Perspective

Is cancer latency an outdated concept? Lessons from chronic myeloid leukaemia.

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Our concept of *cancer latency*, the interval from when a cancer starts until it is diagnosed, has changed dramatically. A prior widely-used definition was the interval between an exposure to a cancer-causing substance and cancer diagnosis (For example, 1,2; Figure 1). However, this definition does not accurately reflect current knowledge of how most cancers develop. It assumes, mostly incorrectly, one exposure is the *sole* cause of a cancer such that we can start to clock on cancer latency at that exposure. It also ignores the possibility the cancer being considered would have developed absent the exposure but the exposure accelerated cancer development. Lastly, it also ignores the randomness in when a cancer is diagnosed. For example, when there are signs and symptoms or when detected incidentally, say a lung cancer detected during a heart computed tomography (CT) angiogram.

Several examples illustrate the difficulty in accurately estimating *cancer latency.* For example, a substantial proportion of persons >65 years have a pre-leukaemia process termed age-related clonal haematopoiesis (ARCH) or clonal haematopoiesis of indeterminate potential (CHIP) 1-2 percent of whom *per annum* will develop leukaemia (reviewed in 3). The question in these persons is when to start the clock to estimate *cancer latency* in these persons. The antecedent mutations resulting in clonal haematopoiesis may have occurred years before these persons developed leukaemia. However, when the final mutation(s) resulting in leukaemia development is unknown but is probably close to when the leukaemia was detected. Should we start the clock to calculate *cancer latency* when the 1st mutations causing ARCH or CHIP occurred, when the final mutation(s) occurred or somewhere in between? The decision is obviously arbitrary. One strategy, starting with the 1st mutation, might result in a very long estimate of *cancer latency* and the other, a very brief estimate *of cancer latency*. Choosing either model is entirely arbitrary and without a scientific basis. Also, some persons receiving anti-cancer drugs such as DNA polymerase-II-inhibitors cancer develop a new cancer within a median of 2-3 years. [4] Others receiving alkylating drugs have a median interval to cancer diagnosis of 5-7 year.

There is also the mistaken notion that cancers accumulate mutations gradually and in a predictable linear order. For example, in a study in pancreas cancer the authours tracked DNA copy number changes and DNA-rearrangements and showed cancer development is not gradual and often does not follow a linear mutation acquisition model. A substantial proportion of cancers had complex rearrangement patterns associated with mitotic errors consistent with punctuated equilibrium as the principal evolutionary trajectory resulting the simultaneous knockout of driver mutations.[5]

Considerable data indicate cancer development is almost always a complex, multi-step process further complicating attempts to define and/or estimate cancer latency (For example, 6-10). Most cancers do not have a cause but rather several or even many causes. In our efforts to better understand cancer latency, we focus on chronic phase chronic myeloid leukaemia (CML), a cancer where one mutation, *BCRABL1,* is widely regarded as a necessary and sufficient cause. [11-16] Although some data suggest *BCRABL*1 transcripts can be detected in normals it is uncertain this mutation occurs in a cell biologically able to cause CML. [17-19]. Also, some data suggest a clonal abnormality may predate *BCRABL1* in some persons with CML. [20,21] Regardless, most data remain consistent with the notion *BCRABL1* necessary and sufficient to cause CML.

Data from several sources including Japanese exposed to the atomic bombs in Hiroshima and Nakasaki, persons, receiving radiation therapy and those occupationally-exposed to radiation have increased risks of developing CML. [22-25] Although the median interval following radiation exposure to CML diagnosis in these settings was about 6 years, an increased relative risk was obseved within 2 years of exposure in children exposed to the A-bombs suggesting a shorter latency (see below). There are other cases of CML in which cancer latency may be less than 2 years. For example, there are reports of CML in infants and toddlers. [26] These reports suggest CML can begin *in utero* and develop after a brief latency. We report an unusual case in which *BCRABL1* but not blood abnormalities were present at birth suggesting an even briefer latency interval.

