

Epigenetic Biomarkers & Biobanking

Despite significant effort, understanding the causes and mechanisms of complex disorders remains a key challenge. In recent years, new discoveries have led to a rethinking of the classical models of age-dependent diseases, shifting the emphasis from genetic causative factors to epigenetic and environmental effects. One of the main bottlenecks in large scale epigenetic research is the availability of suitable tissues that can be used to study biomarkers in complex diseases. The "Blood Donor *Biobank*" may offer a unique resource for studying such epigenetic biomarkers.

Epigenetic drift & complex diseases

Why epigenetic markers? → The **theory of age-dependent epigenetic drift** suggests that, among other causes, aging results from progressive accumulation of epigenetic damage as a direct consequence of evolved limitations in the genetic and epigenetic settings of maintenance and repair functions [1]. Mammalian aging is a complex individual phenotype arising from a variety of risk factors, such as environmental effects, nutrition or stochastic fluctuations, among others, which increase epigenetic variability with age (Fig. 1). Deleterious epigenetic drift occurring after the reproductive phase is relatively neutral to evolutionary selection, because their bearers have already transmitted their (epi)genetic information to the next generation.

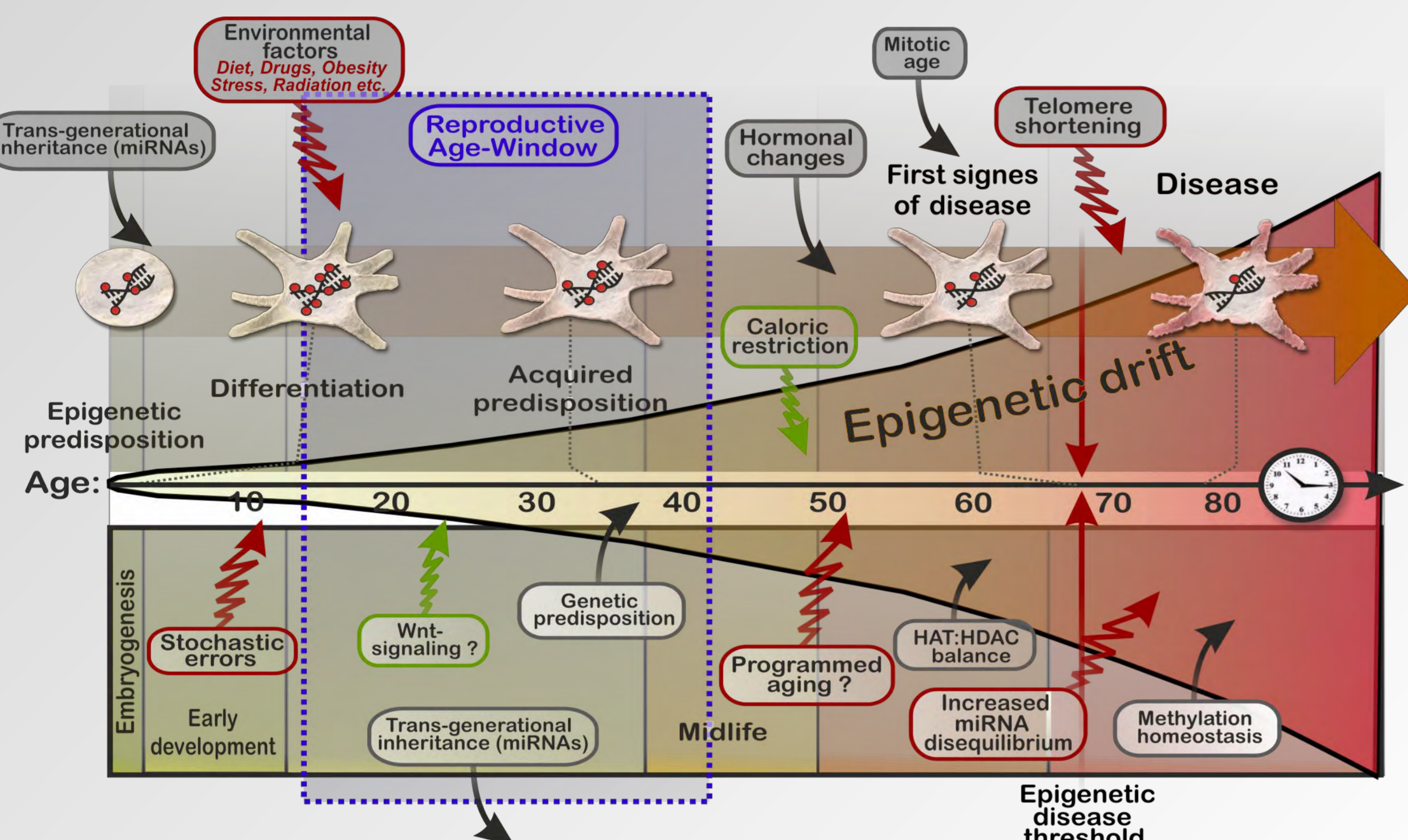


Fig. 1: Model of epigenetic drift. The phenotypic outcome of epigenetic drift depends on the overall effect of the series of pre- and post-natal impacts on the pre-epimutation. Only some predisposed individuals will reach the "threshold" of epigenetic deregulation that causes the phenotypic changes that meet the diagnostic criteria for a clinical disorder. (After A. Schumacher 2010 [1])

What to do with the data? → One approach for disease prevention would be the adjustment of an individual's epigenome before the critical threshold of epigenetic deregulation is reached. There are many lines of evidence that lifestyle interventions and drugs may inhibit or at least postpone the onset of age-related disorders. This is the case for various cancers, where early diagnosis is essential, but treatment becomes very complicated after a certain threshold (i.e. metastasis) is crossed. Prime targets for interventions on epigenetic levels are also the very common disorders, i.e. **Type II Diabetes** and **Alzheimer Disease**. Such intervention potentials underscore the need for **early diagnostic markers** in age-dependent disorders, and epigenetic markers may be excellent tools for development of an efficient treatment strategy.

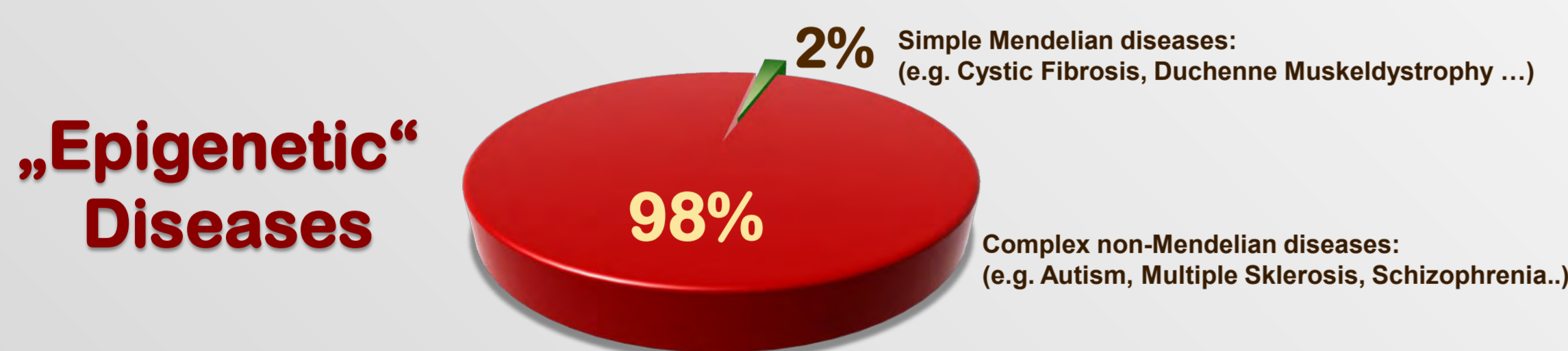
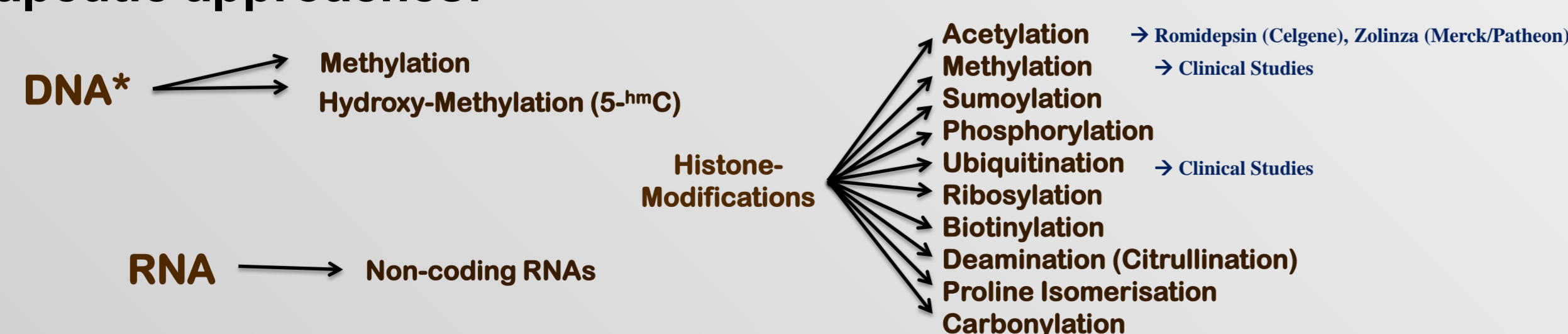


