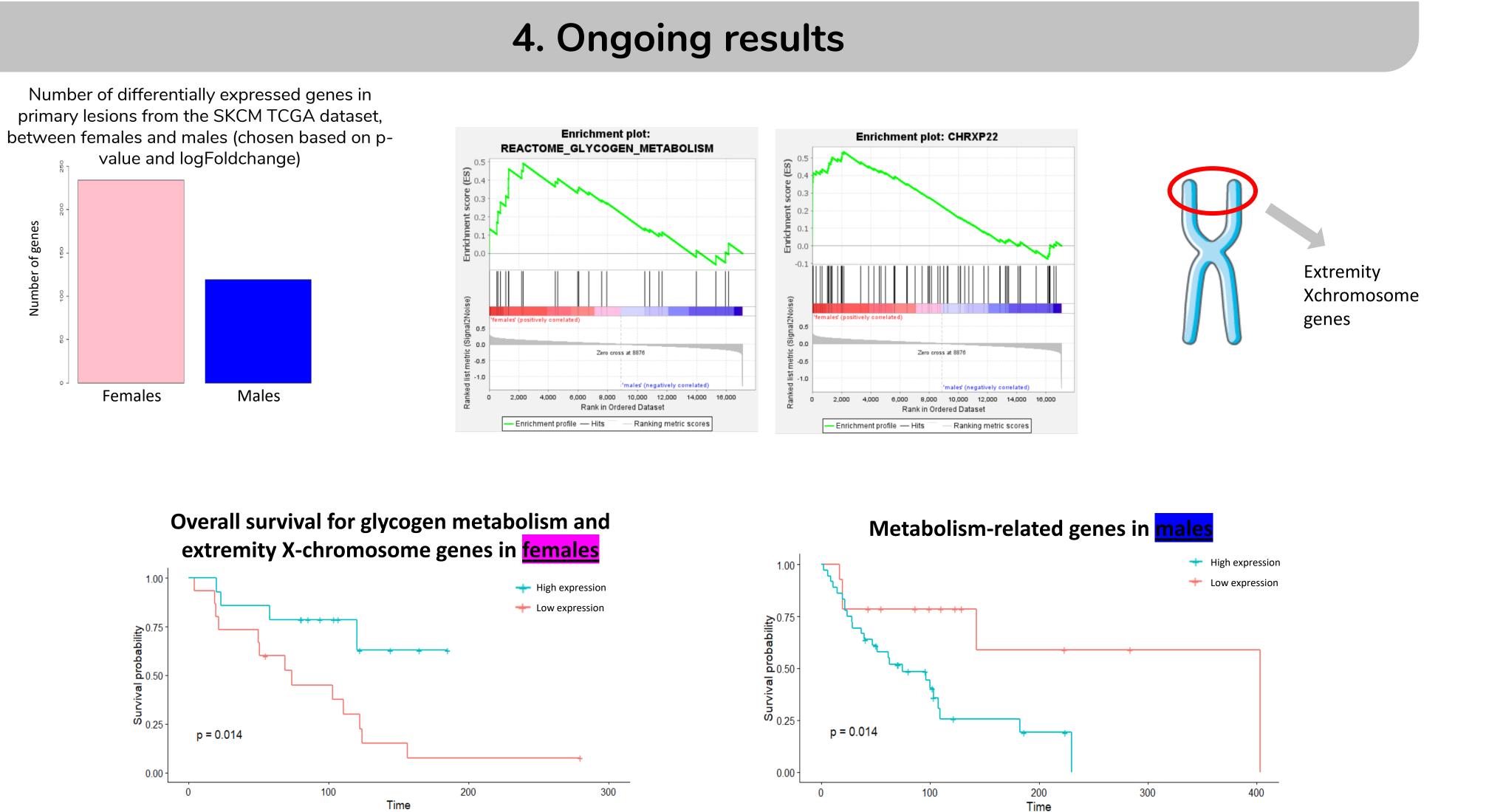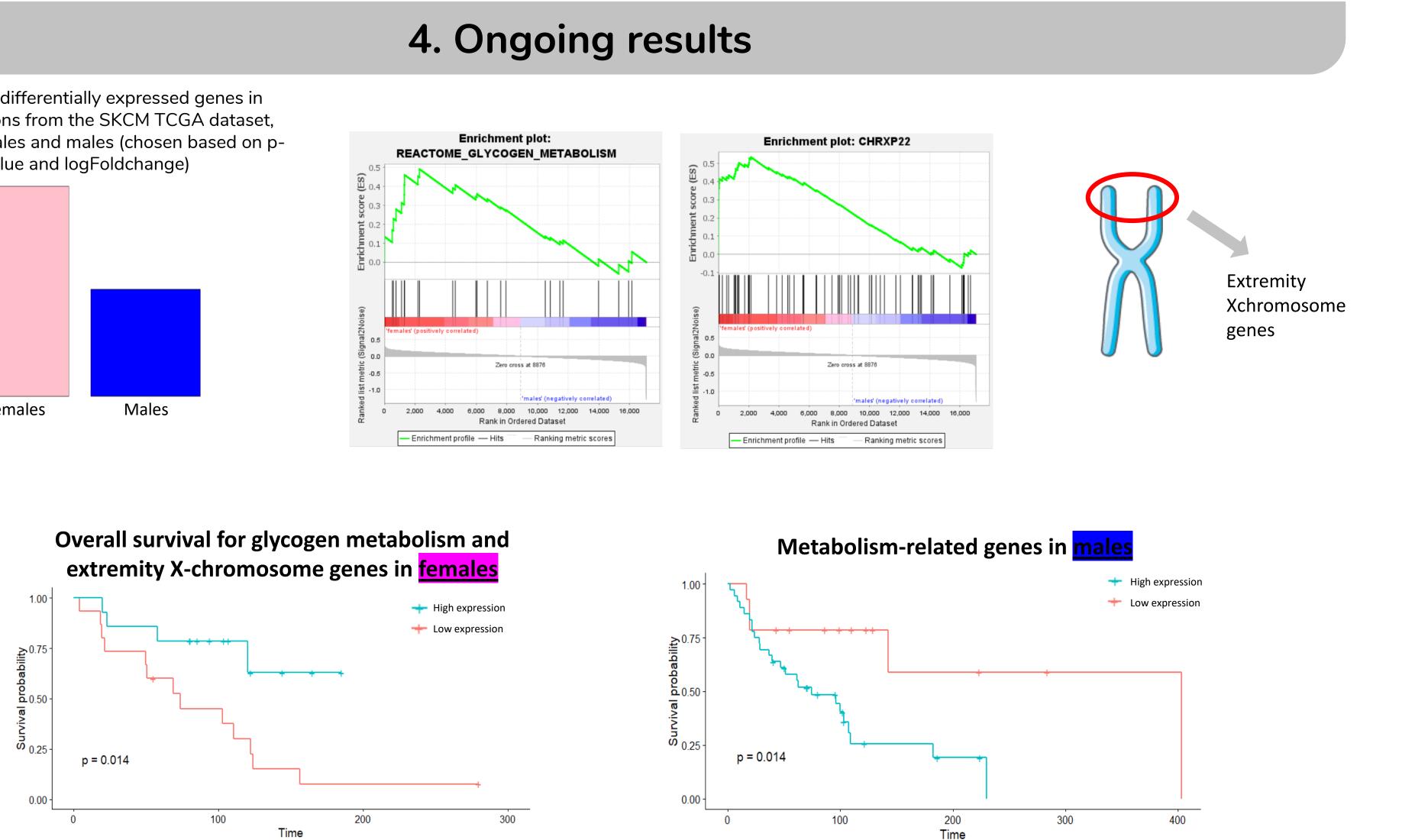
⬆ Mortality rate
⬆ Incidence rate
⬆ Recurrence rate
⬆ Metastatic rate

