Websites:
http://www.sciencepub.net
http://www.cancerbio.net

Emails:
editor@sciencepub.net
sciencepub@gmail.com

Cancer Biology

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Cancer Cell Research Literatures (4)

Mark Herbert, PhD

39-06 Main Street, Flushing, Queens, New York 11354, USA, ma8080@gmail.com

Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.
[Mark H. Cancer Biology 2024;14(1):115-124]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). http://www.cancerbio.net 04. doi:10.7537/marscbj140124.04.

Key words: cancer; life; research; literature; cell

1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Allegretti, M., et al. (2018). "Tearing down the walls: FDA approves next generation sequencing (NGS) assays for actionable cancer genomic aberrations." J Exp Clin Cancer Res **37**(1): 47.

The United States Food and Drug Administration (FDA) recently approved the clinical use of two comprehensive 'mid-size' Next Generation Sequencing (NGS) panels calling actionable genomic aberrations in cancer. This is the first endorsement, by a regulatory body, of a new standard of care in oncology. Herein, we argue that besides its many practice-changing implications, this approval tears down the conceptual walls dividing system biology from clinical practice, diagnosis from research, prevention from therapy, cancer genetics from cancer genomics, and computational biology from empirical therapy assignment.

Armengol, G., et al. (2015). "Driver gene mutations of non-small-cell lung cancer are rare in primary carcinoids of the lung: NGS study by ion Torrent." Lung **193**(2): 303-308.

Lung carcinoids are rare neuroendocrine tumors of the lung. Very little is known about the genetic background of these tumors. We applied Ion Torrent Ampliseq next-generation technology to study hotspot mutations of 22 lung cancer-related genes from typical and atypical lung carcinoid tumors. DNA isolated from 25 formalin-fixed, paraffin-embedded carcinoid tumors were amplified to prepare barcoded libraries covering 507 mutations included in 90 amplicons. The libraries were pooled, purified, enriched, and sequenced on ion personal genome machine. The sequences were aligned and checked for known and novel variations using Torrent Suite Software v.4.0.2. One out of 25 patients had mutations in the targeted regions sequenced. This patient had mutations in BRAF, SMAD4, PIK3CA, and KRAS. All these mutations were confirmed as somatic and are previously known mutations. In summary, mutations in genes commonly mutated in non-small-cell lung cancer are not common in lung carcinoids.

B, S., et al. (2015). "NGS meta data analysis for identification of SNP and INDEL patterns in human airway transcriptome: A preliminary indicator for lung cancer." Appl Transl Genom **4**: 4-9.

High-throughput sequencing of RNA (RNA-Seq) was developed primarily to analyze global gene expression in different tissues. It is also an efficient way to discover coding SNPs and when multiple individuals with different genetic backgrounds were used, RNA-Seq is very effective for the identification of SNPs. The objective of this study was to perform SNP and INDEL discoveries in human airway transcriptome of healthy never smokers, healthy

current smokers, smokers without lung cancer and smokers with lung cancer. By preliminary comparative analysis of these four data sets, it is expected to get SNP and INDEL patterns responsible for lung cancer. A total of 85,028 SNPs and 5738 INDELs in healthy never smokers, 32,671 SNPs and 1561 INDELs in healthy current smokers, 50,205 SNPs and 3008 INDELs in smokers without lung cancer and 51,299 SNPs and 3138 INDELs in smokers with lung cancer were identified. The analysis of the SNPs and INDELs in genes that were reported earlier as differentially expressed was also performed. It has been found that a smoking person has SNPs at position 62,186,542 and 62,190,293 in SCGB1A1 gene and 180,017,251, 180,017,252, and 180,017,597 in SCGB3A1 gene and INDELs at position 35,871,168 in NFKBIA gene and 180,017,797 in SCGB3A1 gene. The SNPs identified in this study provides a resource for genetic studies in smokers and shall contribute to the development of a personalized medicine. This study is only a preliminary kind and more vigorous data analysis and wet lab validation are required.

Barata, P. C., et al. (2017). "Next-generation sequencing (NGS) of cell-free circulating tumor DNA and tumor tissue in patients with advanced urothelial cancer: a pilot assessment of concordance." Ann Oncol **28**(10): 2458-2463.

Background: Advances in cancer genome sequencing have led to the development of various next-generation sequencing (NGS) platforms. There is paucity of data regarding concordance of different NGS tests carried out in the same patient. Methods: Here, we report a pilot analysis of 22 patients with metastatic urinary tract cancer and available NGS data from paired tumor tissue [FoundationOne (F1)] and cell-free circulating tumor DNA (ctDNA) [Guardant360 (G360)]. Results: The median time between the diagnosis of stage IV disease and the first genomic test was 23.5 days (0-767), after a median number of 0 (0-3) prior systemic lines of treatment of advanced disease. Most frequent genomic alterations (GA) were found in the genes TP53 (50.0%), TERT promoter (36.3%); ARID1 (29.5%); FGFR2/3 (20.5%), PIK3CA (20.5%) and ERBB2 (18.2%). While we identified GA in both tests, the overall concordance between the two platforms was only 16.4% (0%-50%), and 17.1% (0%-50%) for those patients (n = 6) with both tests conducted around the same time (median difference = 36 days). On the contrary, in the subgroup of patients (n = 5) with repeated NGS in ctDNA after a median of 1 systemic therapy between the two tests, average concordance was 55.5% (12.1%-100.0%). Tumor tissue mutational burden was significantly associated with number of GA in G360 report ($P < 0.001$), number of known GA ($P = 0.009$) and number of variants of unknown significance (VUS) in F1 report ($P < 0.001$), and with total number of GA (non-VUS and VUS) in F1 report ($P < 0.001$). Conclusions: This study suggests a significant discordance between clinically available NGS panels in advanced urothelial cancer, even when collected around the same time. There is a need for better understanding of these two possibly complementary NGS platforms for better integration into clinical practice.

