Vignettes Apparent in Surviving Non-Hodgkin Lymphoma [Which May Help Others]

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I. I was diagnosed with Aggressive Stage IV Non-Hodgkin Lymphoma (NHL) on April 15, 2014

At the outset, I want to offer my heartfelt thanks to my medical team, Dr. Naomi Mackinlay, Nurse Helen Blackburn, all the staff at Northern Cancer Institute, North Shore Private & Public Hospitals and last but not least all my family and friends without whose support I would not have gotten though this ordeal alive.

My story began with a routine visit to an orthopedic specialist to treat hip pain issues. These were largely not worth treating, but a CT scan showed some unexplained shadows above my hips which warranted further investigation. Subsequent Bone marrow cores, a PET scan and a lymph node biopsy in short order confirmed I had Aggressive, Stage IV NHL. This required cancelling my long awaited overseas holiday and immediately (in 2 days) starting six rounds of chemotherapy and blood transfusions followed by 6 months of recovery.

I said " I am going overseas next week for a canal cruise and will only be gone 3 weeks, I can start the Chemo when I get back." The Doc said "If you go away you won't come back. We will be holding the clinic open on Easter Thursday afternoon, just for you as the initial treatment takes a while". This is a big deal in Australia, stopping people from getting away early at the start of an extra-long weekend. Easter Monday is a holiday here as well

Positron Emission Tomography (PET) was used to develop a more complete diagnosis. PET involves fasting, drinking a glucose rich substance, (something akin to Gatorade), then being locked in a lead lined room with machine which injects a radioactive isotope with a half-life of 100 minutes into your arm. After 20 minutes the cancer has absorbed the glucose to sustain its rapid growth and the isotope attaches to the glucose. The result is a radioactive human body that shows where the cancer is when passed through a scanner.

Here is an image of my results:

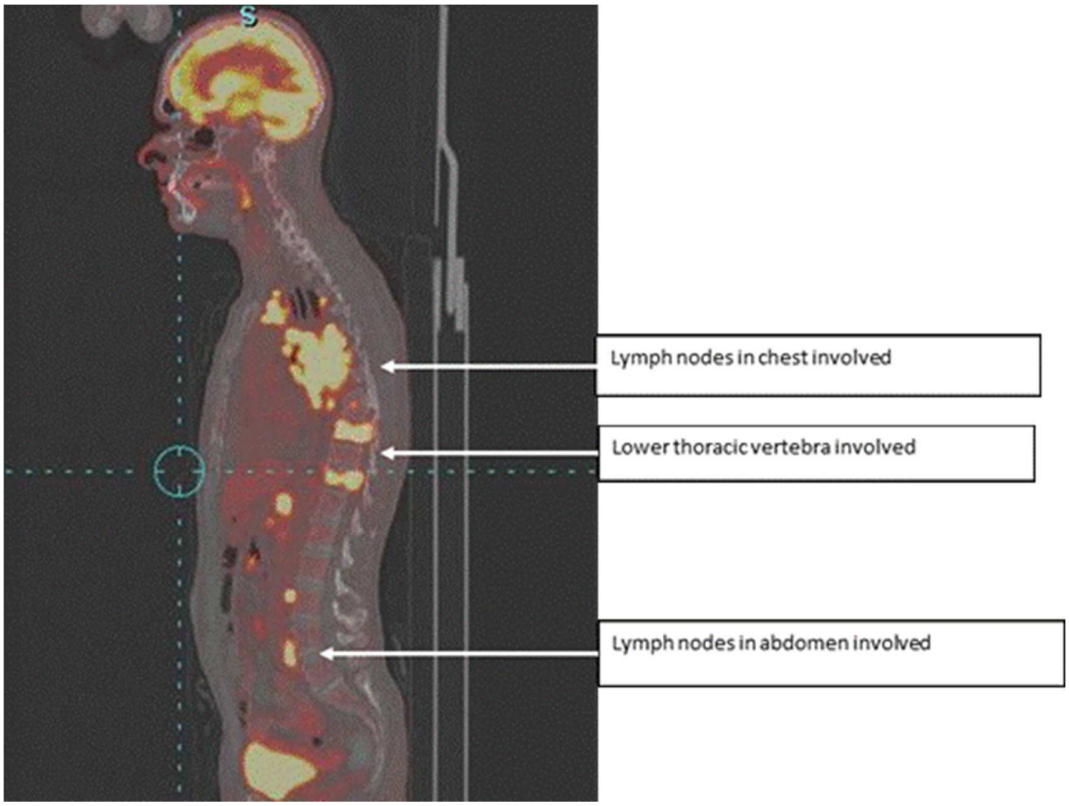


Figure 1: A PET scan confirms NHL

The PET scan shows enlarged lymph nodes and secondary tumors in the spine and which lymph nodes to sample for biopsies. Note the brain also absorbs glucose for normal function

I was scheduled begin what is known as RCHOP-14 chemotherapy immediately. It involves a mix of powerful drugs to be administered in alternate outpatient and impatient settings every 14 days:

(R) Rituximab: the estimated median terminal elimination half-life is 23 days with a range of 9 to 49 days. See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2848172/

(C) Cyclophosphamide: half-life of 3 to 12 hours. It is eliminated primarily in the form of metabolites. See: http://cyclophosphamide.net/

(H – for Hydroxydaunomycin) Doxorubicin: terminal half-life of 20 to 48 hours. See: http://chemocare.com/chemotherapy/drug-info/doxorubicin.aspx

(O – for Oncovin) Vincristine: median half–life of 85 with a range of 19 to 155 hours. See: http://www.rxlist.com/vincristine-sulfate-injection-drug/clinical-pharmacology.htm

(P) Prednisone: Prednisolone has a half-life of 2 to 4 hours. See: https://www.ncbi.nlm.nih.gov/pubmed/2320875

Methotrexate MTX): terminal half-life is eight to 15 hours. See: http://www.rxlist.com/trexall-drug/clinical-pharmacology.htm.

In general, the purpose of these drugs is to interfere with cell division and replication, both healthy cells and cancerous alike. Imagine having a fatal rapidly growing body of cells which need to be destroyed by a mix of drugs that if administered improperly is also fatal.

My story ends well – I am in remission. Survival rates for NHL vary widely, depending on the lymphoma type, stage, age of the patient, and other variables. According to the American Cancer Society, the overall 5-year relative survival rate for patients with Non-Hodgkin lymphoma is **67%** and the 10-year relative survival rate is **55%**.