A 6-month-old previously healthy girl was hospitalized with recent onset nausea, emesis and fever. Blood studies showed a hemoglobin concentration of 65 g/L, WBC, 168 x 10E+9/L with a left shift and 2 percent blasts and platelets, 1,254 x 10E+9/L. The bone marrow showed myeloid hyperplasia consistent with chronic phase CML. Cytogenetic analyses indicated 46,XX, t(9;22)(q34;q11.2) in all 30 metaphases studied. Molecular analsyes detected *BCRABL1* with a P210*BCR-ABL1* e13a2 fusion protein.

Coincidentally, the infant’s umbilical cord blood cells had been collected and cryo-preserved for unrelated reasons with no suspicion of any illness. A sample showed a hemoglobin concentration of 130 g/L (below lower limit of normal), WBC of 9.4 x 10E+9/L with a normal differential and platelets, 215 x 10E+9/L. Umbical cord blood samples were obtained with parenteral consent and DNA extracted. Molecular analyses by nested mRNA RT-PCR was negative for *BCRABL1.* However sensitivity was limited (molecular response; MMR) because of the small amount of DNA. Next, a nested genomic DNA (gDNA)-based PCR was done using subject specific PCR primers after characterizing the genomic breakpoints.[27]  A *BCRABL1* fusion was identified in 2/4 replicates using 136 ng cord blood DNA *per* replicate, suggesting a clonal burden of <1 in 10E+4leukocytes. We found no mutation using a myeloid panel of 11 genes associated with pre-disposition to myeloid cancers, *ACD, ANKRD26, CEBPA, DDX41, ETV6, GATA2, RUNX1, SRP72, TERC, TERT* and *TP53.*

The child received imatinib, 300 mg/mE+2/d, achieving a major cytogenetic response (CyR) by 3 months. Response was down-graded to minor CyR at 6 months and imatinib was increased to 500 mg/mE+2/d. At 9 months of treatment when the blood cell concentrations and bone marrow histology were normal, cytogenetic analyses of 30 bone marrow metaphases showed: 46,XX [18], t(9;22)(q34;q11.2) [9]; 47,XX, t(9;22)(q34;q11.2),+der(22) t(9;22)(q34;q11,2) [3]. Cytogenetic analyses at 12 months of treatment showed 2 Ph1-chromosome positive out of 30 metaphases including one with adouble Ph1-chromosome. The subject had a MMR (*BCRABL1* 0.07%, international scale) at 18 months and the imatinib dose was reduced to 300 mg/mE+2/d. By 36 months sustained MR4.5 was achieved continuing to the present.

Chronic phase CML is rare in children accounting for less than 10 percent of all cases of CML and less than 2 percent of childhood leukaemias. [28] This contrasts with *BCRABL1*-postive ALL occuring in 5 percent of persons with < 18 years. [29] These persons typically have *BCR* and *ABL1* chimeric genes with breakpoints different from adults with CML and from our subject and typically have a P190*BCR-ABL1* rather than a P210*BCR-ABL1* fusion protein. Another 10 to 20 percent of leukaemias in persons < 18 years of age are termed *Ph1-chromosome-like* based on gene expression profiling similar to that of Ph1-chromosome-positive ALL but without *BCRABL1*. [30]

There are some unusual aspects of our subject besides *BCRABL1* being present at birth and probably pre-natally in addition to having normal blood cell parameters at birth. For example, the hemoglobin concentration at birth was 132 g/L (at the lower level of normal), WBC, 9.4 x 10E+9/L and platelets, 215 x 10E+9/L. This implies latency from birth someto develop blood cell concentration abnormalities was < 6 months. Our subject also developed a sub-clone with adverse cytogenetics soon after diagnosis and whilst on imatinib but with normal blood and bone marrow parameters. However, because our initial cytogenetic analysis was with 30 metaphases we cannot conclude this sub-clone was absent at diagnosis or when a major cytogenetic response was achieved. Also, there was no evidence of CML progression to accelerated or acute phase in blood of bone marrow samples when this sub-clone was detected.

The important point of this case is implications for cancer latency and more specifically latency in CML. Our data indicate a somatic translocation, *BCRABL1,* occurred during gestation. Blood cell parameters were normal at birth. Although no blood or bone marow study was done before 6 months of age when CML was diagnosed, abnormal blood cell parameters would likely have been detected earlier had testing been done.