Fig. 2: The vast majority of common diseases, are not simple (2%), but rather complex, non-Mendelian diseases (98%)

Which targets? → The list of important epigenetic targets grows steadily, and only a subset of those is currently used for diagnostic or therapeutic approaches:



Analyses do not have to be restricted to epigenetic components, in fact **ANY downstream biomarker that changes in time due to modifications in the epigenetic machinery can serve as marker for epigenetic drift.**

Biobanking for epigenetic analyses

An ideal strategy for epigenetic biomarker research would consist of:

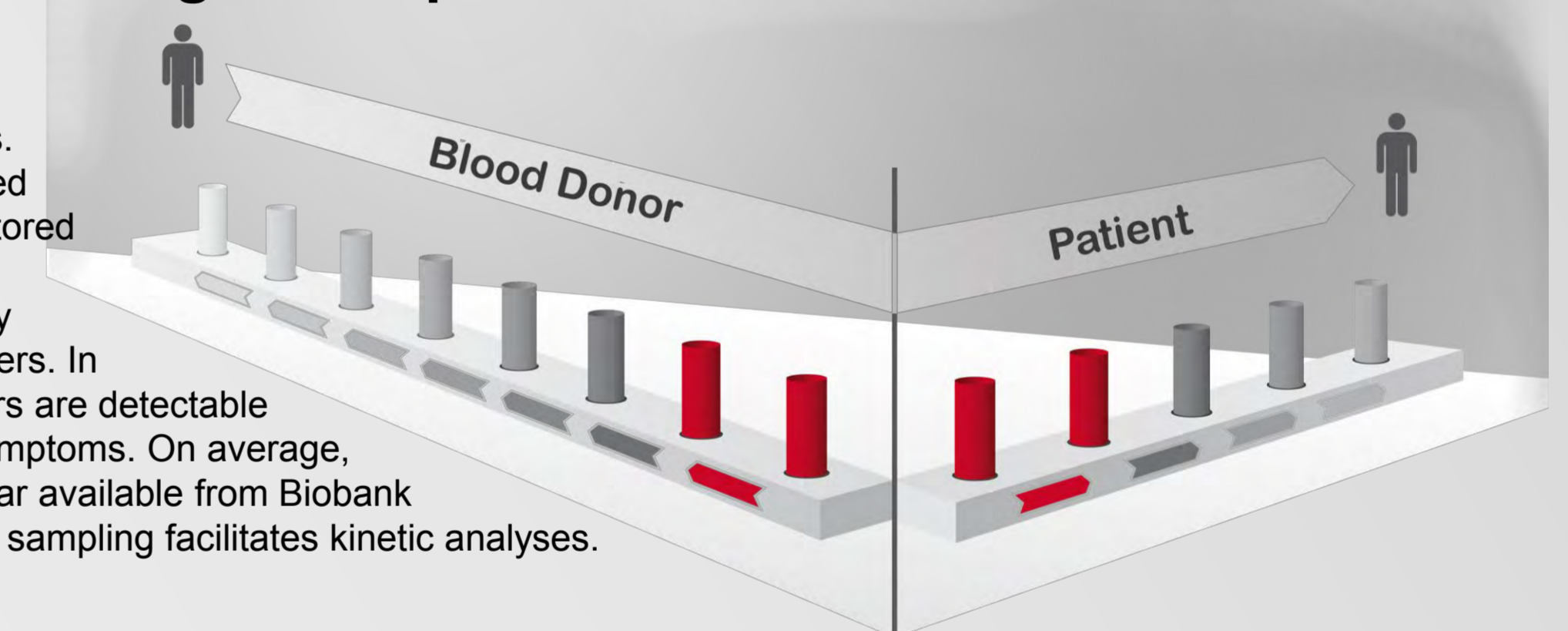
- Easy Accessible Samples (e.g. Blood or Saliva)** covering a
- Large Variety of Diseases** for validation purposes, that were already collected prior to disease onset.
- Large pool of control samples**

