

## Genomics in Spine Health

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### Introduction

In 1953, history was created by Nobel winning discovery of the structure of DNA monograph by Watson and Crick. Research around DNA and cell & molecular biology has changed the face of science and its impact on medicine. Cloning of “Dolly” from a somatic cell strengthened the belief that DNA has the power to create and sustain life. Since then, a lot of research work has been going on in the field of medicine. Research carries a paramount importance, when it comes to application stage. Introduction of a ground-breaking technology, DNA Sequencing by Fred Sanger in 1977 was the one to bring about a paradigm shift and see the advent of a new era. Great advances have been made over the past few years and sequencing has now become a mainstream tool. Scaling to the Human Genome Project, and the emergence of second (massively parallel) and third (real-time, single-molecule) generation DNA sequencing has transformed biomedical research, and is beginning to transform clinical medicine through molecular genomics (1).

Neoplastic conditions are a result of aberrant mutations in proto-oncogenes or tumor suppressor genes, which control cell signaling

and act as checkpoints of various cellular and subcellular processes. These gain/loss of function mutations induce uncontrolled growth of cells, converting them into a tumor. These masses may be benign or malignant, of which benign tumor are slow growing, self-limiting and may take years to bring about any observable change. Malignant tumor or cancer spreads to the neighboring cells and may also invade distant tissues leading to metastasis.

Spinal metastasis is one of the leading causes of morbidity in cancer patients. It causes pain, fracture, mechanical instability, or neurological deficits such as paralysis and/or bowel and bladder dysfunction. Cord compression is normally seen as a pre-terminal event. Spinal metastasis (SM) typically affect the thoracic (60-80%), lumbar (15-30%) and cervical spine (<10%) with the preferred route of metastasis to the spine being via the arterial or venous - Batson's venous plexus - vessels often resulting in multifocal lesions (2)

### Genomics & Healthcare

Genomics is an interdisciplinary field of science, focusing on the structure,

function, evolution, mapping, and editing of genomes. The study of genomics deals with the sequencing and analysis of an organism's genome. It attempts to map the entire genome of an organism and tries to distinguish between the genetic markers to see which one deal with what traits. This information can not only help us to understand the pathophysiology of a disease but also give us the ability to predict performance traits.

The medical implication of individual variation was well known more than a century ago and perhaps, best annotated by Garrod in the early days of the 20th century (3). In medicine, the genetic bases of those differences in response to environmental agents, including medications, and differences that may predispose to the development disorders are of great importance as these explain population genetics as well as inter individual variations. An area which has seen a tremendous advancement as a result of molecular genomics is oncology, where mutational status of patient's tumor is profiled to know the origin of the cancer (driver mutations) and suggest therapy targeting the mutations. Cancer is one of the leading causes of morbidity and mortality worldwide and the number of new cases is expected to rise by about 70% over the next 2 decades. It is the second leading cause of death globally, and was responsible for 8.8 million deaths in 2015. Globally, nearly 1 in 6 deaths is due to cancer (4).

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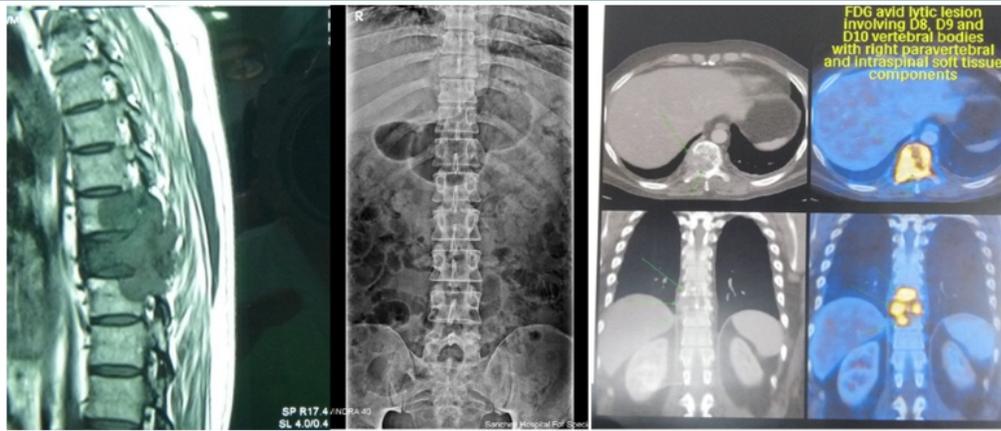


Figure .1 Axial MRIs taken before surgery showing severe compression of the thoracic spinal cord by the patient's tumor (Left). Multiple lesions as seen in MRI scan (Right).