Byers, H., et al. (2016). "Sensitivity of BRCA1/2 testing in high-risk breast/ovarian/male breast cancer families: little contribution of comprehensive RNA/NGS panel testing." Eur J Hum Genet **24**(11): 1591-1597.

The sensitivity of testing BRCA1 and BRCA2 remains unresolved as the frequency of deep intronic splicing variants has not been defined in high-risk familial breast/ovarian cancer families. This variant category is reported at significant frequency in other tumour predisposition genes, including NF1 and MSH2. We carried out comprehensive whole gene RNA analysis on 45 high-risk breast/ovary and male breast cancer families with no identified pathogenic variant on exonic sequencing and copy number analysis of BRCA1/2. In addition, we undertook variant screening of a 10-gene high/moderate risk breast/ovarian cancer panel by next-generation sequencing. DNA testing identified the causative variant in 50/56 (89%) breast/ovarian/male breast cancer families with Manchester scores of >/=50 with two variants being confirmed to affect splicing on RNA analysis. RNA sequencing of BRCA1/BRCA2 on 45 individuals from high-risk families identified no deep intronic variants and did not suggest loss of RNA expression as a cause of lost sensitivity. Panel testing in 42 samples identified a known RAD51D variant, a high-risk ATM variant in another breast ovary family and a truncating CHEK2 mutation. Current exonic sequencing and copy number analysis variant detection methods of BRCA1/2 have high sensitivity in high-risk breast/ovarian cancer families. Sequence analysis of RNA does not identify any variants undetected by current analysis of BRCA1/2. However, RNA analysis clarified the pathogenicity of variants of unknown significance detected by current methods. The low diagnostic uplift achieved through sequence analysis of the other known breast/ovarian cancer susceptibility genes indicates that further high-risk genes remain to be identified.

Chandrani, P., et al. (2015). "NGS-based approach to determine the presence of HPV and their sites of integration in human cancer genome." Br J Cancer **112**(12): 1958-1965.

BACKGROUND: Human papilloma virus (HPV) accounts for the most common cause of all virus-associated human cancers. Here, we describe the first graphic user interface (GUI)-based automated tool 'HPVDetector', for non-computational biologists, exclusively for detection and annotation of the HPV genome based on next-generation sequencing data sets. METHODS: We developed a custom-made reference genome that comprises of human chromosomes along with annotated genome of 143 HPV types as pseudochromosomes. The tool runs on a dual mode as defined by the user: a 'quick mode' to identify presence of HPV types and an 'integration mode' to determine genomic location for the site of integration. The input data can be a paired-end whole-exome, whole-genome or whole-transcriptome data set. The HPVDetector is available in public domain for download: http://www.actrec.gov.in/pi-webpages/AmitDutt/HPVdetector/HPVDetector.html. RESULTS: On the basis of our evaluation of 116 whole-exome, 23 whole-transcriptome and 2 whole-genome data, we were able to identify presence of HPV in 20 exomes and 4 transcriptomes of cervical and head and neck cancer tumour samples. Using the inbuilt annotation module of HPVDetector, we found predominant integration of viral gene E7, a known oncogene, at known 17q21, 3q27, 7q35, Xq28 and novel sites of integration in the human genome. Furthermore, co-infection with high-risk HPVs such as 16 and 31 were found to be mutually exclusive compared with low-risk HPV71. CONCLUSIONS: HPVDetector is a simple yet precise and robust tool for detecting HPV from tumour samples using variety of next-generation sequencing platforms including whole genome, whole exome and transcriptome. Two different modes (quick detection and integration mode) along with a GUI widen the usability of HPVDetector for biologists and clinicians with minimal computational knowledge.

Cole, C., et al. (2014). "Non-synonymous variations in cancer and their effects on the human proteome: workflow for NGS data biocuration and proteome-wide analysis of TCGA data." BMC Bioinformatics **15**: 28.