Data from Australian Institute of Health and Welfare

Figure 6: Lifetime incidence risk, melanoma of the skin, by sex, 1982–2020

Figure 5: Lifetime mortality risk, melanoma of the skin, by sex, 1982–2020

2. Objectives

Use **ONLY** initial stages of Cutaneous Malignant Melanoma (pT1b, pT2, pT3) – primary melanoma samples

1. Understand the role of **sex** in this cutaneous malignant melanoma (based on gene expression and methylation)
2. Identify **quantitative** differences between female and male melanoma patients
3. Identify biomarkers that predict overall survival (OS) and melanoma recurrence/disease free survival(DFS)

Stage 0 Melanoma confined to epidermal region of skin
Stage II Localized disease, thicker than Stage I
Stage IV Spread to other organs
Epidermis
Dermis
Subcutaneous Tissue
Stage I Localized disease, only in skin and very thin
Stage III Spread to lymph nodes

3. Methodology

1. Online available datasets

	Females Nevi	Females Primary Lesion	Males Nevi	Males Primary Lesion

2. Lists of genes groups analyzed

- All **Males** → Nevi **VS** Primary lesion
- All **Females** → Nevi **VS** Primary lesion
- All **Nevi** → **Females VS Males**
- All **Primary lesion** → **Females VS Males**

- Sample's gene expression and methylation separated into **females** and **males**
- Class comparison analysis
- Cox regression survival analysis
- GSEA (gene set enrichment analysis)

4. Ongoing results

Number of differentially expressed genes in primary lesions from the SKCM TCGA dataset, between females and males (chosen based on p-value and logFoldchange)