Based on these data it is likely the interval from *BCRABL1* to the chronic phase CML phenotype evolved within a short period interval, *i.e*. < 6 months from birth. This is much briefer than usual estimates for cancer latency of 10 to 20 years. We acknowledge latency of leukemias may be briefer than solid cancers. However, a recent analysis by the US National Academy of Sciences suggested latency might be as short as one year for leukaemias and 4 years for most solid cancers. [2] We also acknowledge some hematologists and biologists consider chronic phase CML a preleukaemia rather than a leukaemia because of normal cell maturation and regulation. [31-35]

Our study suggests the need to reconsider the concept of cancer latency. For example, solid cancers often have 50 or 100 mutations only some of which are *driver* mutations. At which mutation or combination of mutations would we start the clock to measure cancer latency? This is further complicated by finding of different mutation topographies in different people with the same cancer and that many mutations in people with solid cancers are found in people never developing the relevant cancer in their lifetime (reviewed in 36). Also, the order in which mutations occur, even in the same cancer type, may affect the interval to diagnosis. [37,38]

Some cancers common in infants and toddlers such as acute lymphoid and acute myeloid leukaemias (ALL and AML), central and peripheral neural cancers, Wilms tumor, soft tissue sarcomas and retinoblastoma are consistent with a brief latency. Although some of these cancers are biologically different from those occurring in adults and may be developmental abnormalities, typical solid cancers sometimes occur in children such as lung and pancreas cancers. [39,40] Another example of a brief latency is thyroid cancers in children exposed toiodine-131 after the Chernobyl nuclear power facility accident. [41,42]

Data from studies of genetically-identical twins concordant for infant ALL indicate a prenatal origin and a brief latency. [43] In general concordance for ALL and AML in genetically-identical twins extends to about age 5-years with a median of 1-3 years, again consistent with a brief latency. There are also cases of genetically-identical twins with *ETV6RUNX1* (*T*ELAML1) acquired prenatally developing ALL at ages 5 and 14 years showing the inprecision of estimating latency even for the same intiating mutation.

Neonatal blood spots (Guthrie cards) and umbilical cord blood samples have been used to detect mutations present at birth in seemingly normal neonates although leukaemia developed at diverse interval therafter (reviewed in 44). For example, Gale *et al*. MLLAF4 genomic sequences in 3 cases of ALL in children developing ALL at 2 and 6 months and at 2 years. [45] Other cases of genetically-identical twins concordant for *ETV6RUNX1* are reported as have cases of Ph1-chromsome -positive ALL but not CML. [46,47]

There is also confusion at the other end of the latency interval. Leukemias are relatively easily diagnosed whereas many solid cancers are not. For example, in a woman with breast cancer detected by a screening mammography and a biopsy, do we stop the latency interval clock at this time or when the cancer would have been diagnosed, if at all, during the woman’s remaining lifetime. The same is so for prostate cancers detected by biopsy after prostate specific antigen (PSA) screening many of which would would otherwise not have been diagnosed during a person’s lifetime. And what about a cancer detected during a blood test, CT scan or magnetic resonance imaging (MRI) scan done for other reasons?

Several concepts we discuss are displayed in Figure 2. The top panel is a model of an unusual cancer like CML when 1 mutation causes the cancer. The green circle represents a normal cell and the red circle, a cell with a mutation resulting in the cancer genotype. *t*0 represents the interval between normalcy and the cancer genotype. Sometimes this can be instantaneous, for example in some persons exposed to the A-bombs. In others it occurs after a variable interval. Regardless, the time from this event to cancer diagnosis is also highly variable illustrated by intervals *ti*…*tiiiii*. Sometimes the diagnosis may be made quickly (*ti*) and in others, after several months, years or decades (*tiiiii*). *Cancer latency* in this model varies ranging from *ti totiiiii* even for the same cancer. This interval may be biologically-determined, stochastic or a combination.