BACKGROUND: Next-generation sequencing (NGS) technologies have resulted in petabytes of scattered data, decentralized in archives, databases and sometimes in isolated hard-disks which are inaccessible for browsing and analysis. It is expected that curated secondary databases will help organize some of this Big Data thereby allowing users better navigate, search and compute on it. RESULTS: To address the above challenge, we have implemented a NGS biocuration workflow and are analyzing short read sequences and associated metadata from cancer patients to better understand the human variome. Curation of variation and other related information from control (normal tissue) and case (tumor) samples will provide comprehensive background information that can be used in genomic medicine research and application studies. Our approach includes a CloudBioLinux Virtual Machine which is used upstream of an integrated High-performance Integrated Virtual Environment (HIVE) that encapsulates Curated Short Read archive (CSR) and a proteome-wide variation effect analysis tool (SNVDis). As a proof-of-concept, we have curated and analyzed control and case breast cancer datasets from the NCI cancer genomics program - The Cancer Genome Atlas (TCGA). Our efforts include reviewing and recording in CSR available clinical information on patients, mapping of the reads to the reference followed by identification of non-synonymous Single Nucleotide Variations (nsSNVs) and integrating the data with tools that allow analysis of effect nsSNVs on the human proteome. Furthermore, we have also developed a novel phylogenetic analysis algorithm that uses SNV positions and can be used to classify the patient population. The workflow described here lays the foundation for analysis of short read sequence data to identify rare and novel SNVs that are not present in dbSNP and therefore provides a more comprehensive understanding of the human variome. Variation results for single genes as well as the entire study are available from the CSR website (http://hive.biochemistry.gwu.edu/dna.cgi?cmd=csr). CONCLUSIONS: Availability of thousands of sequenced samples from patients provides a rich repository of sequence information that can be utilized to identify individual level SNVs and their effect on the human proteome beyond what the dbSNP database provides.

Concolino, P., et al. (2018). "A comprehensive BRCA1/2 NGS pipeline for an immediate Copy Number Variation (CNV) detection in breast and ovarian cancer molecular diagnosis." Clin Chim Acta **480**: 173-179.

El-Husny, A., et al. (2016). "CDH1 mutations in gastric cancer patients from northern Brazil identified by Next- Generation Sequencing (NGS)." Genet Mol Biol **39**(2): 189-198.

Gastric cancer is considered to be the fifth highest incident tumor worldwide and the third leading cause of cancer deaths. Developing regions report a higher number of sporadic cases, but there are only a few local studies related to hereditary cases of gastric cancer in Brazil to confirm this fact. CDH1 germline mutations have been described both in familial and sporadic cases, but there is only one recent molecular description of individuals from Brazil. In this study we

performed Next Generation Sequencing (NGS) to assess CDH1 germline mutations in individuals who match the clinical criteria for Hereditary Diffuse Gastric Cancer (HDGC), or who exhibit very early diagnosis of gastric cancer. Among five probands we detected CDH1 germline mutations in two cases (40%). The mutation c.1023T > G was found in a HDGC family and the mutation c.1849G > A, which is nearly exclusive to African populations, was found in an early-onset case of gastric adenocarcinoma. The mutations described highlight the existence of gastric cancer cases caused by CDH1 germline mutations in northern Brazil, although such information is frequently ignored due to the existence of a large number of environmental factors locally. Our report represent the first CDH1 mutations in HDGC described from Brazil by an NGS platform.

Endris, V., et al. (2016). "NGS-based BRCA1/2 mutation testing of high-grade serous ovarian cancer tissue: results and conclusions of the first international round robin trial." Virchows Arch **468**(6): 697-705.

With the approval of olaparib as monotherapy treatment in platinum-sensitive, relapsed high-grade serous ovarian cancer by the European Medical Agency (EMA), comprehensive genotyping of BRCA1 and BRCA2 in tumor tissue has become a mandatory pre-therapeutic test. This requires significant advances in routine tumor test methodologies due to the large size of both genes and the lack of mutational hot spots. Classical focused screening approaches, like Sanger sequencing, do not allow for a sensitive, rapid, and economic analysis of tumor tissue. Next-generation sequencing (NGS) approaches employing targeted panels for BRCA1/2 to interrogate formalin-fixed and paraffin-embedded tumor samples from either surgical resection or biopsy specimens can overcome these limitations. Although focused NGS methods have been implemented by few centers in routine molecular diagnostics for the analysis of some druggable oncogenic mutations, the reliable diagnostic testing of the entire coding regions of BRCA1 and BRCA2 was a new challenge requiring extensive technological improvement and quality management. Here, we describe the implementation and results of the first round robin trial for BRCA1/2 mutation testing in tumor tissue that was conducted in central Europe on May 2015, shortly after the approval and prior to the official release of olaparib. The high success rate of 81 % (21/26 test centers) demonstrates that BRCA1/2 multicenter mutation testing is well feasible in FFPE tumor tissue, extending to other tumor entities beyond ovarian cancer. The high number of test centers passing the trial demonstrates the success of the concerted efforts by German, Swiss, and Austrian pathology centers to ensure quality-controlled NGS-based testing and proves the potential of this technology in routine molecular pathology. On the basis of our results, we provide recommendations for predictive testing of tumor tissue for BRCA1/2 to clinical decision making in ovarian cancer patients.

Furtado, L. V. and W. S. Samowitz (2017). "Colorectal cancer molecular profiling: from IHC to NGS in search of optimal algorithm." Virchows Arch **471**(2): 235-242.

Advances in defining the mutational landscape of colorectal cancer (CRC) over the past decades have revolutionized the molecular understanding and clinical testing algorithms for this disease. Mutation testing is standard of care for the work-up of CRCs. This review focuses on the current indications and strategies for molecular testing in CRC and discusses the potential changes in CRC testing approach associated with the emerging clinical application of genomic-based technologies.