Number of genes
Females
Males

Enrichment plot: REACTOME_GLYCOGEN_METABOLISM

Enrichment plot: CHRXP22

Extremity Xchromosome genes

3. Identify gender-specific biomarkers

Group of female biomarkers
able to predict overall survival and disease-free survival only in **Females**

Group of male Biomarkers
able to predict overall survival and disease-free survival only in **Males**

4. Validation of biomarkers

Melanoma cell lines
- Overexpression and/or inhibition of selected biomarkers

Melanoma tissue biopsies of females and males
- Immunohistochemistry/in situ hybridization to detect biomarkers
- Association with patient's follow-up

Melanoma plasma samples of females and males
- Analysis of circulating molecular /metabolic biomarkers and sex hormones

Overall survival for glycogen metabolism and extremity X-chromosome genes in **females**
High expression
Low expression
Survival probability
p = 0.014
Time

Metabolism-related genes in **males**
High expression
Low expression
Survival probability
p = 0.014
Time

5. Perspectives

- The selected biomarkers will be further verified in cell lines, human melanoma biopsies and potentially tested in plasma serum of primary melanoma patients.
- The biological and functional role of the biomarkers will be defined.
- The biomarkers' eventual goal is to be used in clinic to personalize patient's follow-up in order to prevent melanoma recurrence and improve overall survival in females and males.
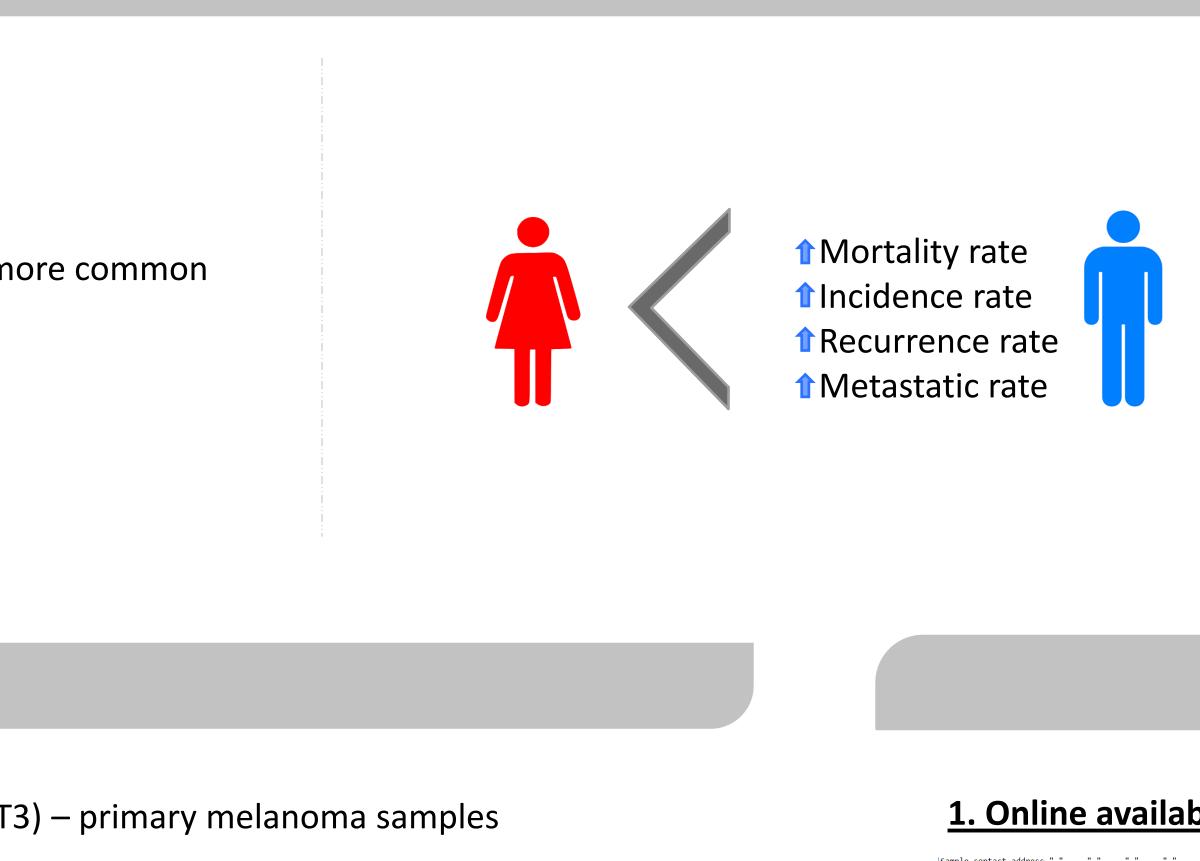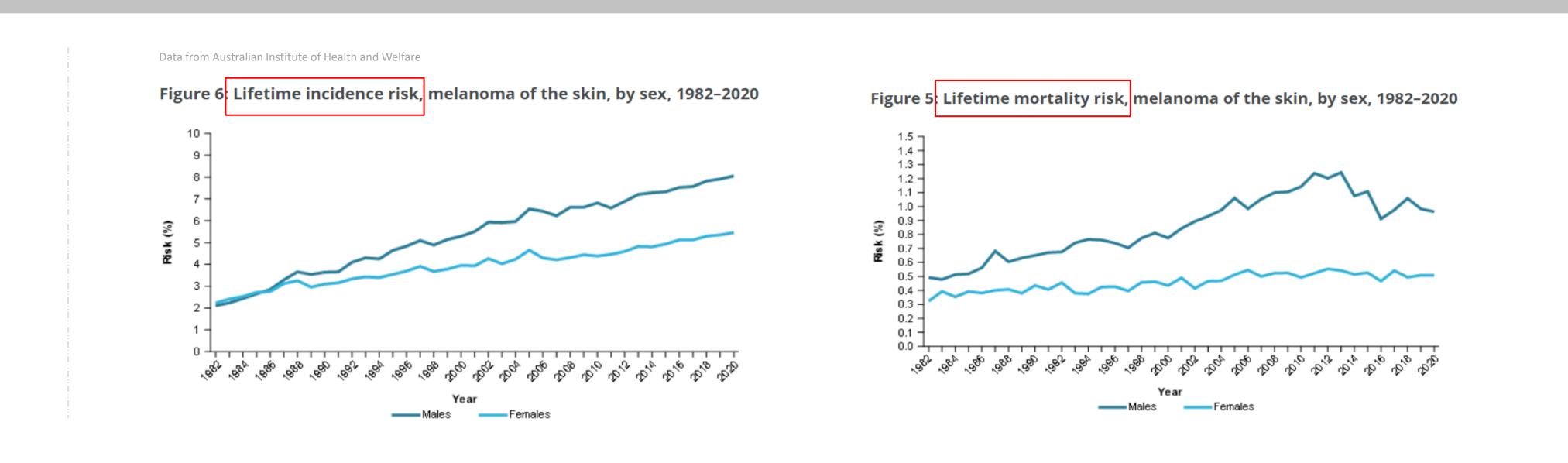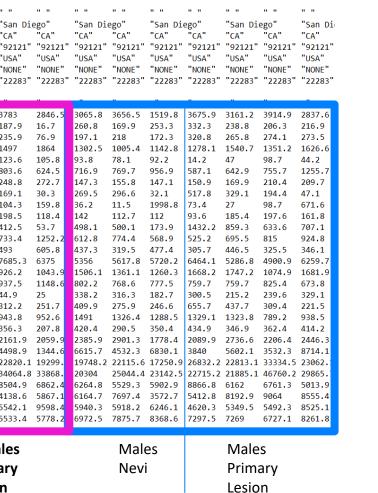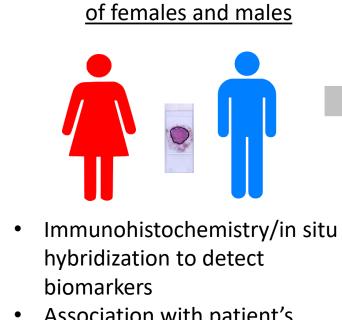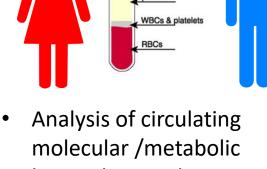
- Based on class comparison and GSEA analysis, X-chromosome extremity genes and glycogen metabolism genes were found to be significantly associated with better overall survival and disease-free survival in underline females
- Metabolism related genes were found to negatively affect overall survival in males

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Abstract

Cutaneous malignant melanoma (CMM) is the most aggressive type of skin cancer and has the highest metastatic rate across all cancers. It is the fifth most common cancer among men and the sixth most common cancer among women CMM has higher mortality, incidence, recurrence, and metastatic rate amongst men compared to women. This project focuses on the understudied field of sexual dimorphism and aims to identify the key factors responsible for the divergence between females and males. Primarily, through online available datasets biomarkers that participate in gene expression, overall survival, and disease-free survival, controversially in the two sexes, will be detected. Furthermore, the identified biomarkers will be verified in melanoma cell lines, tissues biopsies and plasma biopsies of melanoma patients. The biological function of the biomarkers that have this controversial role in females and males, will be further addressed through functional studies. The final goal is to apply these biomarkers in the clinic, in order to personalise patients' follow up aiming at preventing recurrence of melanoma and improving overall survival id females and males.