The middle panel is a model of more typical cancer development with several mutations, here, 4 mutations. This model is greatly simplified as most human cancers have 50-150 mutations [6-10]. Again, the green circle represents a normal cell. The yellow, orange and blue circles represent cells, clones or sub-clones with successive mutations. *t*0…*t*3 represent intervals between these mutations. The red circle represents a cell with the complete complement of mutations resulting in cancer, the cancer genotype. Mutation acquisition in the model is displayed as linear but, as discussed above, the process is known to be branching in most cancers with heterogeneous clones and sub-clones. Again the interval between the cell, clone or sub-clone with the cancer genotype to the diagnosis of cancer can be immediate, intermediate or after a long interval illustrated by *ti*…*tii* but could be *tn*. This pattern differs in different persons with the same cancer and can differ in one person with the same cancer at different sites, say the primary site and within each metastatic site. Someone with 10 metastases could have 10 related but distinct mutation topographies. The challenge is how to compute *cancer latency* in model 2. One extreme is assuming it is *ti or ti + tii*. However, it is equally valid to choose the sum of the intervals *t*0…*t*3 + *ti*…*tii*. Other combinations and permutations are similarly plausible and there is no scientific basis for choosing one combination *versus* another. Because of this the definition of *cancer latency* in this model is arbitrary.

The model in the lower panel resembles the middle panel model except the order of mutation acquisition differs. Consequently, the length of intervals *t*0…*t*3 will likelydiffer from the intervals in the in the middle panel, briefer, longer or a mixture. It is impossible to ascertain the order of acquiring mutations in most cancers. Similarly, it is impossible to determine the duration of intervals *t*0…*t*3 in most human cancers. As in the model in the middle panel the interval between the cell, sub-clone or clone with the full complement of mutations to the diagnosis of cancer can be immediate, intermediate or after a long interval indicated by *ti*…*tii* but could be *tn*. This pattern differs in different persons with the same cancer and can also be different in one person with the same cancer at different sites, say at the primary site and within each site of metastases. The challenge, again, is how to compute *cancer latency* in the lower panel. One extreme is assuming it is *ti or ti + tii*. However, it is equally valid to choose the sum of the intervals *t*0…*t*3 + *ti*…*tii*. Other combinations and permutations are equally plausible and there is no scientific basis for choosing one combination *versus* another. Because of this the definition of *cancer latency* in this model is also arbitrary.

The bottom line is defining cancer latency is not as simple as it once seemed. It is difficult or impossible to know at which event or mutation to start to clock to measure cancer latency. It is equally difficult to know when to stop the clock given the stochastic nature of when cancers are diagnosed. Importantly, even in genetically-identical twins with the same driver mutation intervals to develop cancer vary substantially. And there are other confonders we discuss above. We clearly need a new definition of cancer latency or abandon the concept of cancer latency entirely in the modern era of cancer biology.

**Acknowledgement** KMS is funded by the Leukemia & Lymphoma Society Translational Research Program (6587-20), Cure Childhood Cancer, Hyundai Hope on Wheels, Pediatric Cancer Research Foundation, Stanford SPARK program, and Stanford Maternal Child Health Research Institute. RPG acknowledges support from the National Institute of Health Research (NIHR) Biomedical Research Centre funding scheme.

**Conflict of Interest** NH and NCPC are consultants for Novartis and Incyte.

**References**

1. Nadler DL, Zurbenko IG. Developing a Weibull Model extension to estimate cancer latency. [International Scholarly Research Notices](https://www.hindawi.com/journals/isrn/). Vol 2013. Article ID: 750857: <https://doi.org/10.5402/2013/750857>.
2. <https://www.cdc.gov/wtc/pdfs/policies/wtchpminlatcancer2014-11-07-508.pdf>
3. Bejar R. CHIP, ICUS, CCUS and other four-letter words. Leukemia. 2017; 31:1869-71.
4. [Ezoe S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ezoe%20S%5BAuthor%5D&cauthor=true&cauthor_uid=22851953) Secondary leukemia associated with the anti-cancer agent, etoposide, a topoisomerase II inhibitor. [Int J Environ Res Public Health.](https://www.ncbi.nlm.nih.gov/pubmed/22851953" \o "International journal of environmental research and public health.) 2012;9:2444-53.
5. [Notta F](https://www.ncbi.nlm.nih.gov/pubmed/?term=Notta%20F%5BAuthor%5D&cauthor=true&cauthor_uid=27732578), [Chan-Seng-Yue M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chan-Seng-Yue%20M%5BAuthor%5D&cauthor=true&cauthor_uid=27732578), [Lemire M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lemire%20M%5BAuthor%5D&cauthor=true&cauthor_uid=27732578), Li Y, Wilson GW, Connor AA, *et al.* A renewed model of pancreatic cancer evolution based on genomic rearrangement patterns.[Nature.](https://www.ncbi.nlm.nih.gov/pubmed/27732578" \o "Nature.) 2016;538:378-82.