Goncalves, A., et al. (2016). "Targeted NGS, array-CGH, and patient-derived tumor xenografts for precision medicine in advanced breast cancer: a single-center prospective study." Oncotarget **7**(48): 79428-79441.

BACKGROUND: Routine feasibility and clinical impact of genomics-based tumor profiling in advanced breast cancer (aBC) remains to be determined. We conducted a pilot study to evaluate whether precision medicine could be prospectively implemented for aBC patients in a single center and to examine whether patient-derived tumor xenografts (PDX) could be obtained in this population. RESULTS: Thirty-four aBC patients were included. Actionable targets were found in 28 patients (82%). A targeted therapy could be proposed to 22 patients (64%), either through a clinical trial (n=15) and/or using already registered drugs (n=21). Ten patients (29%) eventually received targeted treatment, 2 of them deriving clinical benefit. Of 22 patients subjected to mouse implantation, 10 had successful xenografting (45%), mostly in triple-negative aBC. METHODS: aBC patients accessible to tumor biopsy were prospectively enrolled at the Institut Paoli-Calmettes in the BC-BIO study (ClinicalTrials.gov, NCT01521676). Genomic profiling was established by whole-genome array comparative genomic hybridization (aCGH) and targeted next-generation sequencing (NGS) of 365 candidate cancer genes. For a subset of patients, a sample of fresh tumor was orthotopically implanted in humanized cleared fat pads of NSG mice for establishing PDX. CONCLUSIONS: Precision medicine can be implemented in a single center in the context of clinical practice and may allow genomic-driven treatment in approximately 30% of aBC patients. PDX may be obtained in a significant fraction of cases.

Koduru, S. V., et al. (2017). "A Comprehensive NGS Data Analysis of Differentially Regulated miRNAs, piRNAs, lncRNAs and sn/snoRNAs in Triple Negative Breast Cancer." J Cancer **8**(4): 578-596.

Cancer is the second leading cause of death in the United States and is a major public health concern worldwide. Basic, clinical and epidemiological research is leading to improved cancer detection, prevention, and outcomes. Recent technological advances have allowed unbiased and comprehensive screening of genome-wide gene expression. Small non-coding RNAs (sncRNAs) have been shown to play an important role in biological processes and could serve as a diagnostic, prognostic and therapeutic biomarker for specific diseases. Recent findings have begun to reveal and enhance our understanding of the complex architecture of sncRNA expression including miRNAs, piRNAs, lncRNAs, sn/snoRNAs and their relationships with biological systems. We used publicly available small RNA sequencing data that was derived from 24 triple negative breast cancers (TNBC) and 14 adjacent normal tissue samples to remap various types of sncRNAs. We found a total of 55 miRNAs were aberrantly expressed ($p<0.005$) in TNBC samples (8 miRNAs upregulated; 47 downregulated) compared to adjacent normal tissues whereas the original study reported only 25 novel miRs. In this study, we used pathway analysis of differentially expressed miRNAs which revealed TGF-beta signaling pathways to be profoundly affected in the TNBC samples. Furthermore, our comprehensive re-mapping strategy allowed us to discover a number of other differentially expressed sncRNAs including piRNAs, lncRNAs, sn/snoRNAs, rRNAs, miscRNAs and nonsense-mediated decay RNAs. We believe that our sncRNA analysis workflow is extremely comprehensive and suitable for discovery of novel sncRNAs changes, which may lead to the development of innovative diagnostic and therapeutic tools for TNBC.

Kotelnikova, E. A., et al. (2016). "Practical aspects of NGS-based pathways analysis for personalized cancer science and medicine." Oncotarget **7**(32): 52493-52516.

Nowadays, the personalized approach to health care and cancer care in particular is becoming more and more popular and is taking an important place in the translational medicine paradigm. In some cases, detection of the patient-specific individual mutations that point to a targeted therapy has already become a routine practice for clinical oncologists. Wider panels of genetic markers are also on the market which cover a greater number of possible oncogenes including those with lower reliability of resulting medical conclusions. In light of the large availability of high-throughput technologies, it is very tempting to use complete patient-specific New Generation Sequencing (NGS) or other "omics" data for cancer treatment guidance. However, there are still no gold standard methods and protocols to evaluate them. Here we will discuss the clinical utility of each of the data types and describe a systems biology approach adapted for single patient measurements. We will try to summarize the current state of the field focusing on the clinically relevant case-studies and practical aspects of data processing.

Lapunzina, P., et al. (2014). "Impact of NGS in the medical sciences: Genetic syndromes with an increased risk of developing cancer as an example of the use of new technologies." Genet Mol Biol **37**(1 Suppl): 241-249.

