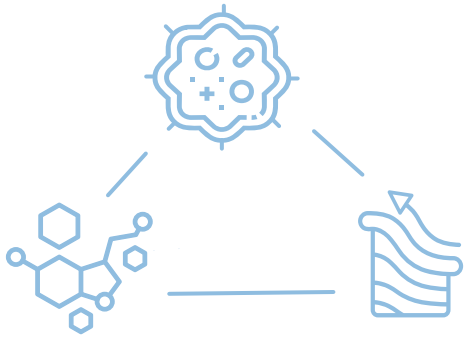
YOUR MITOTIC CLOCK REPORT

And The Epigenetic Timer Of Cancer

TruDiagnostic™
The Epigenetic Company

The link between cellular replication and cancer: **The "Bad Luck" Hypothesis**

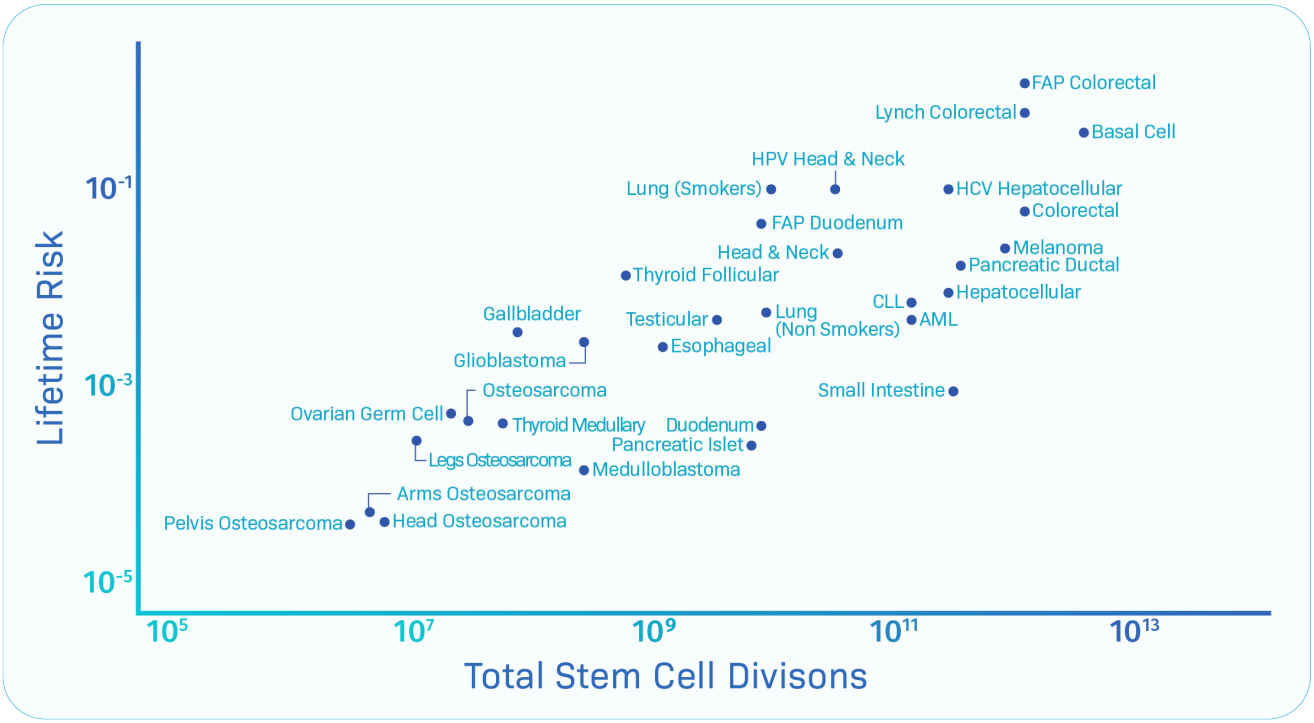


Some tissue types give rise to human cancers millions of times more often than other tissue types. For example, the lifetime risk of being diagnosed with cancer is 6.9% for lung, 1.08% for thyroid, 0.6% for brain and the rest of the nervous system, and 0.003% for pelvic bone.

Some of these differences are associated with well-known risk factors such as smoking, alcohol use, ultraviolet light, or human papilloma virus (HPV). However, such exposures cannot explain why cancer risk is so vastly different in different tissues. Cancers of the small intestinal epithelium are three times less common than brain tumors, even though small intestinal epithelial cells are exposed to much higher levels of environmental mutagens than are cells within the brain, which are protected by the blood-brain barrier. Therefore, the main driver is probably not environmental exposures.

Another well-studied contributor to cancer is inherited genetic variation. However, only 5 to 10% of cancers have a heritable component, and even when hereditary factors in predisposed individuals can be identified, the way in which these factors contribute to differences in cancer incidences among different organs is difficult to determine. Therefore, genetics are probably not the main driver.

A study by Andrew Teschendorff, PhD found that inflammatory conditions also increased mitotic rates in tissue (Teschendorff 2020). ***Increased mitotic rates measured with this algorithm could also indicate stem cell depletion.***

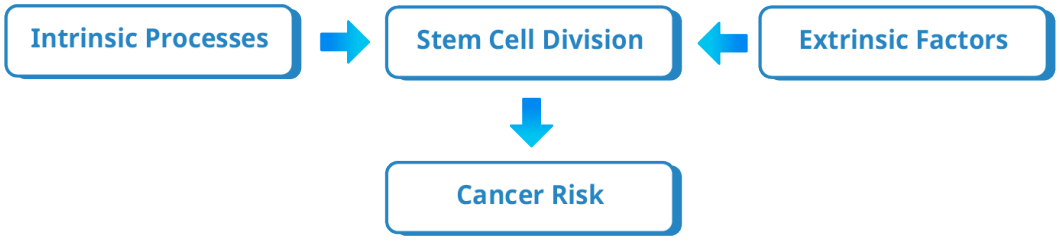


If hereditary and environmental factors cannot fully explain the differences in organ-specific cancer risk, how else can these differences be explained?