To avoid interindividual epigenetic variation, tissues should represent

- Retrospective, Serial Tissue Samples (Same Individuals)** Collected in high quality
- Standardized Processes**

Serial blood samples are a logical resource as they are collected regularly. The **Bavarian Red Cross Bloodbank** maintains such an unrivalled collection of over 4.5 million blood samples stored under standardised conditions. A pool of more than 400,000 regular blood donors allows for the conduction of large scale prospective studies. Annually, about 2,000 donors are diagnosed with severe diseases. Their previously stored **prediagnostic plasma samples**, obtained in regular time-intervals before diagnosis, represent unique resources for the identification of early diagnostic markers that will facilitate many aspects of **personalized medicine**. The obtained markers are valuable tools for earlier diagnosis, preventive strategies and drug development.

Fig. 3: Serial, pre-diagnostic plasma samples from blood donors with diseases. Numerous blood samples may be examined from one person, which were taken and stored before the diagnosis. Classically, disease samples have been compared to a healthy reference group when examining biomarkers. In the serial approach, changes of biomarkers are detectable potentially long before manifestation of symptoms. On average, There are 2 serial plasma samples per year available from Biobank participants. This high frequency between sampling facilitates kinetic analyses.



The advantage of using a bloodbank samples is that the blood donors usually represent the general population [3], facilitating large scale epidemiological studies. Although DNA concentrations in plasma are low, recent advances in DNA screening technologies should enable the interrogation of typical blood cancer markers such as DNA methylation or the recently discovered 5-hydroxymethylcytosine (hmC)*. hmC may be a suitable marker for certain forms of leukemia [4].

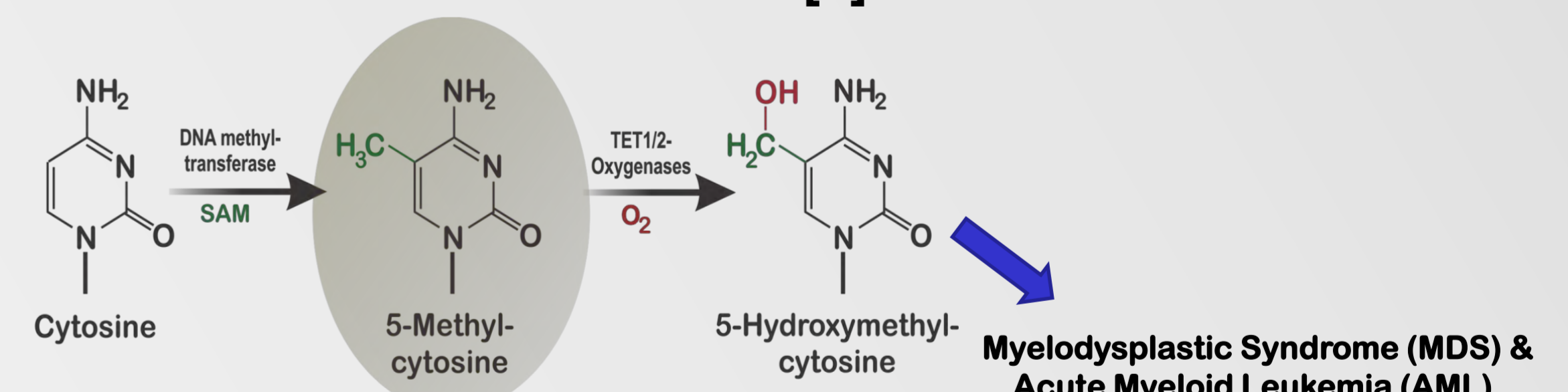


Fig. 4: hmC as diagnostic marker. This DNA modification is essential for myelopoiesis and low hmC may cause tumor development. hmC could be a suitable biomarker for diagnostic purposes, prognosis and response after treatment.

The Blood Donor Biobank would like to contribute to the development of improved diagnostic and therapeutic approaches by making its resources available to medical research. If you are interested in a pilot epigenetics project, please do not hesitate to contact us.

Outlook

- Recent advances in screening technologies, such as single cell epigenetics, single cell whole genome amplification and microfluidics protocols for analysis of the proteome, make exploitation of markers that reflect epigenetic drift a reality.
- Epigenetic profiles may help in the identification of suitable therapies.
- Understanding epigenetic drift will help in rational drug design.
- Pharmacoepigenetic studies may predict age-dependent changes in the epigenome and hence will facilitate better personalized medicine.