The increased speed and decreasing cost of sequencing, along with an understanding of the clinical relevance of emerging information for patient management, has led to an explosion of potential applications in healthcare. Currently, SNP arrays and Next-Generation Sequencing (NGS) technologies are relatively new techniques used to scan genomes for gains and losses, losses of heterozygosity (LOH), SNPs, and indel variants as well as to perform complete sequencing of a panel of candidate genes, the entire exome (whole exome sequencing) or even the whole genome. As a result, these new high-throughput technologies have facilitated progress in the understanding and diagnosis of genetic syndromes and cancers, two disorders traditionally considered to be separate diseases but that can share causal genetic alterations in a group of developmental disorders associated with congenital malformations and cancer risk. The purpose of this work is to review these syndromes as an example of a group of disorders that has been included in a panel of genes for NGS analysis. We also highlight the relationship between development and cancer and underline the connections between these syndromes.

Lim, M. C. and L. M. Randall (2017). "Role and clinical application of next-generation sequencing (NGS) for ovarian cancer." J Gynecol Oncol **28**(4): e51.

Lopez-Doriga, A., et al. (2014). "ICO amplicon NGS data analysis: a Web tool for variant detection in common high-risk hereditary cancer genes analyzed by amplicon GS Junior next-generation sequencing." Hum Mutat **35**(3): 271-277.

Next-generation sequencing (NGS) has revolutionized genomic research and is set to have a major impact on genetic diagnostics thanks to the advent of benchtop sequencers and flexible kits for targeted libraries. Among the main hurdles in NGS are the difficulty of performing bioinformatic analysis of

the huge volume of data generated and the high number of false positive calls that could be obtained, depending on the NGS technology and the analysis pipeline. Here, we present the development of a free and user-friendly Web data analysis tool that detects and filters sequence variants, provides coverage information, and allows the user to customize some basic parameters. The tool has been developed to provide accurate genetic analysis of targeted sequencing of common high-risk hereditary cancer genes using amplicon libraries run in a GS Junior System. The Web resource is linked to our own mutation database, to assist in the clinical classification of identified variants. We believe that this tool will greatly facilitate the use of the NGS approach in routine laboratories.

Machackova, E., et al. (2016). "[Retrospective NGS Study in High-risk Hereditary Cancer Patients at Masaryk Memorial Cancer Institute]." Klin Onkol **29 Suppl 1**: S35-45.

BACKGROUND: Currently, more than 200 hereditary cancer syndromes have been described, yet, in most countries genetic testing is restricted to a narrow spectrum of genes within a limited group of people tested. METHODS: For this retrospective study we used the TruSight cancer panel (Illumina)--NGS panel targeting 94 cancer predisposition genes in order to analyze 50 high-risk cancer patients with significant personal and family history of cancer who did not carry mutations in BRCA1, BRCA2, MLH1, MSH2, MSH6, TP53 or APC genes. All pathogenic and potentially pathogenic mutations detected by NGS technology have been confirmed by Sanger sequencing. RESULTS: There were several deleterious (frame-shift/nonsense) mutations detected in ATM, BAP1, FANCC, FANCI, PMS2, SBDS, ERCC2, RECQL4 genes. Various pathogenic or potentially pathogenic (missense, predicted splice site, in-frame insertion/deletion) mutations were detected in ATM, BRIP1, CDH1, CHEK2, ERCC2, ERCC3, ERCC4, FANCA, MC1R, MEN1, MRE11A, MUTYH, PALB2, RAD51C, RET, SDHB, STK11. These mutations affect highly conserved protein domains and affect their function as proved by the available functional assays. They were confirmed to be pathogenic as an "Parent No2 " in serious recessive diseases such as Ataxia telangiectasia or Fanconi anemia. The clinical significance of the majority of detected missense variants still remains to be identified. CONCLUSION: Moderate or low penetrance variants are of limited clinical importance. Panel genetic testing in high-risk individuals with cancer provides important information concerning the cause of the investigated cancer, and may assist in the risk assesment and optimal management of the cancer, as well as in further preventive care.

Olmedillas-Lopez, S., et al. (2018). "Liquid biopsy by NGS: differential presence of exons (DPE) in cell-free DNA reveals different patterns in metastatic and nonmetastatic colorectal cancer." Cancer Med.

Next-generation sequencing (NGS) has been proposed as a suitable tool for liquid biopsy in colorectal cancer (CRC), although most studies to date have focused almost exclusively on sequencing of panels of potential clinically actionable genes. We evaluated the clinical value of whole-exome sequencing (WES) of cell-free DNA (cfDNA) circulating in plasma, with the goal of identifying differential clinical profiles in patients with CRC. To this end, we applied an original concept, "differential presence of exons" (DPE). We determined differences in levels of 379 exons in plasma cfDNA and used DPE analysis to cluster and classify patients with disseminated and localized disease. The resultant bioinformatics analysis pipeline allowed us to design a predictive DPE algorithm in a small subset of patients that could not be initially classified based on the selection criteria. This DPE suggests that these nucleic acids could be actively released by both tumor and nontumor cells as a means of intercellular communication and might thus play a role in the process of malignant transformation. DPE is a new technique for the study of plasma cfDNA by WES that might have predictive and prognostic value in patients with CRC.

Rovigatti, U. (2015). "Cancer modelling in the NGS era - Part I: Emerging technology and initial modelling." Crit Rev Oncol Hematol **96**(2): 274-307.