**Current status in Spine Oncology**

Spinal tumors represent a significant tumor burden, contributing to morbidity associated with long-term survival. Metastatic spinal tumors occur with sufficient frequency, spine being the third most common site for cancer cells to metastasize and are generally indicative of a late stage malignancy. This amounts to 70% of all osseous metastases. Approximately 5–30% of patients with systemic cancer will have spinal metastasis; some studies have estimated that 30–70% of patients with a primary tumor have spinal metastatic disease at autopsy (5). Objective of spinal metastases surgery remains the treatment for pain, instability, and neurological deterioration due to tumor infiltration of the spine. Genetic subtyping, Identification of driver

mutations and novel immunotherapies have allowed personalized treatments, significantly improving survival and quality of life. Application of molecular biology and genetics to better understand and hence treat vertebral neoplastic conditions is shrinking the gap between diagnosis and mortality.

**Case Study**

A 42 year-old male had been taking treatment for Tuberculosis of spine for about 6 months without any significant symptomatic relief. With worsened condition and severe paraplegia, he was referred to us. PET studies unveiled hypermetabolic lytic sclerotic lesions involving D8-D9 and D10 vertebral bodies with involvement of right sided pedicles, laminae and transverse processes. His spinal canal was significantly

compromised at D8-D9 level and lytic erosion of posterior end of 9th and 10th rib was noted. A hypermetabolic heterogeneously enhancing mass lesion was seen involving peripheral region of right lower lobe of lung, representing primary neoplastic pathology (Fig. 1). Tissue biopsy revealed Non-small cell lung adenocarcinoma and the patient was diagnosed with advance stage IV NSCLC with spinal cord metastasis.

A collaborative association between the patient's physicians ensured that he received expeditious diagnosis, prompt treatment initiation and efficient coordination of care. Following diagnosis, the patient underwent resection of the tumor and fusion from D7 through D10. (Fig. 2). With the spinal cord decompressed and his back pain



Fig. 2 Postoperative X-rays showing spinal fusion from D7 to D10 following resection of the tumor.

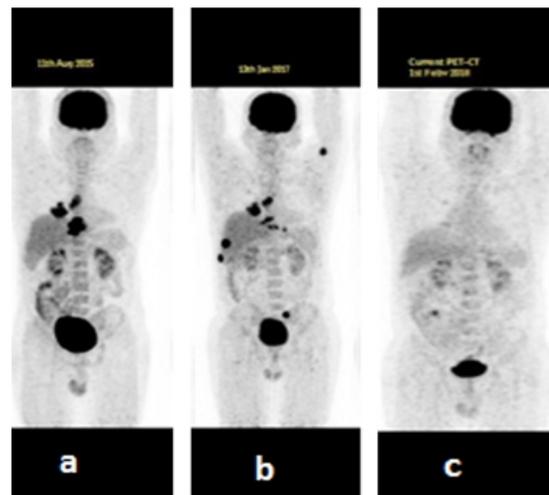


Fig. 3 PET scans before start of the treatment (a); during the treatment (b) and recent most (Feb, 2018). The latest PET-CT scan did not show any

significantly improved, the next steps of treatment were carried out. Patient regained motor power back over a period of six months. His previous line of chemotherapies had not been working with disease progression after 6 months. With a diagnosis where survival rate is 30-40% in the first and 10-15 % in the second year, the patient was referred to our genomics lab for comprehensive genomics testing of tumor sample. The multigene mutation and expression analysis showed an activating mutation, for which a targeted therapy was suggested. The patient was put on the new therapy regimen, directed to his mutational status. Patient regained v/v neurology with advent of 360o tumor resection and prevention of further progression of metastasis by targeted genomic guided therapy regimen.

Recent PET-CT scan has revealed that the patient's primary lung adenocarcinoma as well as the spinal metastasis have disappeared. The patient is in complete recovery and remains recurrence free after more than 2 years. (Fig. 3)

As highlighted in this case, a patient with a spine tumor requires a diagnosis of tumor pathology and the activating mutations. Surgery is indicated for decompression of delicate neural structures and spinal cord. Spinal instability is the indication for surgery in neoplastic and metastatic spinal diseases. Once relieved of these complications, the molecularly guided accurate diagnosis should be made so that the treatment is tailored to address the nature of metastatic tumor. A multidisciplinary strategy makes important differences in patients' treatment and overall quality of life. Failure of previous chemotherapy regimens provides a proof of concept for inclusion of genetic testing based molecular diagnosis to ensure a treatment based on the mutational

landscape of the patient's tumor.

### Discussion

Genetic technologies encompass a range of laboratory technologies that provide detailed sequence and other information on genomes – whether related to an individual's germline or somatic cells such as the altered genome within cancer cells, or non-human genomes such as those of bacteria or parasites. The plethora of applications in healthcare arises from an understanding of clinical relevance of emerging information for effective patient management. Diagnostic power of clinical genetics for individuals and families affected by, or at risk of, a genetic disorder or congenital abnormality has enabled early diagnosis and effective patient management.