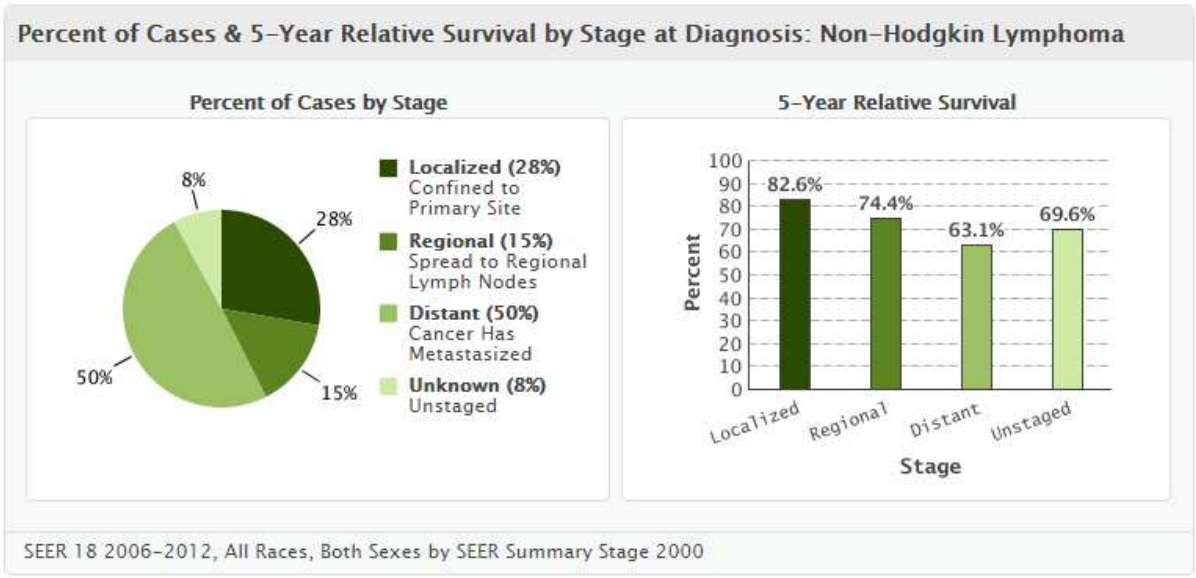


Figure 2. See: http://umm.edu/health/medical/reports/articles/nonhodgkins-lymphoma

I was concerned about how well prepared I was to withstand the treatment, about the burdens I would impose upon my family and friends, and what to expect in the weeks ahead. I'm writing this because along the way I found some System Dynamics tools to be quite helpful in navigating a difficult journey back to health.

I hope that my experiences in this application of the tools we use in practice can help someone else. Further, perhaps we can raise some questions which could benefit from a more rigorous approach.

II. A Medical Intervention is Part of a Balancing Loop

The first observation I offer is that a medical intervention is a response to some less than desired health situation. This creates a context to understand what's going on by surfacing a number of familiar questions. What really is the "target level of health" I should aspire to and how might I quantify it? Why must a series of interventions be followed and what can I do to maximize the effectiveness of each step? What are the delays I should expect and how will they impact perceived and actual progress? While the successive interventions are aimed at recovery, what unintended consequences (side effects) will occur, when will they occur, and how can I best deal with them.

As the treatment began, I reflected on how this loop would play out and how best to respond.

III. An Overview of NHL

NHL is a commonly occuring cancer worldwide.

As my doctor informed me, it is fatal if not treated, but it can be treated.

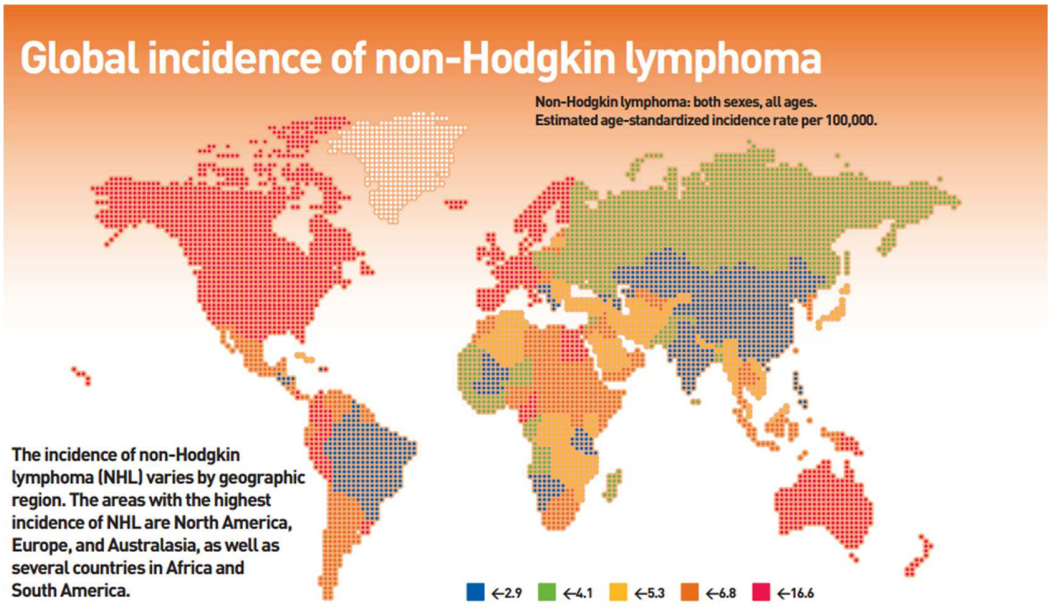


Figure 3. Globocan (2011) Graphs and maps. http://globocan.iarc.fr/ (URL accessed 20.02.12).

Current USA Statistics at a glance

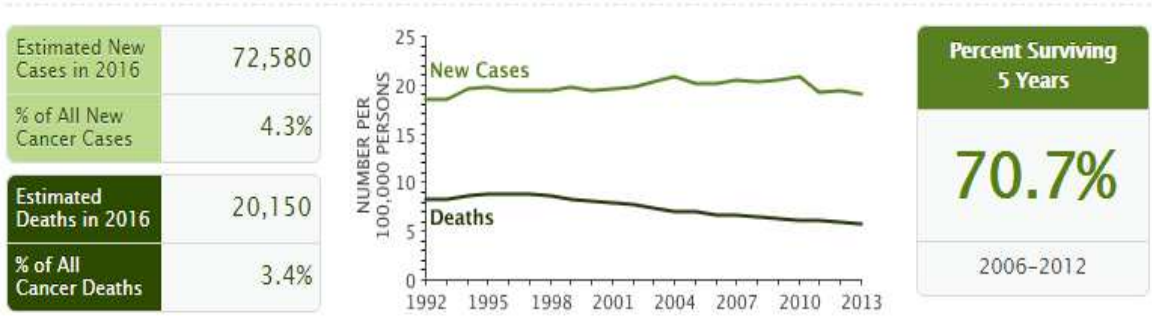


Figure 4. See: https://seer.cancer.gov/statfacts/html/nhl.html

IV. **Stages of NHL, its effects and pathologies** (see: http://www.cancer.net/cancer-types/lymphoma-non-hodgkin/stages)

Stage I: Either one of these conditions:

The cancer is found in one lymph node region (stage I)

The cancer has invaded one extralymphatic organ or site (stage IE)

Stage II: Either one of these conditions:

The cancer is in two or more lymph node regions on the same side of the diaphragm (stage II)

The cancer involves a single organ and its regional lymph nodes, with or without cancer in other lymph node regions on the same side of the diaphragm (stage IIE)

Stage III-IV: There is cancer in lymph node areas on both sides of the diaphragm (stage III), or the cancer has spread throughout the body beyond the lymph nodes (stage IV). Lymphoma most often spreads to the liver, bone marrow, or lungs. Stage III-IV lymphomas are common and are still very treatable. Stage III and IV are now considered one category because treatment and prognosis do not differ between them.

V. I put a BOT together as a road map for how I might feel

The examples I'd seen in Rogers (2011) of behavior over time (BOT) graphs of swings of hemoglobin values, and how they could describe patient well-being, caused me to wonder how useful they might be in helping me understand how the chemotherapy would make me feel to varying degrees. I decided to plot my sense of well-being to see if I could anticipate how I might feel after two successive treatments.

My sense of well-being was really the only thing I could measure. I expected that I would go into decline after my treatments but recover sufficiently before the next one. In my naivety, I assumed that this would be a smooth, periodic cycle with each successive zenith a little lower than its predecessor.

Fig 5 shows a hand drawn BOT which I updated daily charting my subjective feeling of well-being. After two treatments, I sketched a linear projection of how I thought I would be feeling throughout all six treatments – I was expecting to feel much worse that I actually did. Finally, after I completed all treatments, I sketched the red line. This curve indicates an updated but still naïve view of how I would feel.

I'm including both the original hand drawn document, a document I became familiar with over some 84 days and one of which I've grown quite fond. I've also including a cleaned up version which might be easier for you to read.

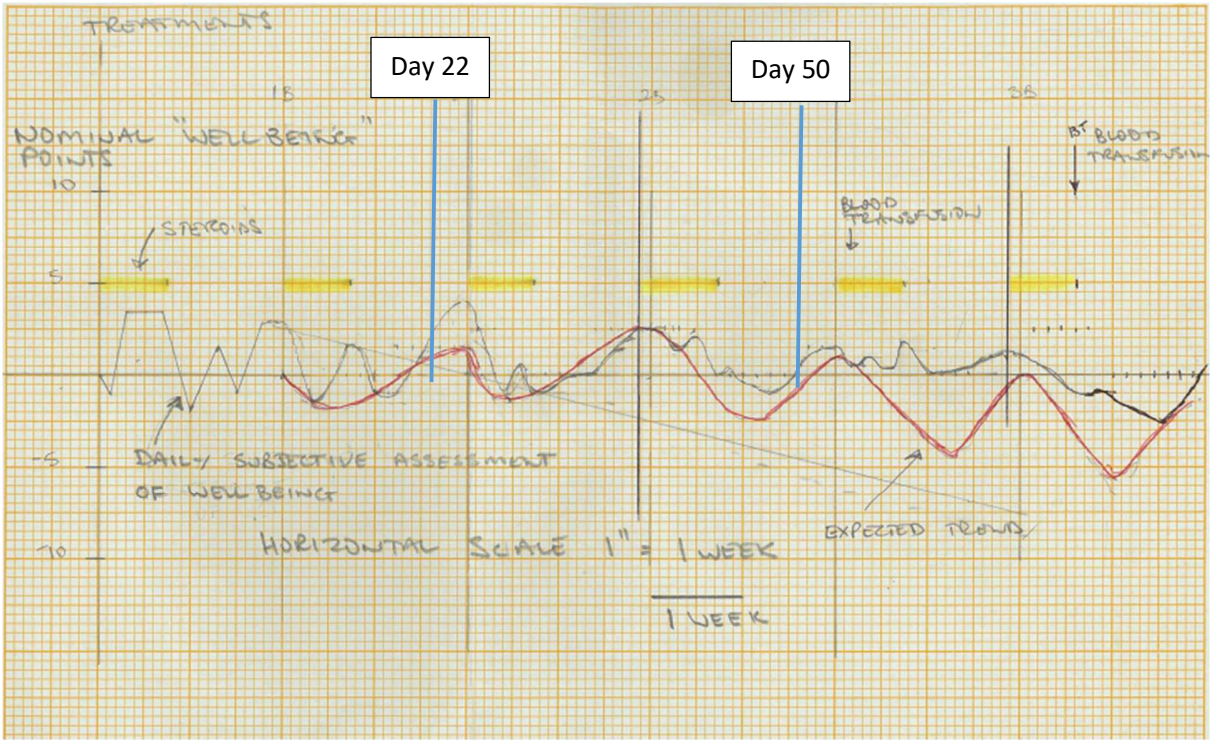


Figure 5. A hand drawn BOT that evolved throughout treatment provided a handy map.