It is today indisputable that great progresses have been made in our molecular understanding of cancer cells, but an effective implementation of such knowledge into dramatic cancer-cures is still belated and yet desperately needed. This review gives a snapshot at where we stand today in this search for cancer understanding and definitive treatments, how far we have progressed and what are the major obstacles we will have to overcome both technologically and for disease modelling. In the first part, promising 3rd/4th Generation Sequencing Technologies will be summarized (particularly IonTorrent and OxfordNanopore technologies). Cancer modelling will be then reviewed from its origin in XIX Century Germany to today's NGS applications for cancer understanding and therapeutic interventions. Developments after Molecular Biology revolution (1953) are discussed as successions of three phases. The first, PH1, labelled "Clonal Outgrowth" (from 1960s to mid 1980s) was characterized by discoveries in cytogenetics (Nowell, Rowley) and viral oncology (Dulbecco, Bishop, Varmus), which demonstrated clonality. Treatments were consequently dominated by

a "cytotoxic eradication" strategy with chemotherapeutic agents. In PH2, (from the mid 1980s to our days) the description of cancer as "Gene Networks" led to targeted-gene-therapies (TGTs). TGTs are the focus of Section 3: in view of their apparent failing (Ephemeral Therapies), alternative strategies will be discussed in review part II (particularly cancer immunotherapy, CIT). Additional Pitfalls impinge on the concepts of tumour heterogeneity (inter/intra; ITH). The described pitfalls set the basis for a new phase, PH3, which is called "NGS Era" and will be also discussed with ten emerging cancer models in the Review 2nd part.

Salim, A., et al. (2017). "An approach to forecast human cancer by profiling microRNA expressions from NGS data." BMC Cancer **17**(1): 77.

BACKGROUND: microRNAs are single-stranded non-coding RNA sequences of 18 - 24 nucleotides in length. They play an important role in post-transcriptional regulation of gene expression. Evidences of microRNA acting as promoter/suppressor of several diseases including cancer are being unveiled. Recent studies have shown that microRNAs are differentially expressed in disease states when compared with that of normal states. Profiling of microRNA is a good measure to estimate the differences in expression levels, which can be further utilized to understand the progression of any associated disease. METHODS: Machine learning techniques, when applied to microRNA expression values obtained from NGS data, could be utilized for the development of effective disease prediction system. This paper discusses an approach for microRNA expression profiling, its normalization and a Support Vector based machine learning technique to develop a Cancer Prediction System. Presently, the system has been trained with data samples of hepatocellular carcinoma, carcinomas of the bladder and lung cancer. microRNAs related to specific types of cancer were used to build the classifier. RESULTS: When the system is trained and tested with 10 fold cross validation, the prediction accuracy obtained is 97.56% for lung cancer, 97.82% for hepatocellular carcinoma and 95.0% for carcinomas of the bladder. The system is further validated with separate test sets, which show accuracies higher than 90%. A ranking based on differential expression marks the relative significance of each microRNA in the prediction process. CONCLUSIONS: Results from experiments proved that microRNA expression profiling is an effective mechanism for disease identification, provided sufficiently large database is available.

Schweiger, M. R., et al. (2011). "The power of NGS technologies to delineate the genome organization in cancer: from mutations to structural variations and epigenetic alterations." Cancer Metastasis Rev **30**(2): 199-210.

The development of cancer is characterized by the joined occurrence of alterations on different levels--from single nucleotide changes via structural and copy number variations to epigenetic alterations. With the advent of advanced technologies such as next generation sequencing, we have now the tools in hands to put some light on complex processes and recognize systematic patterns that develop throughout cancer progression. The combination of single hypothesis-driven experiments with a system-wide genetic view enables us to prove so far not addressable questions such as the influence of DNA methylation on gene expression or the disruption of genome homeostasis by structural variations and miRNA expression patterns. Out of this enormous amount of information, specific biomarkers for cancer progression have been discovered, which pave the way for the development of new therapeutic strategies. Here, we will review the status quo of integrative cancer genomic approaches, give an overview over the power of next generation sequencing technologies in oncology, and outline future perspective. Both sides--clinical as well as basic research aspects--will be considered.

Tappeiner, E., et al. (2017). "TIminer: NGS data mining pipeline for cancer immunology and immunotherapy." Bioinformatics **33**(19): 3140-3141.

Summary: Recently, a number of powerful computational tools for dissecting tumor-immune cell interactions from next-generation sequencing data have been developed. However, the assembly of analytical pipelines and execution of multi-step workflows are laborious and involve a large number of intermediate steps with many dependencies and parameter settings. Here we present TIminer, an easy-to-use computational pipeline for mining tumor-immune cell interactions from next-generation sequencing data. TIminer enables integrative immunogenomic analyses, including: human leukocyte antigens typing, neoantigen prediction, characterization of immune infiltrates and quantification of tumor immunogenicity. Availability and implementation: TIminer is freely available at http://icbi.i-med.ac.at/software/timiner/timiner.shtml. Contact: zlatko.trajanoski@i-med.ac.at. Supplementary information: Supplementary data are available at Bioinformatics online.

Thangam, M. and R. K. Gopal (2015). "CRCDA--Comprehensive resources for cancer NGS data analysis." Database (Oxford) **2015**.