Various studies have highlighted the importance of molecular diagnosis in more effective treatment process. Ebert et al, (6) in their study on large series of intramedullary spinal and intracranial ependymomas strongly found that spinal E II constituted distinct tumor entity characterized by a high incidence of LOH on 22q and NF2 gene mutations. These findings suggest that a considerable fraction of spinal ependymomas are associated with molecular events involving chromosome 22 and that mutations in the NF2 gene may be of primary importance for their genesis. Their data suggested that the more favorable clinical course of spinal ependymomas may relate to a distinct pattern of genetic alterations different from that of intracerebral ependymomas. A comprehensive, high-resolution genomic analysis of pediatric DIPG showed recurrent changes distinct from those of pediatric supratentorial high-grade astrocytomas. Thirty-six percent of DIPGs had copy number gains in PDGFRA (4 to 18 copies) and all showed PDGFR- expression. Low-

level gains in poly (ADP-ribose) polymerase (PARP) -1 were identified in three cases. Pathway analysis revealed genes with loss of heterozygosity were enriched for DNA repair pathways. This study by Zarghooni et al (7) highlighted two potential, therapeutic targets which pave way for targeted therapy for patients with this devastating disease. Hawkins et al, 2011 also conducted molecular analyses on 70 patients who had clinically relevant PLGA (i.e., incompletely resected optic pathway, brainstem, or spinal cord tumors). Thirty-seven patients had B-K fused tumors, with mean survival of 5.4 years. PLGAs with B-K fusion had better PFS regardless of their location, treatment, or pathologic subtype. This study showed that B-K fusion serves as an important prognostic marker in PLGA. Liang et al (9) evaluated the expression of Aurora Kinase A and B in chondrosarcomas and found it to be an independent factor predicting poorer survival. Another group found that the loss of RUNX3 expression, a tumor suppressor gene, was significantly associated with more aggressive chondrosarcoma types and decreased survival. Brachyury, the protein encoded by the T gene, is a transcription factor that plays a key role in the development of the notochord. It has been suggested that a single nucleotide polymorphism in the T gene is strongly linked to chordoma formation (10). Massacesi et al (11) investigated chordoma tumors from 104 patients where, 16% of the tumor samples possessed genetic mutations in PI3K signaling genes, targeted by many existing drugs, known as PI3K inhibitors.

Lu et al (12) studied the transcription profiles of 12 individuals (TB patients, latent TB infection individuals and healthy controls) and identified distinctive gene expression patterns associated with stimulated

peripheral blood mononuclear cells, infectious status and provided new insights into human immune responses to MTB. Furthermore, this study indicated that a combination of CXCL10, ATP10A and TLR6 could be used as novel biomarkers for the discrimination of TB from LTBI. DNA microarray analysis by Niu et al (13) showed that effective treatment of spinal TB in patients led to upregulation of genes that are associated with immune response pathway, providing a useful tool to evaluate the effects of spinal TB treatment in future. Whole Genome Sequencing has been used to retrospectively investigate M. tuberculosis transmission networks and drug susceptibility (14). Taken together, advent of molecular technologies and genomic medicine and are set to have a major impact on healthcare, patient outcomes and the health of the every individual by providing a personalized, tailor made regimen.

### Conclusion

Knowledge about the mutations in an individual's tumor can more precisely define a patient's prognosis and risk for cancer recurrence. Outcome studies based on genetics may prompt reconsideration of standard therapies for broad tumor categories, as clinical evidence may suggest tailored chemotherapies. Enticingly, a deeper genetic understanding provides the opportunity to investigate targeted therapies, particularly to combat aggressive tumors and recurrence in long-term survivors. Identifying the molecular signature of a specific tumor can lead to targeted therapy and improved outcomes. Although improved knowledge about the molecular workings of tumors is unlikely to challenge the primacy of surgical treatment in the immediate future, a better understanding of tumor genetics may lead to better treatment for vertebral neoplastic conditions which involves primary and secondary metastases. Genomics are going to be adjuvant in

management of tumour conditions. Surgery, chemotherapy and Radiotherapy cannot be replaced but can be directed with more efficacy with genomic guidance.

1. Since 19th century, human genomics have gone ahead in research by leaps and bound. Its application in clinical practice has benefitted the society at large.
2. Above discussed case is a representation of result of targeted therapy regimen for the driver mutation responsible for prolific adenocarcinoma of lung and its metastasis.
3. Genomics is helping to identify the driver mutations, responsible for oncogenesis, hence identifying new targets for therapy.
4. Every individual may have different response to the chemotherapy, newer research in pharmacogenomics will help in better clinical results and better outcome.

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