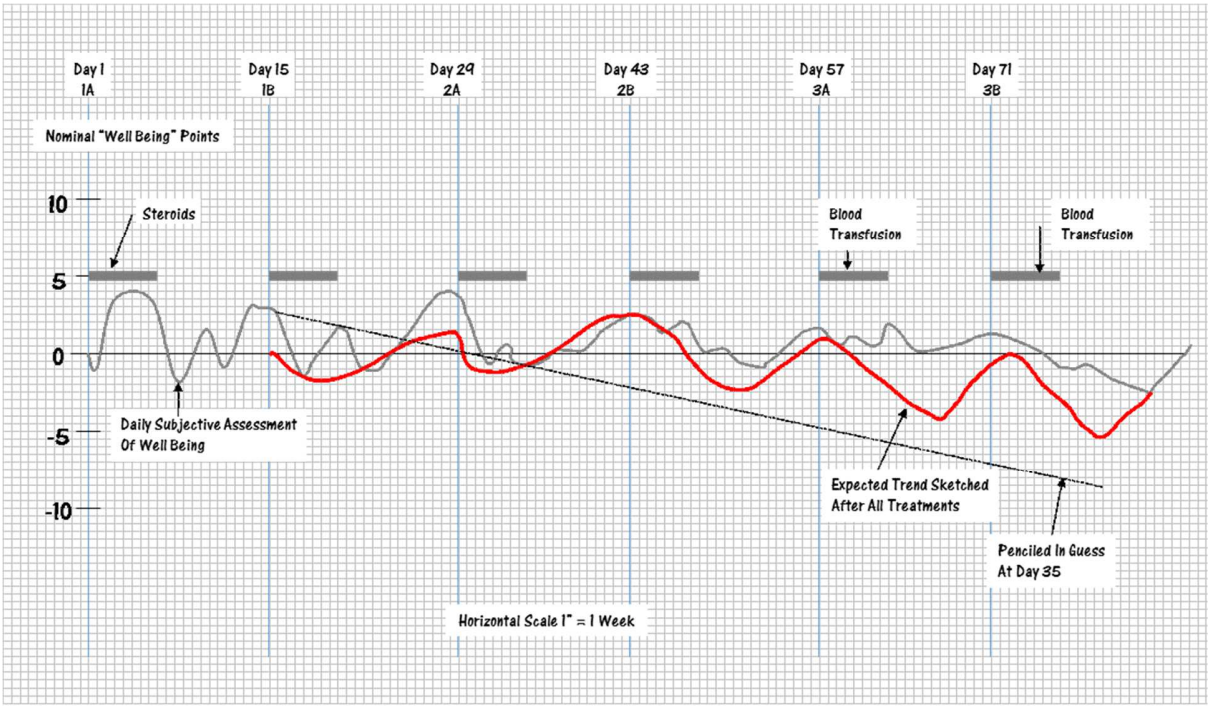
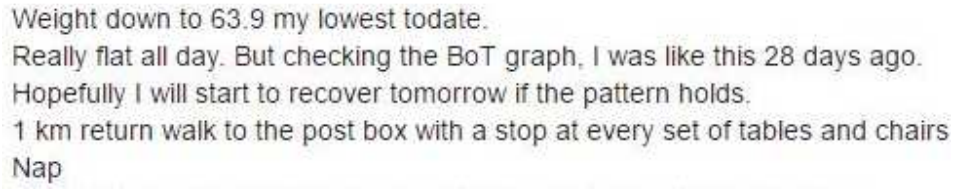


Figure 5B. A cleaned up copy for you to read.

As this Facebook Day 50 post excerpt shows, I came to rely on this graph to pull me thru the tough days:



To some extent this graph also shows the cumulative toll that the poisons take on your body. You never quite get back to your highs and your recovery rates are slower. The impact of the blood transfusions are shown in the reduced decay rates immediately following the transfusions. The impact of going "Cold Turkey" on the steroids is shown in the immediate decay after the 5 days of steroid intake.

After treatments 3A and 3B, I had blood transfusions as my red and white cells had been destroyed. Tests showed I was neutropenic. The blood transfusions certainly arrested my decline and made me feel better. However, I did not recover to initial highs. This reflects the fact that the doctors are trying to poison you within an inch of your life. One of the doctors actually said "If we had had to give you another dose we would have had to back it off a bit, otherwise it might prove fatal".

VI. Using System Dynamics to Better Understand MTX Concentration Levels

Among all the drugs I was receiving, MTX was the one monitored most closely. But I wondered if the idea behind monitoring levels could be improved. This section covers my lessons learned.

MTX has been in use since 1947. It is used in chemotherapy to inhibit the synthesis of DNA and RNA which are essential for cell replication and proliferation. As with the other drugs in the mix, MTX has risks associated with its use. If the concentration of the drug is high (above 0.05) it may crystallize in the kidneys unless the urine ph is kept above 7.5. This may cause significant damage. I received doses of MTX in both the inpatient and outpatient parts of my treatments schedule as indicated in the table below:

Date	Day Number	Treatment Number	Setting	MTX Administered	MTX Route
4/17/14	1	1A	Outpatient	Minute Dose	Lumbar Puncture
5/1/14	15	1B	Inpatient	Large Dose	IV
5/15/14	29	2A	Outpatient	Minute Dose	Lumbar Puncture
5/29/14	43	2B	Inpatient	Large Dose	IV
6/12/14	57	3A	Outpatient	No	-
6/26/14	71	3B	Inpatient	Large Dose	IV

Table 1. MTX administrations to monitor.

The small doses I received in the spinal column in the outpatient setting did not create concentrations high enough to risk any kidney damage. On the other hand the large doses I received in the inpatient settings were large enough to create risky concentrations. As a result, of part of the therapy was to remain hospitalized with a Sodium Bi Carb drip (4 litres per day) until the concentration dropped to safe levels.

As it turns out, the care team's method of predicting when I would be released from the hospital could underestimate my requirement of stay by up to 24 hours or more.

The PH level of urine is measured every two hours to ensure that it is at least 8.0. If the PH level gets near 7.0, alkaline tablets are administered to avoid the MTX crystalizing in the kidneys. The tablets are unpleasant.

Waiting for MTX levels to drop to safe concentrations can take up to five days after the original MTX dose. The care team administers blood tests periodically to monitor MTX concentration. When the concentration level is judged to be safe, then and only then can the patient be discharged from the hospital.

	Treatment 2B		**Treatment 3B**	
Lab Test #	**Hour from MTX**	**Concentration**	**Hour from MTX**	**Concentration**
1	48	0.17	46	0.22
2	72	0.09	70	0.13
3	90	0.06	92	0.08
4	NA	NA	103	0.06

Table 2. MTX Concertation data for treatments 2B and 3B.

After the results of two blood tests are available the nursing staff provides an estimate of when discharge may occur. It turned out on each occasion that these estimates where overly optimistic, perhaps deliberately, so that the patient can see the light at the end of the tunnel.

More likely, the overly optimistic projection was due to assuming a linear projection of the first two lab tests, indicating a possible discharge at 84 and 91 hours respectively, as show in Figure 6.