Next generation sequencing (NGS) innovations put a compelling landmark in life science and changed the direction of research in clinical

oncology with its productivity to diagnose and treat cancer. The aim of our portal comprehensive resources for cancer NGS data analysis (CRCDA) is to provide a collection of different NGS tools and pipelines under diverse classes with cancer pathways and databases and furthermore, literature information from PubMed. The literature data was constrained to 18 most common cancer types such as breast cancer, colon cancer and other cancers that exhibit in worldwide population. NGS-cancer tools for the convenience have been categorized into cancer genomics, cancer transcriptomics, cancer epigenomics, quality control and visualization. Pipelines for variant detection, quality control and data analysis were listed to provide out-of-the box solution for NGS data analysis, which may help researchers to overcome challenges in selecting and configuring individual tools for analysing exome, whole genome and transcriptome data. An extensive search page was developed that can be queried by using (i) type of data [literature, gene data and sequence read archive (SRA) data] and (ii) type of cancer (selected based on global incidence and accessibility of data). For each category of analysis, variety of tools are available and the biggest challenge is in searching and using the right tool for the right application. The objective of the work is collecting tools in each category available at various places and arranging the tools and other data in a simple and user-friendly manner for biologists and oncologists to find information easier. To the best of our knowledge, we have collected and presented a comprehensive package of most of the resources available in cancer for NGS data analysis. Given these factors, we believe that this website will be an useful resource to the NGS research community working on cancer. Database URL: http://bioinfo.au-kbc.org.in/ngs/ngshome.html.

Wu, T. J., et al. (2014). "A framework for organizing cancer-related variations from existing databases, publications and NGS data using a High-performance Integrated Virtual Environment (HIVE)." Database (Oxford) **2014**: bau022.

Years of sequence feature curation by UniProtKB/Swiss-Prot, PIR-PSD, NCBI-CDD, RefSeq and other database biocurators has led to a rich repository of information on functional sites of genes and proteins. This information along with variation-related annotation can be used to scan human short sequence reads from next-generation sequencing (NGS) pipelines for presence of non-synonymous single-nucleotide variations (nsSNVs) that affect functional sites. This and similar workflows are becoming more important because thousands of NGS data sets are being made available through projects such as The Cancer Genome Atlas (TCGA), and researchers want to evaluate their biomarkers in genomic data. BioMuta, an integrated sequence feature database, provides a framework for automated and manual curation and integration of cancer-related sequence features so that they can be used in NGS analysis pipelines. Sequence feature information in BioMuta is collected from the Catalogue of Somatic Mutations in Cancer (COSMIC), ClinVar, UniProtKB and through biocuration of information available from publications. Additionally, nsSNVs identified through automated analysis of NGS data from TCGA are also included in the database. Because of the petabytes of data and information present in NGS primary repositories, a platform HIVE (High-performance Integrated Virtual Environment) for storing, analyzing, computing and curating NGS data and associated metadata has been developed. Using HIVE, 31 979 nsSNVs were identified in TCGA-derived NGS data from breast cancer patients. All variations identified through this process are stored in a Curated Short Read archive, and the nsSNVs from the tumor samples are included in BioMuta. Currently, BioMuta has 26 cancer types with 13 896 small-scale and 308 986 large-scale study-derived variations. Integration of variation data allows identifications of novel or common nsSNVs that can be prioritized in validation studies. Database URL: BioMuta: http://hive.biochemistry.gwu.edu/tools/biomuta/index.php; CSR: http://hive.biochemistry.gwu.edu/dna.cgi?cmd=csr; HIVE: http://hive.biochemistry.gwu.edu.

Zhang, Y. C., et al. (2017). "The emerging roles of NGS-based liquid biopsy in non-small cell lung cancer." J Hematol Oncol **10**(1): 167.

The treatment paradigm of non-small cell lung cancer (NSCLC) has evolved into oncogene-directed precision medicine. Identifying actionable genomic alterations is the initial step towards precision medicine. An important scientific progress in molecular profiling of NSCLC over the past decade is the shift from the traditional piecemeal fashion to massively parallel sequencing with the use of next-generation sequencing (NGS). Another technical advance is the development of liquid biopsy with great potential in providing a dynamic and comprehensive genomic profiling of NSCLC in a minimally invasive manner. The integration of NGS with liquid biopsy has been demonstrated to play emerging roles in genomic profiling of NSCLC by increasing evidences. This review summarized the potential applications of NGS-based liquid biopsy in the diagnosis and treatment of NSCLC including identifying actionable genomic alterations, tracking spatiotemporal tumor evolution, dynamically monitoring response and resistance to targeted therapies, and diagnostic value in early-stage NSCLC, and discussed emerging challenges to

overcome in order to facilitate clinical translation in future.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

References

[1]. Allegretti, M., et al. (2018). "Tearing down the walls: FDA approves next generation sequencing (NGS) assays for actionable cancer genomic aberrations." J Exp Clin Cancer Res **37**(1): 47.

[2]. Baidu. http://www.baidu.com. 2019.

[3]. Barata, P. C., et al. (2017). "Next-generation sequencing (NGS) of cell-free circulating tumor DNA and tumor tissue in patients with advanced urothelial cancer: a pilot assessment of concordance." Ann Oncol **28**(10): 2458-2463.