Vogelstein B, Kinzler KW. The multistep nature of cancer. Trends. Genet. 1993;4:138-41.

The Cancer Genome Atlas Research Network. Genomic epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med. 2013;368:2059-74.

The Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. Nature.2012;489:519-25.

The Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer**.** 2015: doi <https://doi.org/10.1016/j.Cell.2015.10.025>

The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490:61-70.

Goldman JM, Melo JV. Chonic myeloid leukemia — advances in biology and new approaches to treatment. N Engl J Med. 2003;349: 1451-64.

1. Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. Science. 1990; 247: 824-30.
2. Dreazon O, Canaani E, Gale RP. Molecular biology of chronic myelogenous leukemia. Semin. Hematol. 1988;1:35-48.
3. Shtivelman E, Lifshitz B, Gale RP, Canaani E. Fused transcript of abl and bcr genes in chronic myelogenous leukaemia. Nature. 1985;315:550-4.
4. Apperley JF. Chronic myeloid leukaemia. Lancet. 2015;385:1447-59.
5. Deininger MW, Goldman JM, Melo V. The molecular biology of chronic myeloid leukemia. Blood.2000;96:3343-56.

Bose S, Deininger M, Gora-Tybor J, Goldman JM, Melo JV. The presence of typical and atypical BCR-ABL fusion genes in leukocytes of normal individuals: biologic significance and implications for the assessment of minimal residual disease. Blood.1998;92:3362-7.

1. Biernaux C, Loos M, Sels A, Hues G, Stryckmans P. Detection of major Bcr-Abl gene expression at a very love lewel in blood cells of some healthy individuals. Blood.1995;86:3118-22.

Kuan JW, Su AT, Leong CF, Osato M, Sahida G. Systematic reciew of normal subjects harboring BCR-ABL1 fusion gene. Acta Haematol. 2020;143:96-111.

1. Fialkow PJ, Martin PJ, Najfeld V. Evidence of a multi-step pathogenesis of chronic myelogenous leukemia. Blood.1982;58:158-63.
2. Schmidt M, Rinke J, Schäfer V, Schnittger S, Kohlman A, Obstfelder*, et al.* Molecular-definded clonal evolution in patients with chronic myeloid leukemia independent of teh BCR-ABL status. Leukemia 2014;28:2292-9.
3. Hsu WL, Preston DL, Soda M, Sugiyama H, Funamoto S, Kodoma K, *et al.* The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. Radiat Res. 2013;179: 361-82.
4. Corso A, Lazzarino M, Morra E, Merante S, Astori C, Berensconi P, *et al.* Chronic myelogenous leukemia and exposure to ionizing radiation--a retrospective study of 443 patients. Annals f Hematology. 1995;70:79-82.
5. Smith PG, Doll R. Morality among patients with ankylosing spondylitis after a single treatment course with x rays. Br Med J. 1982;449-60.

Rinke ET, Hagen J, Dmytrenko I, Hochhaus A, Dyagli I. Molecular-defined clonal evolution in patients with chronic myeloid leukemia who were exposed to ionizing radiation following the Chernobyl nuclear disaster. Leukemia. 2020;34:645-50.

