CLAIMS

1. A method for the diagnosis and/or prognosis of drug resistance, wherein single cell chromatin states are profiled in cells obtained from a subject by using a microfluidic system, wherein chromatin states comprise DNA and/or histone modifications, wherein the emergence of the drug resistance can be due to epigenetic heterogeneity, the method comprising the steps of:

a. providing at least a droplet of first type, wherein said droplet of first type comprises:

i. a biological element,

ii. a lysis buffer, and

iii. a nuclease,

b. collecting said droplet of first type under conditions that temporarily inactivate said nuclease, wherein the conditions comprise selecting a temperature degree ranging from -20°C to 10°C,

c. incubating said droplet of first type, thereby reactivating said nuclease, wherein incubating comprises selecting a temperature degree ranging from 20°C to 40°C,

d. providing at least a droplet of second type, wherein said droplet of second type comprises a nucleic acid sequence,

e. merging said droplets of first and second type, thereby generating a droplet of third type,

f. incubating said droplet of third type, thereby linking said nucleic acid sequence to one or more genomic region(s) of interest, and

g. sequencing said one or more genomic region(s) of interest,

wherein the one or more genomic region(s) of interest includes one or more modified genomic region(s),

wherein drug resistance is determined by loss of epigenetics marker at genomic regions that promote drug resistance.

2. The method according to claim 1, wherein the drug resistance might be an emerging drug resistance and/or a present drug resistance.

3. The method of claim 1 or claim 2, wherein the modified genomic region comprises a nucleic acid sequence and/or a protein complex associated with a nucleic acid sequence, wherein the modified

genomic region comprises a post-translational modification and/or a histone variants and/or modified DNA sequence.

4. The method of claim 3, wherein the modified DNA sequence is selected from the group comprising methylation and its derivatives, modified nucleotides like EdU, BrdU, ldU, CldU, methylation of cytosines and adenines, resulting in 5mC, N4-methylcytosine (N4mC), or 6-methyladenine (6mA), 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC).

5. The method of any one of the preceding claims, wherein the cells are derived from a subject in a diseased state and/or suspected to be in a diseased state or in a healthy subject.

6. The method of claim 5, wherein the diseased state comprises cancer, infectious disease, auto-immune disease, metabolic disease, inflammation disease, genetic and non-genetic diseases.

7. The method of claim 5, wherein the cells are untreated and/or treated or wherein the subject is untreated or treated.

8. The method of any one of the preceding claims, wherein the diagnosis and/or prognosis of drug resistance in said subject is performed before, during, or after said subject underwent a treatment or therapy, or at any other time point.

9. The method of claim 8, wherein the treated cells from the treated subject are treated with a chemotherapeutic drug, a chemical drug, or biologic drugs.

10. The method of claim 1, wherein the chromatin marks are histone modifications H3K4me3 and H3K27me3.

11. A method of identifying one or more genomic region(s) of interest using a microfluidic system, the method comprising the steps of:

a. providing at least a droplet of first type, wherein said droplet of first type comprises:

i. a biological element,

ii. a lysis buffer, and

iii. a nuclease,

b. collecting said droplet of first type under conditions that temporarily inactivate said nuclease, wherein the conditions comprise selecting a temperature degree ranging from -20°C to 10°C,

c. incubating said droplet of first type, thereby reactivating said nuclease, wherein incubating comprises selecting a temperature degree ranging from 20°C to 40°C,

d. providing at least a droplet of second type, wherein said droplet of second type comprises a nucleic acid sequence,

e. merging said droplets of first and second type, thereby generating a droplet of third type,

f. incubating said droplet of third type, thereby linking said nucleic acid sequence to at least one genomic region(s) of interest, and

g. sequencing said one or more genomic region(s) of interest.

12 The method of claim 11, wherein the modified genomic region comprises a protein complex associated with a nucleic acid sequence and/or a nucleic acid sequence.

13. The method of claim 12, wherein the modified genomic region comprises a post-translational modification selected from the group comprising acetylation, amidation, deamidation, carboxylation, disulfide bond, formylation, glycosylation, hydroxylation, methylation, myristoylation, nitrosylation, phosphorylation, prenylation, ribosylation, sulphation, sumoylation, ubiquitination and derivatives thereof.

14. The method of claim 12 or claim 13, wherein the nucleic acid sequence is asymmetrically linked to said at least one or more genomic region(s) of interest.

15. Use of a nucleic acid sequence comprising:

a. at least one index sequence,

b. a sequencing adaptor, and

c. at least one protecting function positioned at 3'- and/or 5'-end.

16. The use of claim 15, wherein said nucleic acid sequence further comprises at least one cleavage site.

17. The use of claim 16, wherein the at least one cleavage site is a restriction site comprising a palindromic region.

18. The use of claim 15 or claim 16, wherein the protecting function is selected from the group comprising a spacing element on a 3'-end and a dideoxy-modified base on 5'-end, or inversely.