In 2016, a paper tried to explain why cancer risk is so different in some tissues than others. The research done by a group at Johns Hopkins (Tomasetti, Et. al), showed that the lifetime risk of cancers of many different types is strongly correlated (r2=0.81) with the total number of divisions of the normal self-renewing cells maintaining that tissue's homeostasis.

These results suggest that only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions. The rest is due to the "Bad Luck Hypothesis". This hypothesis points out that your cells are statistically more likely to make mistakes while copying DNA when they are replicating more often. As these mistakes accumulate, they can lead to cancer. Unfortunately, some of us just have bad luck and have more of these (intrinsic) errors than others.

"Intrinsic processes" include those that result in mutations due to random errors in DNA replication. "Extrinsic factors" are environmental factors that affect mutagenesis rates (such as UV radiation, ionizing radiation, and carcinogens).



How do I know how many stem cell divisions I have?

Cells replicate in a process called mitosis, where the DNA is fully copied during cell division. This process is fundamentally important to our survival, since cell replication is necessary for growing, healing and repairing our tissues. As time passes we end up creating trillions of cells, each with a tiny risk of making a mistake during cell division. With each small mistake our risk of cancer also slowly increases.

So how do we measure how much our cells are turning over? With epigenetic based mitotic clocks.

The Mitotic Clock score is estimated by looking at 385 locations (PCGT/PRC2-marked promoter CpGs) that are unmethylated at birth, but gain DNAm as chronological age increases. The algorithm to sort through this data was trained on a large cohort of healthy individuals, as assessed in one tissue type (blood). You can read the algorithm itself below.

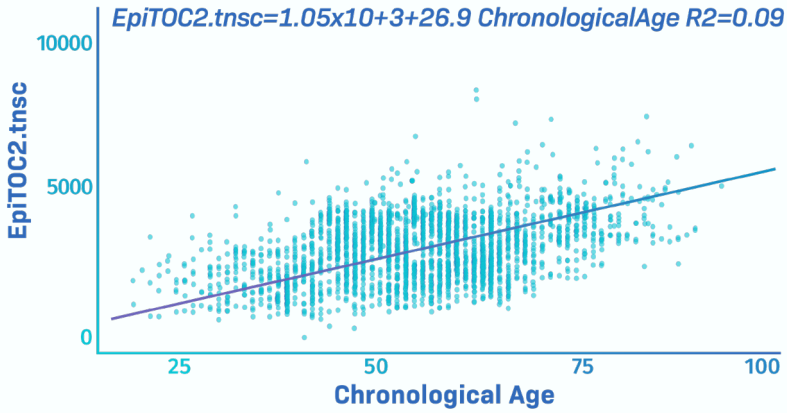
$$TNSC(s) = \frac{1}{n}\sum_{i=1}^{n} w_i \beta_{is} = \frac{1}{n}\sum_{i=1}^{n} \frac{2\,\beta_{is}}{\delta_i}$$

YOUR RESULTS:

Your ***cumulative number of stem cell divisions*** per stem cell per year:

3001

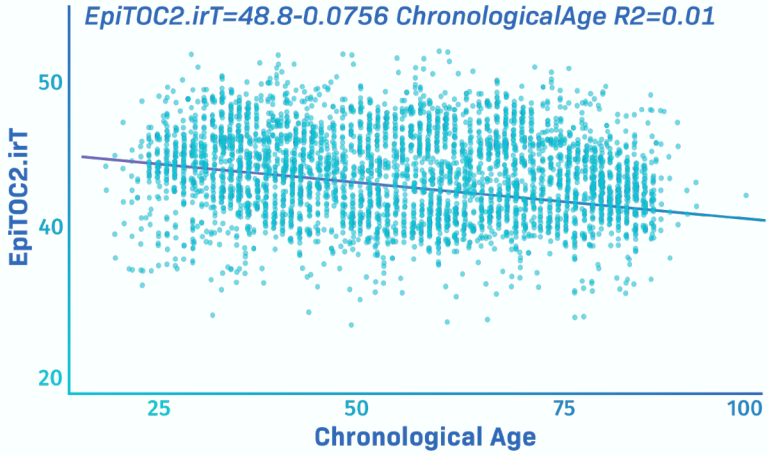
Based on your results, you would be in the **60th** percentile of Cell Division compared to others of your same chronological age.



Your ***median estimate for the intrinsic rate of stem-cell division*** for the tissue:

4004

Based on your results, you would be in the **70th** percentile of intrinsic rate of stem-cell divison compared to others of your same chronological age.



WHAT DOES THIS MEAN FOR ME?

The Impact To You

It is important to note that this report **does not detect cancer.** This algorithm has been trained to predict the amount of stem cell division in tissue samples. While tissue turnover is generally correlated with increased risk of cancer, It is NOT a definitive diagnostic.

A study by Andrew Teschendorff found that inflammatory conditions also increased mitotic rates in tissue. Increased mitotic rates measured with this algorithm could also indicate stem cell depletion.

Still, it does highly correlate to cancer development **risk.** The mitotic clock exhibits age acceleration in normal buccal tissue from smokers compared with nonsmokers, and in normal breast tissue from patients with cancer compared with healthy women, making it aunique biological clock for estimating cancer risk.

If you are reading **exceptionally high** in this category, we would encourage you to pay special attention to getting regularly examined for any health issues with your physician.