We have reached a point where in the last 30 years your chance of surviving cancer has increased from 1 in 4 to roughly 50%. This is the good news, but the bad news is that your chance of getting cancer has also doubled over the same period, and the trend of increasing incidences shows no sign of abating. The problem is that cancer like dementia and cardiovascular disease is largely a disease of old age, and we as a society grow ever older, and live to ages our grandparents generation never dreamed of. Our progress against these diseases has been very mixed. Against cardiovascular disease we have made great strides, only to find ourselves as older people between the Scylla and Charybdis of cancer and dementia. How could we get ahead of the game and start curing people at a faster rate than the incidence is rising?

For 25 years we have been telling people that the answer is “personalized” therapy, and what we usually meant by that is somehow using information derived from the genetics of cancer to treat cancer: using biologically targeted agents in therapies driven by biomarkers or genomic sequencing. The first evidence that cancer was a genetic disease came from the recognition of the Philadelphia chromosome by Nowell and Hungerford in 1960. They noticed a consistent rearrangement between chromosomes 9 and 22 in patients with CML. Further knowledge about this chromosomal re-arrangement showed that the two regions involved were the abl gene on chromosome 9 and a region on chromosome 22 called the breakpoint cluster region (or bcr) on 22. This re-arrangement producing a new gene, called the break point cluster region or the bcr. This new gene produced a new protein called the bcr-abl. Almost by serendipity one of the earliest biologically active drugs was also produced against this gene. When Glivec was given to patients with CML a large percentage went into what appeared to be sustained complete remission. Brian Druker, the clinician who led many of these early studies, was quoted as saying, “This is one of the best examples I’ve ever seen of science triumphing over disease.” Indeed, many oncologists thought the long awaited revolution in cancer care had arrived.

The fact that as time went on we confronted the reality that cancer had a bewilderingly large number of mutations was somewhat discouraging, but Hanahan and Weinberg, in two now classic publications, calmly nerved us somewhat by introducing the idea that although there were many, many mutations, they could be clustered into certain “hallmarks” or shared functions that all cancer cells must have in order to become cancer. Thus all cancers had to evade growth suppression or induce angiogenesis. Their idea was that we needed to understand the unique hallmarks that were driving each cancer. This hallmark would be a clonally dominant trait; and for each hallmark there would be a drug. Knowledge of the hallmarks would produce new therapies that would work for each cancer the way Glivec worked for CML. Certainly the pharmaceutical industry seemed to buy into this view. As each new hallmark was identified there was a rush to bring targeted agents into the clinic. Thus, for example, sustained angiogenesis often seemed to be driven by altered expression of VEGF or VEGFR, and there are now close to 150 drugs targeting this pathway either already in the clinic or in preclinical testing.

We have now reached a point where we can begin to examine how this hypothesis is holding up. Within the last ten years we have recognized that 40-60% of patients with melanoma are carrying activating mutations of the BRAF oncogene. A number of drug companies tried to produce inhibitors of BRAF and Plexonix was the first to get their drug, PLX4032 or Vemurafenib, into clinical trial. When this drug was first given to patients the results were often astonishing. Patients with widespread metastases saw their disease melt away. The results were so astonishing that they were widely reported in the lay press, and there was even some controversy about proceeding with the clinical trial. The New York Times managed to find two cousins both with metastatic melanoma, only one of whom was randomized to receive the drug, and they asked whether it was ethical to withhold such an obviously effective drug. In 2004, however, when Wagle et al. published the results of the trial a more disturbing picture emerged. It was true that many patients did have dramatic responses but equally within a relatively short time all relapsed. The median overall improvement in survival was nine weeks. Indeed, in a recent review by Fojo et al. of the 71 drugs approved for treatment of disseminated cancer from 2002-2014, they showed that the median improvement in Overall Survival for all 71 drugs was 2.1 months. Vemurafenib turns out to be much closer to the norm that Glivec.

Some insight into what may be going on comes from the work of Swanton. He studied renal cell carcinoma and instead of sequencing a single sample he took samples from different parts of the same tumor and from several sites of metastatic disease. As predicted he found many mutations. He then classified the
mutations into whether they were ubiquitous, shared or private. By ubiquitous he mean they were found in all the samples regardless of where the biopsy was taken. Shared meant that some but not all of the biopsy sites showed the mutation, and by private he meant they were unique to the site of the biopsy. What he found was that the ubiquitous mutations were uncommon, indeed rare, and that by far the largest number of mutations were private, i.e. not shared with any other site even within the same tumor from a single patient. When he expanded the study to look at a larger number of tumors from multiple patients an even more discouraging result emerged. Different biopsy sites from the same tumor within a single patient were often no more related to one another than were tumors derived from different patients. This was a very disturbing result for the concept of personalized therapy. We had always anticipated that each patient might need a unique solution, but if different parts from even a single tumor were not more related than tumors from different people how could personalized therapies be developed? Swanton’s own conclusion was that clonal dominance was an illusion, and this was a key concept for the application of therapy targeting hallmark lesions. Furthermore, he suggested, “The presence of subclonal driver events in solid tumours may provide and explanation for the inevitable acquisition of resistance to targeted therapeutics.” This study was limited to renal cell carcinoma, but Vogelstein’s group had come to a very similar conclusion looking at the evolution of “acquired” resistance to targeted EGFR blockade in colorectal cancer. The resistance was not “acquired” in response to treatment but was present as resistant subclones before treatment was initiated, and what appeared to the clinician as a “response” was simply the time required for the resistant subclones to re-populate the lesion. “Resistance is therefore a fait accompli,” they concluded.

