Part A – Main effects of genetic variation and interaction with smoke exposure

**Step 1**: Are GSTM2-5 diplotypes influencing methylation of CpG sites in GSTM2-5 cluster?

**YES**

**NO**

**Reject CpG site**

**Step 2**: Are GSTM2-5 SNPs influencing lung function growth during adolescence?

**Step 3**: Are smoke exposures modifying the effect of GSTM2-5 diplotypes on lung function growth during adolescence?

**Step 4**: Are GSTM2-5 CpG site methylation levels modifying the effect of GSTM2-5 diplotypes on lung function at age 18?

**YES**

**NO**

**No further analysis needed**

Part B – Main effects of epigenetic variation and interaction with genetic variation

**Step 1**: Are GSTM2-5 diplotypes influencing methylation of CpG sites in GSTM2-5 cluster?

**YES**

**NO**

**Reject CpG site**

**Step 2**: Are methylation levels in GSTM2-5 CpG sites associated with GSTM2-5 diplotype-smoke interaction?

**YES**

**NO**

**Reject CpG site**

**Step 3**: Are methylation levels in GSTM2-5 CpG sites associated with lung function at age 18?

**YES**

**NO**

**Step 4**: Are GSTM2-5 CpG site methylation levels modifying the effect of GSTM2-5 diplotypes on lung function at age 18?