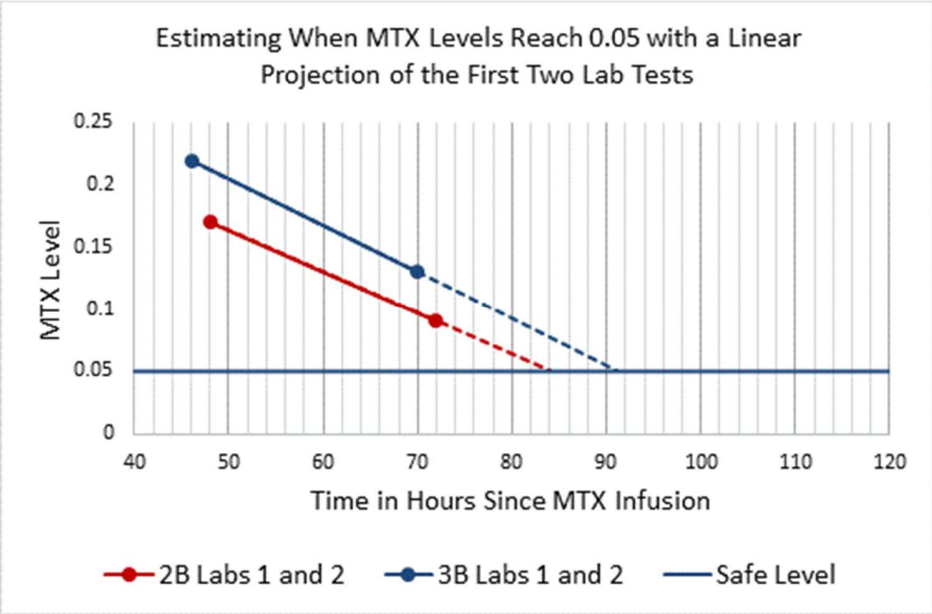


Figure 6. Optimistic linear projections

I wondered if the amount of MTX clearance each hour depends upon the MTX remaining in my body. That would make the decay rate exponential instead of linear, like many other drugs. If it is exponential, then the estimated time at which concentrations would reach safe levels would be longer than the nursing staff projections. To explore, I plotted results of all 3 labs for treatment 2B and all 4 for treatment 3B on a log linear plot, as shown in Figure 7:

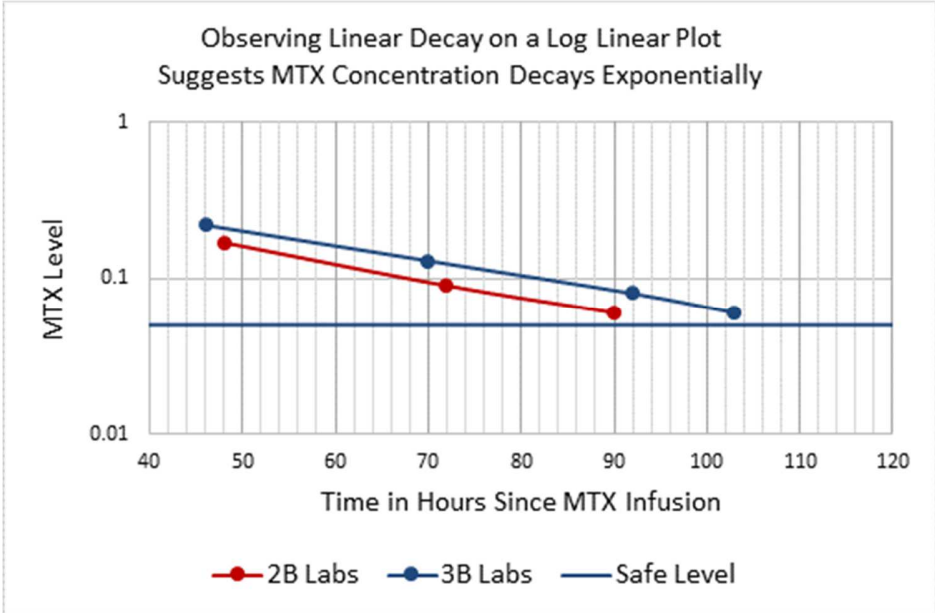


Figure 7. A log-linear exploration of the data for possible exponential decay

The almost straight lines for both treatments reinforced my thinking. On the assumption MTX decays exponentially, and suspecting that the decay time for 3B was longer than that for 2B, Ed Gallaher built simple models of MTX concentrations for treatments 2B and 3B, parameterized by MTX half-life. By experimenting with different MTX half-life values, he fitted the simulated curves to actual lab test data presented in Table 2. The half-lives that fit the data were 28 hours for treatment 2B and 36 hours for treatment 3B.

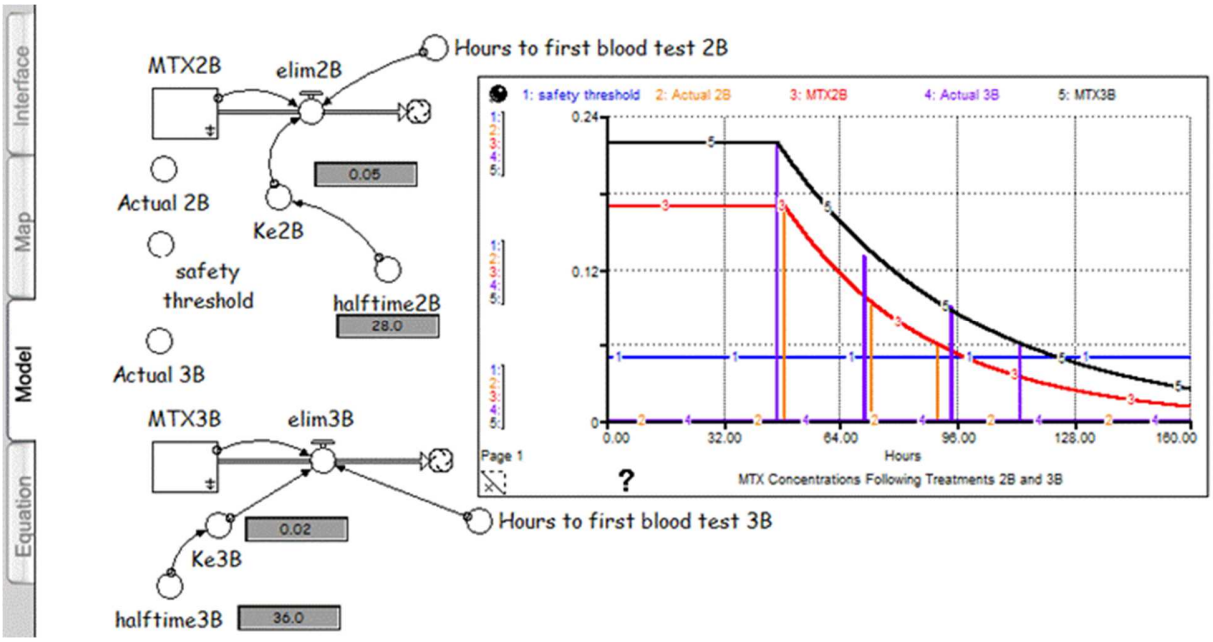


Figure 8. A simple model providing better insight into MTX concentration over time.