[4]. Byers, H., et al. (2016). "Sensitivity of BRCA1/2 testing in high-risk breast/ovarian/male breast cancer families: little contribution of comprehensive RNA/NGS panel testing." Eur J Hum Genet **24**(11): 1591-1597.

[5]. Chandrani, P., et al. (2015). "NGS-based approach to determine the presence of HPV and their sites of integration in human cancer genome." Br J Cancer **112**(12): 1958-1965.

[6]. Cole, C., et al. (2014). "Non-synonymous variations in cancer and their effects on the human proteome: workflow for NGS data biocuration and proteome-wide analysis of TCGA data." BMC Bioinformatics **15**: 28.

[7]. Concolino, P., et al. (2018). "A comprehensive BRCA1/2 NGS pipeline for an immediate Copy Number Variation (CNV) detection in breast and ovarian cancer molecular diagnosis." Clin Chim Acta **480**: 173-179.

[8]. El-Husny, A., et al. (2016). "CDH1 mutations in gastric cancer patients from northern Brazil identified by Next- Generation Sequencing (NGS)." Genet Mol Biol **39**(2): 189-198.

[9]. Endris, V., et al. (2016). "NGS-based BRCA1/2 mutation testing of high-grade serous ovarian cancer tissue: results and conclusions of the first international round robin trial." Virchows Arch **468**(6): 697-705.

[10]. Furtado, L. V. and W. S. Samowitz (2017). "Colorectal cancer molecular profiling: from IHC to NGS in search of optimal algorithm." Virchows Arch **471**(2): 235-242.

[11]. Goncalves, A., et al. (2016). "Targeted NGS, array-CGH, and patient-derived tumor xenografts for precision medicine in advanced breast cancer: a single-center prospective study." Oncotarget **7**(48): 79428-79441.

[12]. Google. http://www.google.com. 2019.

[13]. Koduru, S. V., et al. (2017). "A Comprehensive NGS Data Analysis of Differentially Regulated miRNAs, piRNAs, lncRNAs and sn/snoRNAs in Triple Negative Breast Cancer." J Cancer **8**(4): 578-596.

[14]. Kotelnikova, E. A., et al. (2016). "Practical aspects of NGS-based pathways analysis for personalized cancer science and medicine." Oncotarget **7**(32): 52493-52516.

[15]. Lapunzina, P., et al. (2014). "Impact of NGS in the medical sciences: Genetic syndromes with an increased risk of developing cancer as an example of the use of new technologies." Genet Mol Biol **37**(1 Suppl): 241-249.

[16]. Lim, M. C. and L. M. Randall (2017). "Role and clinical application of next-generation sequencing (NGS) for ovarian cancer." J Gynecol Oncol **28**(4): e51.

[17]. Lopez-Doriga, A., et al. (2014). "ICO amplicon NGS data analysis: a Web tool for variant detection in common high-risk hereditary cancer genes analyzed by amplicon GS Junior next-generation sequencing." Hum Mutat **35**(3): 271-277.

[18]. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.

[19]. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.

[20]. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7-15.

[21]. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf.

[22]. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11. Nature and science 2007;5(1):81-96.

[23]. Machackova, E., et al. (2016). "[Retrospective NGS Study in High-risk Hereditary Cancer Patients at Masaryk Memorial Cancer Institute]." Klin Onkol **29 Suppl 1**: S35-45.

[24]. Marsland Press. http://www.sciencepub.net. 2019.

[25]. National Center for Biotechnology Information, U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/pubmed. 2019.

[26]. Olmedillas-Lopez, S., et al. (2018). "Liquid biopsy by NGS: differential presence of exons (DPE) in cell-free DNA reveals different patterns in metastatic and nonmetastatic colorectal cancer." Cancer Med.

[27]. Rovigatti, U. (2015). "Cancer modelling in the NGS era - Part I: Emerging technology and

initial modelling." Crit Rev Oncol Hematol **96**(2): 274-307.
[28]. Salim, A., et al. (2017). "An approach to forecast human cancer by profiling microRNA expressions from NGS data." BMC Cancer **17**(1): 77.
[29]. Schweiger, M. R., et al. (2011). "The power of NGS technologies to delineate the genome organization in cancer: from mutations to structural variations and epigenetic alterations." Cancer Metastasis Rev **30**(2): 199-210.
[30]. Tappeiner, E., et al. (2017). "TIminer: NGS data mining pipeline for cancer immunology and immunotherapy." Bioinformatics **33**(19): 3140-3141.
[31]. Thangam, M. and R. K. Gopal (2015). "CRCDA--Comprehensive resources for cancer NGS data analysis." Database (Oxford) **2015**.
[32]. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2019.
[33]. Wu, T. J., et al. (2014). "A framework for organizing cancer-related variations from existing databases, publications and NGS data using a High-performance Integrated Virtual Environment (HIVE)." Database (Oxford) **2014**: bau022.
[34]. Zhang, Y. C., et al. (2017). "The emerging roles of NGS-based liquid biopsy in non-small cell lung cancer." J Hematol Oncol **10**(1): 167.

3/4/2024