Exercise 1: Game on multiple testing

Suppose that a researcher tests the association between 7 common diseases (e.g. diabetes, asthma, cancer, multiple sclerosis, thyroid disease, liver disease, arthritis) and 6 candidate "risk factors" (pisces zodiac sign, purple as favorite colour, born between 0:00 and 1:00, red hair, first-name begins with letter 'C', both parents born in summer) based on a large cohort ($n = 10000$). The researcher decides to use chi-square tests to test all $6 \times 7 = 42$ associations and to store the results in a table of the form

	diabetes	asthma	cancer	MS	thyroid D	liver	arthritis
pisces							
purple							
0:00-1:00							
red hair							
firstname C							
summer							

The purpose of this exercise is to convince you that multiple testing is an issue. We will simulate the data of the 10000 patients, assuming for simplicity that each disease has an incidence of 10% in our cohort and that the diseases are independent of each other. Similarly, for the candidate risk factors we assume independence and a frequency of 5% for each. Most importantly, we simulate the data so that there is no true association between risk factors and diseases.

1. Simulate the data set using the R function `rbinom`.

2. Perform each of the $6 \times 7 = 42$ chi-square tests and put a cross in the corresponding cell of the table if the p-value is significant (i.e. < 0.05).

3. How many significant results did you obtain? For which associations? Compare your results with those of your class mates.

4. Simulate another data set ($n = 10000$) using the same code (replication) and look whether the associations you found significant on the first data set are again significant with this one.

Exercise 2: Bonferroni and Holm procedures

Suppose we perform 10 tests (e.g. test the association between 10 different outcomes and a potential prognostic factor) and obtain the p-values 0.0140, 0.2960, 0.9530, 0.0031, 0.1050, 0.6410, 0.7810, 0.9010, 0.0053, 0.4500.

1. Which hypotheses are rejected after Bonferroni correction?

2. Order the p-values.

3. Which hypotheses are rejected after Holm correction?

Exercise 3: Multiple testing with R
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1. Load the data set 'CLL' and look at the first rows and columns to understand its structure.

2. For each of the 12625 genes, test whether its mean expression is equal for patients with stable and progressive disease and store the corresponding p-value.

3. Compute "by hand" the adjusted p-values using Bonferroni's correction method.

4. How many hypotheses are rejected without correction and with Bonferroni correction?

5. Compute the adjusted p-values using Bonferroni's correction, Holm's correction and Benjamini-Hochberg's correction as implemented in the function `p.adjust`. Compare these p-values among themselves and with the Bonferroni p-values calculated above.

6. How many hypotheses are rejected with each of the correction methods?