This allowed creating an estimate for the time at which the MTX concentration would reach 0.05. The revised times for safe concentration estimated for treatment 2B was 98 hours, for 3B the estimate was 125 hours.

The fact that I was not allowed to be discharged until a few hours after the last blood tests (note the results came back a few hours after the actual tests were taken), indicates that the simple model projections were very close.

My take away is inside the body processes can be reliably modeled. This is only a one stock model but it is a good proof of concept to show that more detailed modeling calibrated against actual results should be possible. This would provide a rapid, no risk test for possible adverse drug interactions.

This experience has convinced me there is much we as SD practitioners have to contribute to individualizing chemotherapy protocols.

VII. Sense Making in Hindsight

After the “Chemo Brain” fog cleared a little it occurred to me that there were a few key factors in my recovery. This Facebook post from Day 70 after the treatments were completed shows what I was thinking at the time:

Apart from getting good and timely medical care I believe there are 6 things that effect a cancer journey
Not in any order
A positive attitude
A stable home life
Financial security
Being fit and otherwise healthy at the start
Having a drug tolerant body
And
Having a extensive and enthusiastic support network

I think you can get by without 2 of these but beyond that it's gunna be tough

Although this looks like a laundry list, the systems thinkers amongst you will realise that these factors are not independent but rather interdependent and all positive reinforcing. Having been the recipient of many FB comments and visits I encourage to comment often and early whenever you can if you have a friend that is doing it tough for whatever reason

I have turned these thoughts into a CLD to show how I think they interact:

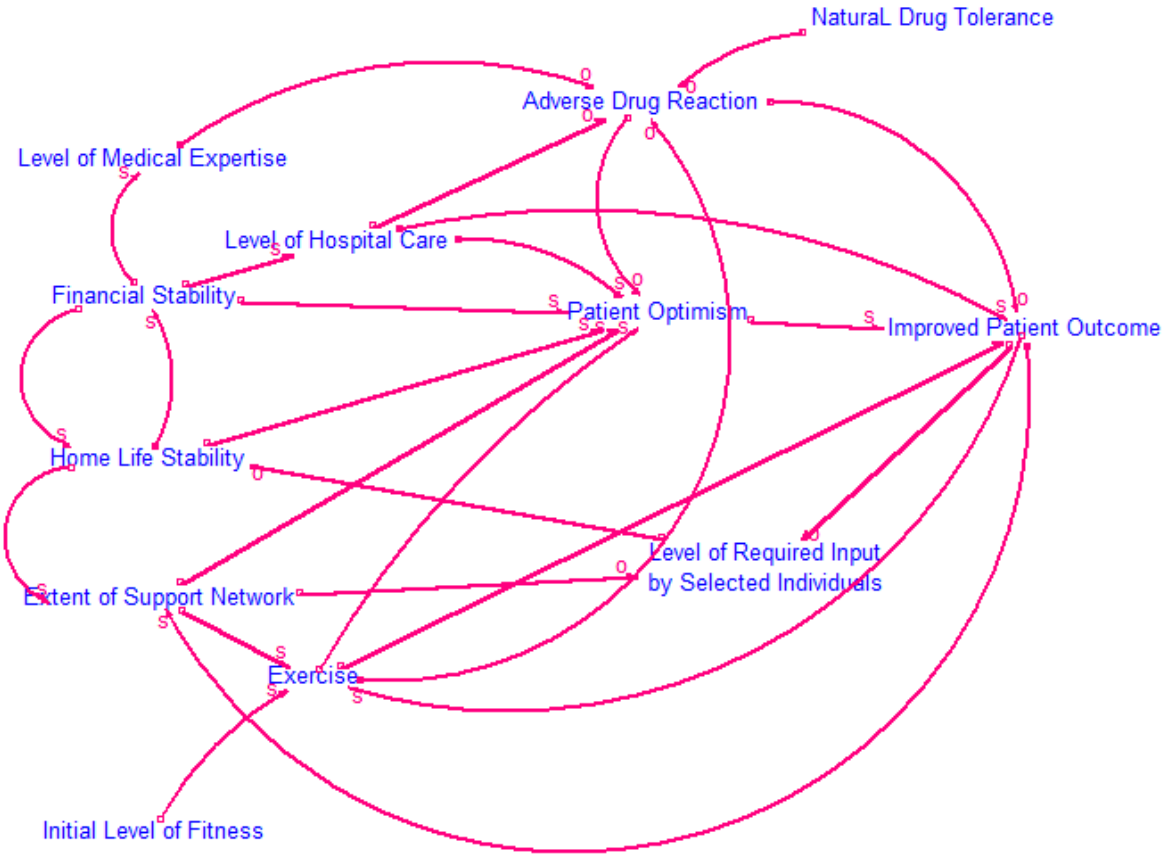


Figure 9. Thinking about causal psychosocial factors leading to positive outcomes

There are lots of things going on in this CLD. I will start with Financial Stability. If you have reasonable health insurance and some savings you can get good care and not have to worry about working. Having enough money to live on means your significant other does not have to work or at least not excessively and things are calm at home and domestic disputes are less likely to arise. Also, its just one less thing you have to worry about.

If your home life is stable then friends are likely to hang around. The more friends you have, the less everyone else has to do, reducing the likelihood of carer burnout. With a wider network of friends the more likely it is that someone will exercise with you or just take you somewhere where you have to walk.

Certainly, the converse would seem to be true, if you were in the middle of a messy divorce, then at least half of your finances and half your friends could soon disappear and you could be looking for somewhere to live at the end of treatment, if not a reason to live.

I believe that patient optimism or power of positivity has a great deal to do with improving your chances of survival. The better your outcome the easier it is for people to help out. I believe that it would be very

difficult to stay involved if someone was dying in front of your eyes. As you feel better you can exercise more and keep the poisons circulating in your body rather than collecting at some site.

It really helps if you are not throwing up all the time. The choice of drug cocktail is somewhat limited so it helps if you do not have any adverse reactions. Luckily, I did not, but I had a great team monitoring my progress, just in case. Also, I was reasonably fit at the start of this and hence had a predisposition to exercise and a good base level to decline from. Some patients looked worse starting their treatment than I did when I finished (IMHO)

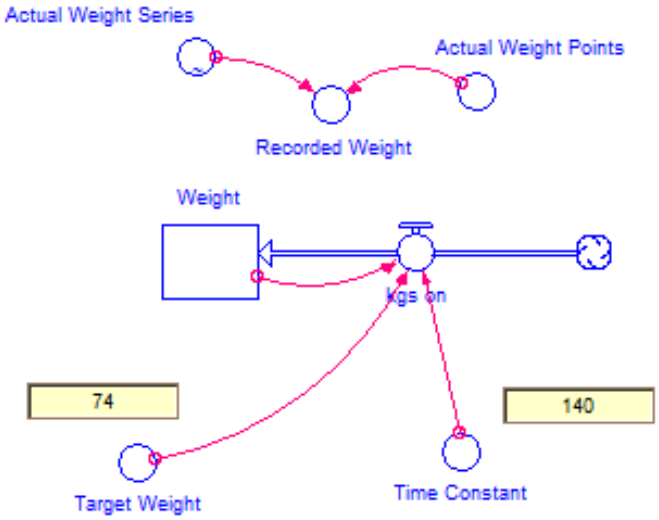
I was comforted by the fact that I had the essentials in place, either by good luck or good management. It kept me working on the exercise and social networking things as they were the only one I could control.