These disturbing results may explain some other equally disturbing data. Oncology has the lowest success rate for introducing new therapies into the clinic of any field of medicine. 95% of the drugs in the pipeline never make it into the clinic. Drugs for cancer fail at all stages of development, from phase 1 trials to registration. 70% of oncology drugs that enter phase 2 fail to enter phase 3. 95% of oncology drugs that enter phase 3 also fail. And some evidence suggests that the failure rate may be increasing for the novel targeted agents. The simple fact is that although we have been talking about personalisation of cancer therapy for 25 years, nobody knows how to do it. And as a consequence is that what we brand success seems to be purchasing ever smaller increments in survival at ever increasing cost. This is hardly surprising since Pharma seeks to recover the high costs of failure from the trickle of novel agents that reach the clinic. Drugs costing hundreds of thousands of dollars for a course of treatment become ever more common and the million dollar drug may be in sight.
I started this opinion piece however by pointing out that the chance of surviving cancer had never been higher. How can this be true? If we examine the trend lines it is apparent that 90% of all the patients who are cured of cancer are still cured by surgery or radiation therapy, and two factors have enabled them to maintain their predominant role in curative cancer therapy: early diagnosis and the development in minimally invasive treatments. Although less is known about mortality, that we will not die from the tumor per se, neither surgery nor radiotherapy have stood still in the 75 years. From the first developments in laparoscopic (keyhole) surgery in the 1960s to modern robotic surgery surgeons have continuously moved to improve therapy by reducing the physical and toxic debilitating treatments. New tools continue to be developed for them in imaging, and in adjuncts to resection such as HBFI, cryotherapy and PDT. Radiotherapy has in some ways followed a very similar trajectory. Beginning with the widespread availability of linear accelerators by the 1970s, radiation oncologists too have continuously refined their technology and techniques towards more precise and less toxic treatment. Intensity Modulated Radiation Therapy (IMRT) and Image Guided Radiation Therapy (IGRT) are routinely available in clinics around the world. These developments in surgery and radiotherapy were largely driven by the revolution in imaging that has occurred in the last 75 years. The earliest CT scanners in the 1970s gave fuzzy views of the brain, but the full gamut of modern imaging with MRI, PET, dynamic imaging, image fusion and so on, mean that not only is diagnosis and staging immensely more accurate, but also means that the surgeons and radiation oncologists are working in a much more precise space with much more knowledge of how to plan and execute their therapies. Given this, how do we derive from this a new strategy to improve the outcomes of cancer treatment? It can not be the case that we conclude that there is no future in molecularly targeted therapies. Cancer is fundamentally a genetic disease, where we are failing in using this knowledge to develop strategies for improving the outcomes of cancer treatment. It is possible that the genetic diversity is cancer is so great even in very early disease that the efforts to identify biologically targeted agents provide more that very temporary extensions of survival. Another possibility is that we are looking for effect in the wrong population. That by always assessing novel agents in the setting of very advanced disease that has already failed treatment we are maximizing the probability that we will fail to detect a true response. It may be that we are even discarding agents that might have been useful if used in another setting. The successes in cancer treatment in the last few decades have come from combined modality treatment in patients with early stage disease. Early-stage disease is a concept of Precision Medicine to change the paradigm for looking for novel therapies to that setting. Could we transform the paradigm into one where we focus on early stage, therapy naïve patients and use them to look for combinations of molecular and interventional therapies that would optimize the chance for cure?

To do this would require an integration of a number of elements into the treatment plan. Target discovery would have to be linked with capabilities from big data analysis and molecular and functional imaging into to pathways that would still offer the patients access to state of the art interventional therapies that would maximize then opportunity for cure. This definition starts by optimizing the physically targeted interventions that would yield the maximum opportunity for cure with minimal toxicity. This means having capabilities to continually upgrade the interventional facilities to provide capabilities such as robotic therapy, cryo-ablation or particle therapy of HBFI, as the case demands. It requires state of the art functional and molecular imaging, not only to guide therapy but also to monitor therapy, since imaging may frequently be used as a surrogate endpoint for detection of response. Finally it is in this setting that one would seek to introduce molecularly targeted therapies, biologically targeted agents or trials driven by genomic sequence information or biomarkers. A Precision Cancer Medicine Clinic to carry out such research would require five components. Molecular Diagnostics, Molecular Imaging. A Window of Opportunity Trials Unit, Advanced Radiotherapy and a Minimally Invasive Interventions Center.