1. Gunes AM, Millot F, Kalwak K*, et al.* Features and outcome of chronic myeloid leukemia (CML) at very young age: Data from the International Pediatric CML Registry (I-CML-Ped Study). Blood. 2018**;**132 (Suppl. 1):1748.
2. Score J, Calasanz MJ, Ottman O, Pane F, Yeh RF, Sobrinho-Simões MA, *et al.* [Analysis of genomic breakpoints in p190 and p210 BCR-ABL indicate distinct mechanisms of formation.](https://www.ncbi.nlm.nih.gov/pubmed/20703256) Leukemia. 2010;24:1742-50.
3. Biondi A, Gandemer V, De Lorenzo P. Imatinib treatment of paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (EsPhALL2010): a prospective, intergroup, open-label, single-arm clinical trial. The Lancet Hematol. 2018;5:e641-52.
4. Hijiya N, Schultz KR, Metzler M, Millot F, Suttorp M. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. Blood. 2016;127: 392-99
5. Tasian SK, Lohl ML, Hunger SP. Philadelphia chromosome-like acute lymphoblastic leukemia. Blood 2017; 130: 2064-72.
6. Aye L, Loghavi S, Yound KH, Siddiq I, Yin CC, Routhort MJ, *et al.* Preleukemic phase of chronic myelogenous leukemia: morphilogic and immunohistochemical characterization of 7 cases. [Ann Diagn Pathol.](https://www.ncbi.nlm.nih.gov/pubmed/27040932) 2016;21:53-8.
7. Hudnall SD, Northup J, Panova N, Suleman K, Velagaleti G. Prolonged preleukemic phase of chronic myelogenous leukemia. Exp Mol Pathol. 2007;83:484-89.
8. Bennett JM, Dsouza KG, Patel M, O’Dwyer K. “Preleukemic or smoldering” chronic myelogenous leukemia (CML): BCR-ABL1 positive: A brief case resport. Leuk Res Rep. 2014;4:12-14.
9. Clarkson B, Strife A, Wisniewski D, Lambek CL, Liu C. Chronic myelogenous leukemia as a paradigm of early cancer and possible curative strategies. Leukemia. 2003;17:1211-62.
10. Gale, RP, Apperley J. What does chronic myeloid leukaemia tell us about other leukaemias? Curr Hematol Malig Rep. 2019;14:477–79 <https://doi.org/10.1007/s11899-019-00555-3>
11. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Kinzer KW. Cancer genome landscapes. Science. 2013;339:1546-58.
12. Ortman CA, Kent DG, Nagalia J, Silber Y, Wedge DC, Grinfield J, *et al.* Effect of mutation order on myeloproliferative neoplasms. N Engl J Med. 2015;372:601-12.

Kent DG, Green AR. Order matters: The order of somatic mutations infucences cancer evolution. Cold Sprin Harbor Perspect Med. 2017;7:a027060

Grasveld jL Vana DW, Rscoruia, FJ, McGuire W, West KW. Pancreatic tumors in children: Analysis of 13 cases. J Pediatr Surg. 1990;25: 1057-62.

Yu DC, Grabowski MJ, Kozakewich HP, Perez-Atayde AR, Voss SD, Shamberger RC, *et al.* 2010. Primary lung tumors in children and adolescents: A 90-year experience. Pediatr Surg. 45: 1090-5.

1. Kazakov VS, Demidchik EP, Astakhova LN. Thyroid cancer after Chernobyl. Nature. 1992;359:21.
2. Baverstock K, Egloff B, Pinchera A*,* Ruchti C, Williams D. Thyroid cancer after Chernobyl. Nature. 1992;359 :21–2.

Greaves MF, Maia AT, Wiemels JL, Ford AM. Leukemia in twins: lessons in natural history. Blood. 2003;102;2321-33.

Greaves, M. A causal mechanism for childhood acute lymphoblastic leukaemia. Nat Rev Cancer. 2018;18:471–84.

1. Gale KB, Ford AM, Repp R, et al. Backtracking leukemia to birth: identification of clonotypic gene fusion sequences in neonatal blood spots.  Proc Natl Acad Sci U S A 1997;94 13950-54.
2. Cazzaniga, G. et al. Developmental origins and impact of BCR-ABL1 fusion and IKZF1 deletions in monozygotic twins with Ph+ acute lymphoblastic leukemia. Blood. 2011;118:5559–65.

Alpar, D., Wren, D., Ermini, L. et al. Clonal origins of ETV6-RUNX1+ acute lymphoblastic leukemia: studies in monozygotic twins. Leukemia. 2015;29:839–46.

Figure 1. Estimated cancer latencies. [1]



Figure 2. Competing models of cancer latency (see text).