Others facing a battle with this cancer may not be so fortunate. It is my hope that the components and relationships presented in this diagram might be helpful to others. In particular, these ideas might help allied healthcare workers such as social workers, patient's family member, and of course, patients, in the form of guidance like "Now that you are diagnosed, how to prepare for the road ahead?"

AS a footnote. During the conference, it occurred to me that this diagram has all Reinforcing loops with little in the way of Balancing or Negative Feedback loops. As a result, it would be easy to put this system into a downward spiral. It is just possible that lack of access to medical care and increased financial stress imposed by the introduction of TrumpCare 2.0 could be sufficient to initiate such a downward spiral. From my own experience, I know that delays in diagnosis of a few weeks or delays in obtaining post chemo treatment for infections of a few hours could prove fatal. Given that the CBO concludes that about 22million people (ie about 1/15 of the population) could lose coverage. Assuming an equal distribution across the population then 1/15 of the 72,000 new cases pa ie 5,000 sufferers may lose coverage. About 1,500 of these would likely die anyway, but, the other 3,500 could be placed at extreme risk of also dying.

VIII. My Recovery

During the Chemo treatment you typically lose a lot of weight. I went from 74kgs to 58kgs in 8 weeks (more than a 20% loss). Putting it back on takes a lot longer. As it turns out this can also be modeled. But maybe this is taking SD too far! For the obsessive compulsive amongst you, I recall that what get measured gets improved, so I kept very detailed records of what I ate, exercise, and my weight every day for 90 days post final discharge.



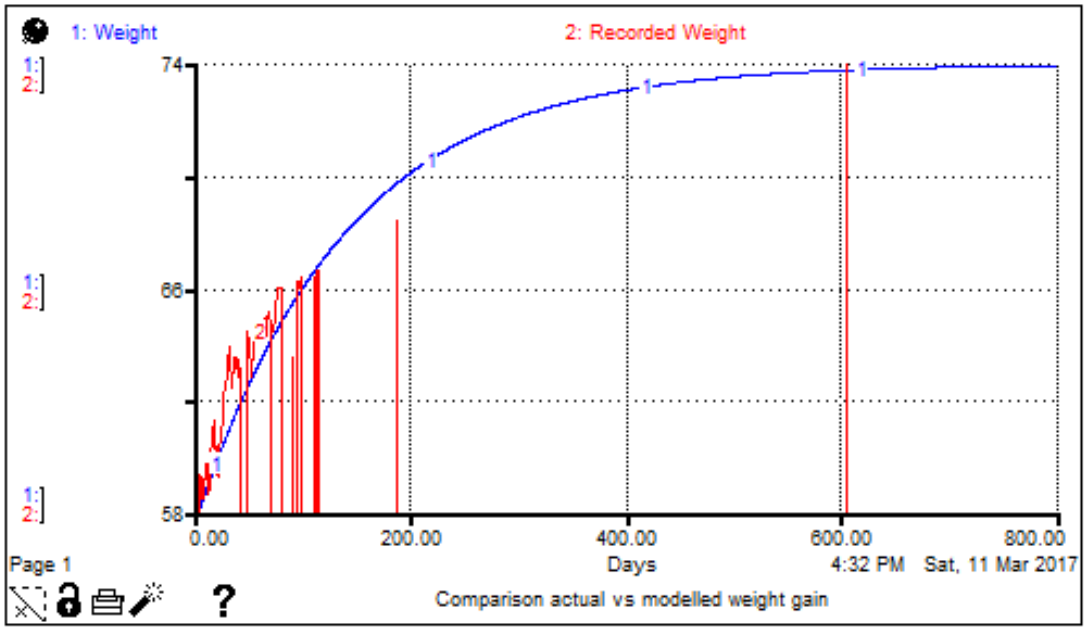


Figure 10. Modeling weight recovery.

IX. System Dynamics Helped Me in My Recovery

While not intending to state the obvious, I must say personally facing a deadly disease and a treatment protocol which can be just as deadly can be terrifying. I needed many types of resources to maintain a positive outlook. Systems thinking played a key role.

Systems, both inside and outside the skin are at play and involve complex dynamics.

We know as practitioners how insightful SD tool are.

I've offered this story and my experience in hopes that others may find some encouragement and real practical help.

And perhaps, to motivate a more rigorous look at cancer and individualizing its treatment

X. Summary

Just anticipating how the good days and not so good days would play out over time helped me stay engaged in my recovery.

SD helped me develop a better understanding of MTX clearance, and allowed me to better predict my discharge times.

SD helped me pay attention to working with the multifactor dynamics of my recovery support system so that I may help others.

Our biophysical systems control the course of our lives! SD helps us understand them and do a better job of interacting with them.

It was somewhat disappointing that I could not generate any interest from my medical team in modelling any of this stuff. Maybe they just don't get modeling because I am a poor salesman and hence see no value in it, or there is some of the "Not invented here" syndrome in play, **or they were just too busy saving lives**. I hope this little example will add to the examples of where and how SD can be used in the biomedical context. I hope someone can take this experience to the next level and build a model which looks at the body's response to the combination of different drugs that are administered to provide better outcomes.