Molecular Diagnostics is a critical component because early stage treatment and trial design need to be driven by a full characterization of a patient’s tumor before entry into any trial. This must go beyond DNA sequence analysis to RNA sequencing and proteomics and the ability to analyse microRNAs and epigenetics. Analysis of histopathology must extend to digital pathology and cloud pathology, use of novel antibodies and superfine resolution microscopy. These must all be linked by enhanced clinical informatics with a data warehouse and the ability to create extended integrated genotype-phenotype reporting. Molecular Diagnostics must be forward looking and trial agents, in a window of opportunity trial, with the use of molecular imaging as a surrogate endpoint of response. We have carried out such studies looking for a response to arrest in breast cancer patients prior to lumpectomy, to focus on agents that improve tumor hypoxia prior to radiation treatment in lung cancer and in other similar studies. Window of opportunity trials will not tell you about efficacy but will enable you determine whether a drug is hitting its proposed target and whether it’s having a desired biological response. Data from the FDA Data Standard suggests that even among the top 15 approved molecularly targeted agents more than half the span of multiple billions of dollars was in giving the drugs to non-responders. Establishing response early in a drug’s development could not only improve the path to the clinic and so could do so with substantial societal benefit.

To enter a window of opportunity trial for a patient with a potentially curative intervention, there must be no trade off for the patient. Therefore, a precision medicine clinic must offer access to state-of-the-art interventional therapies. Surgery and radiotherapy have maintained their pre-eminent role in curative cancer management by continuously moving towards less invasive, more accurate and less toxic treatment. These qualities have not only enabled curative treatment to be extended to more patients, but they are also the qualities that allow surgery or radiotherapy to be more easily combined with systemic treatment, avoiding unnecessary normal tissue toxicity and enabling synergistic interaction. Particle therapy centers offer many possibilities for such trials. Since there is no normal tissue that benefits from any dose of radiation, and since radiation side effects typically occur in irradiated tissue, the targeted nature of Particle Therapy in combining the high dose region offer many unique opportunities to explore radiation – drug interactions. Furthermore they offer unique opportunities for hypofractionation, and again use the more efficient and more effective mechanism for maximizing the response to immune modulators as one of many examples. This is not the only technology that should be considered. The MR-Linac offers not only the ability to perform some forms of functional imaging already during radiotherapy delivery, but again by tracking intrafraction motion during treatment offer the possibility for correcting treatment failures that may result from tumor motion. There are similar opportunities for adding additional imaging capabilities during robotic surgery that would extend the surgeon’s view of vision outside the visible spectrum, creating the possibility of intraoperative molecular imaging. A precision cancer medicine clinic should be in intent to go beyond simply the delivery of molecularly targeted agents or improved molecular imaging but also aim to continuously refine the interventional techniques that continue to play such a key role in curative cancer management.

While cancer outcomes have improved over the decades, the advances have not been uniform. Many cancer types have shown little improvement in that time. These would include brain tumors, esophagus, pancreas and lung. These are all tumors in which surgery and radiotherapy are the only therapies that offer any curative potential, but where the outcomes even with the most aggressive treatments remain poor. These are ideal tumors to be addressed in a Precision Medicine Center. Applications of molecular diagnosis, molecular imaging and molecularly targeted agents could be readily assessed and the outcomes of such interventions could be readily detected. Surgery and radiotherapy could still remain central to the management but there would substantial opportunities to improve the translational pipeline toward more effective treatment.

Professor Gilles McKenna is a world expert in radiotherapy research. In 2006, he was recruited to the UK from the US to lead the Cancer Research UK - SRCI Gray Institute for Radiation Oncology and Biology in Oxford. Professor McKenna has focused his research on the role of cancer cells and on mechanisms of resistance to radiation with the peak of sensitizing cells to radiation by blocking mechanisms that control cell survival. Specifically he is interested in oncogenically activated signal transduction pathways that exhibit a reductive effect on tumor cells. His group has shown that the EGF-Ras-FOSK-PTD-AhI pathway appears to the major radioresistance pathway in active-sick solid tumors and this pathway then presents targets that could be manipulated in a clinical setting to modify the biological role of the EGF-Ras-FOSK-PTD-AhI. The research has focused on exploring the treatment of lung cancer, soft tissue sarcomas, skin cancer, head and neck cancer, and melanomas.