This paper presents a “Call to Action” for modelers. Winston Ledet in his Manufacturing Game workshops uses the following slide:

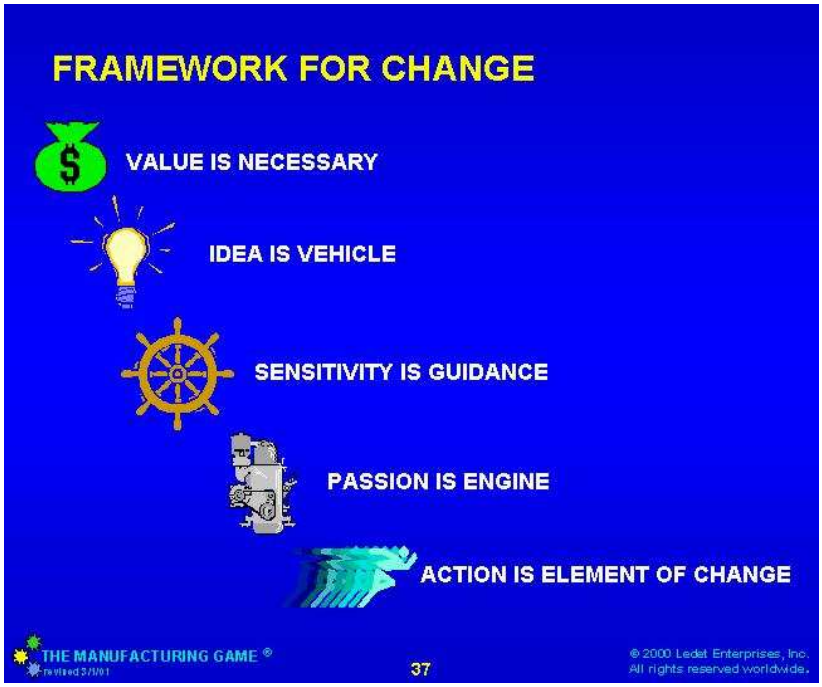


Figure 11. Ledet’s framework.

Applying Winston’s framework to improving NHL recovery possibilities, we have:

Value: There are lives to be saved - 35% of NHL patients in the UK don't make it past 1 year and only 50% make it to 5 years:

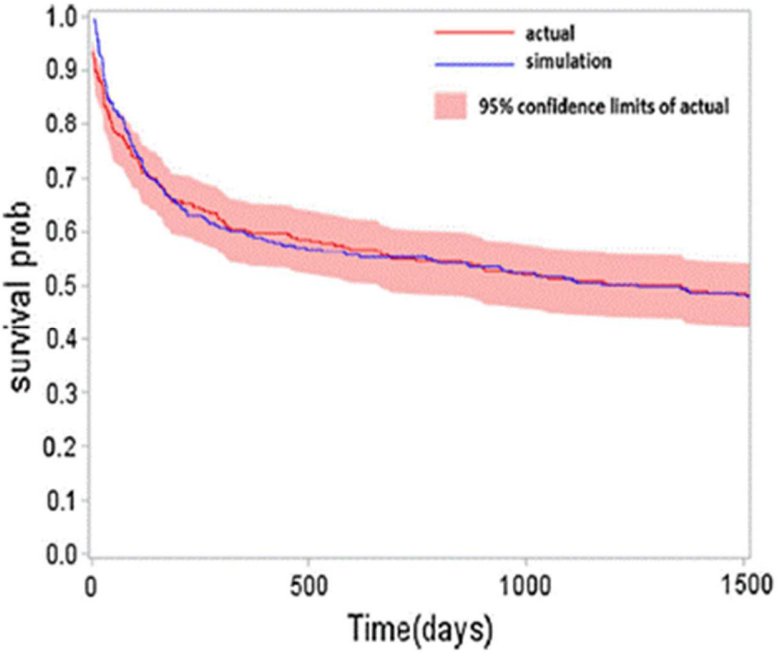


Figure 12. NHL survival probabilities in the UK from the paper referenced in Fig 13

US figures are slightly better, but there are still more deaths from NHL (20,150 in 2016) than murders in the USA.

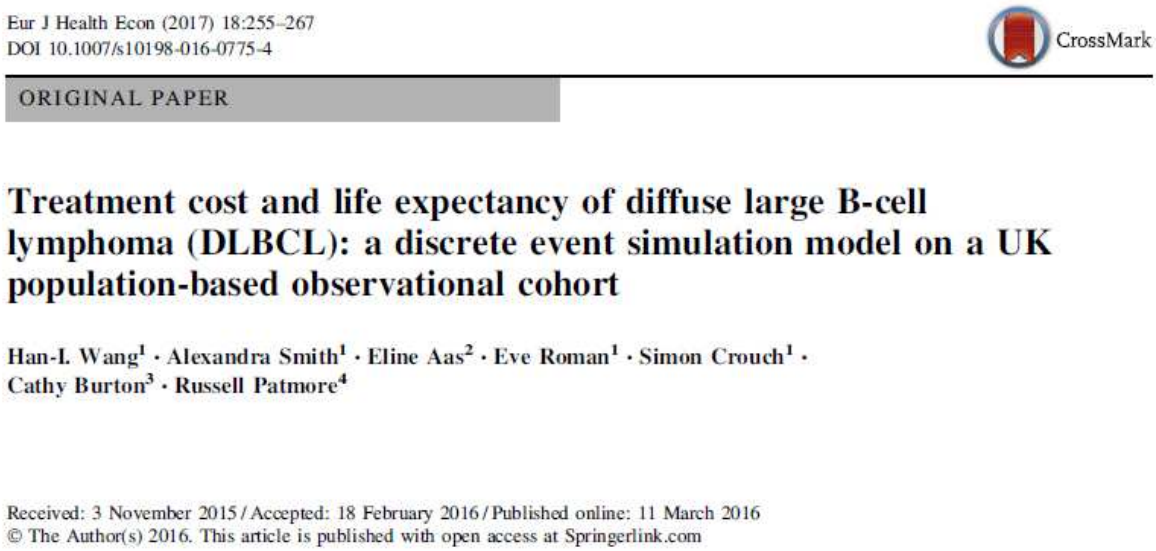
Among some of the other statistics contained in *Crime in the United States, 2015*: The estimated number of murders in the nation was 15,696. (see https://www.fbi.gov/news/stories/latest-crime-statistics-released)

Idea: System Dynamics can help patients have better outcomes.

Sensitivity: We can apply the various tools System Dynamics offers to NHL - and other diseases.

Passion: You and I are passionate about this stuff, I have a vested interest!

Action: We need to get others involved, this paper is part of that process. It is advertising collateral to sell the idea to health care providers. How can we get others involved? What can we do to create studies and applications like the one in Fig 13



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ORIGINAL PAPER

Treatment cost and life expectancy of diffuse large B-cell lymphoma (DLBCL): a discrete event simulation model on a UK population-based observational cohort

Han-L Wang[1] · Alexandra Smith[1] · Eline Aas[2] · Eve Roman[1] · Simon Crouch[1] · Cathy Burton[3] · Russell Patmore[4]

Received: 3 November 2015 / Accepted: 18 February 2016 / Published online: 11 March 2016

Figure 13. The SD community can do studies like this to produce actionable insights

XI. References

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